8. Grondin C. *et al.* Slow-acting antirheumatic drugs in chronic arthritis of childhood. *Semin Arthritis Rheum* 1988; 18: 38–47.
9. Richardson MR, Zalin AM. Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; 294: 741.
10. Hanonen P, *et al.* Treatment of palindromic rheumatism with chloroquine. *BMJ* 1987; 294: 1289.
11. Youssef W, *et al.* Palindromic rheumatism: a response to chloroquine. *J Rheumatol* 1991; 18: 35–7.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p. 1612.2) as alternatives or adjuncts to corticosteroid therapy. For references to the use of hydroxychloroquine, see under Chloroquine, p. 651.1.

Skin disorders. For reference to the use of hydroxychloroquine in a variety of skin disorders, see under Chloroquine, p. 651.2.

Systemic lupus erythematosus. Antimalarials have been widely used in the treatment of lupus erythematosus (p. 1613.3), particularly its cutaneous manifestations, although much of the evidence is based on case series and reports.[1] Hydroxychloroquine is most widely used,[1,2] as it is thought to have fewer adverse effects than chloroquine, although any benefit with chloroquine generally starts to become evident within several weeks of starting treatment, whereas it may take up to 2 months for any effect of hydroxychloroquine to be seen. For extracutaneous disease, antimalarials are often combined with other drugs; treatment may be continued for many years. For reference to precautions to reduce the risk of retinopathy see Effects on the Eyes, under Adverse Effects of Chloroquine, p. 651.2. There is evidence from a case-control study[3] that long-term hydroxychloroquine treatment is associated with improved survival in patients with SLE, and some consider it to be underused.[2] It has been suggested that hydroxychloroquine may also have a role in reducing the thrombotic symptoms of SLE, including in patients with antiphospholipid syndrome.[4]

1. Wozniacka A, McCauliffe DP. Optimal use of antimalarials in treating cutaneous lupus erythematosus. *Am J Clin Dermatol* 2005; 6: 1–11.
2. Costedoat-Chalumeau N, *et al.* Hydroxychloroquine dans le traitement du lupus: le renouveau. *Rev Med Interne* 2008; 29: 735–7.
3. Alarcón GS, *et al.* Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA I). *Ann Rheum Dis* 2007; 66: 1168–72.
4. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. *Curr Rheumatol Rep* 2011; 13: 77–80.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism (p. 1274.1) is usually with an anticoagulant. Hydroxychloroquine has been described by some as an antiplatelet agent[1] and although its mechanism of action is uncertain the incidence of fatal pulmonary embolism has been reduced in patients given hydroxychloroquine prophylactically after total hip replacement;[2] the usual daily divided oral dose was about 800 mg from the day before surgery until discharge; larger doses had been used.

See also Systemic Lupus Erythematosus, above.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; 308: 235–46.
2. Loudon JR. Hydroxychloroquine and postoperative thromboembolism after total hip replacement. *Am J Med* 1988; 85: (suppl 4A): 57–61.

Adverse Effects, Treatment, and Precautions

As for Chloroquine, p. 651.2.

Breast feeding. Hydroxychloroquine has been detected in human breast milk[1,2] but no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers[3] that it is therefore usually compatible with breast feeding.

1. Nation RL, *et al.* Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol* 1984; 17: 368–9.
2. Østensen M, *et al.* Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol* 1985; 28: 357.
3. 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 19/04/04)

Effects on the eyes. The main adverse effects of chloroquine and hydroxychloroquine on the eye are keratopathy and retinopathy. With respect to retinopathy, precautions should be taken in patients undergoing long-term treatment, as described under Chloroquine on p. 651.2.

Further references.

1. Jones SK. Ocular toxicity and hydroxychloroquine: guidelines for screening. *Br J Dermatol* 1999; 140: 3–7.
2. Tripp JM, Malbach HL. Hydroxychloroquine-induced retinopathy: a dermatologic perspective. *Am J Clin Dermatol* 2006; 7: 171–5.
3. Tehrani R, *et al.* Ocular toxicity of hydroxychloroquine. *Semin Ophthalmol* 2008; 23: 201–9.
4. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2010; 62: 775–84.
5. Bergholz R, *et al.* Evaluation of risk factors for retinal damage due to chloroquine and hydroxychloroquine. *Br J Ophthalmol* 2010; 94: 1637–42.
6. Payne JF, *et al.* Clinical characteristics of hydroxychloroquine retinopathy. *Br J Ophthalmol* 2011; 95: 245–50.
7. Michaelides M, *et al.* Retinal toxicity associated with hydroxychloroquine and chloroquine: risk factors, screening, and progression despite cessation of therapy. *Arch Ophthalmol* 2011; 129: 30–9.

Effects on glucose metabolism. For the effects of hydroxychloroquine on glucose metabolism, see under Chloroquine, p. 651.3.

Overdosage. References[1-4] to the management of hydroxychloroquine overdose. Management has largely been based on that used for overdoses of chloroquine (p. 652.2).

1. Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose. *Am J Emerg Med* 2001; 19: 420–4.
2. Ling Ngan Wong A, *et al.* Hydroxychloroquine overdose: case report and recommendations for management. *Eur J Emerg Med* 2008; 15: 16–8.
3. Olgers TJ, *et al.* Ernstige intoxicatie met hydroxychloroquine, met hemodynamische instabiliteit: casuistische ondersteuning voor behandeling met diazepam. *Ned Tijdschr Geneeskd* 2008; 152: 509–12.
4. Gunja N, *et al.* Survival after massive hydroxychloroquine overdose. *Anaesth Intensive Care* 2009; 37: 130–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydroxychloroquine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

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

Pregnancy. In a study[1] of 133 pregnancies in 90 women treated with hydroxychloroquine, no statistical difference in pregnancy outcome was found compared with a control group consisting of 70 pregnancies in 53 women. It was concluded that the findings supported preliminary evidence for the safety of hydroxychloroquine treatment in pregnancy, and that treatment should probably therefore be maintained during pregnancy in patients with SLE. A later systematic review[2] also concluded that there was no increased risk of congenital defects, spontaneous abortion, fetal death or prematurity associated with use of hydroxychloroquine for auto-immune diseases during pregnancy.

1. Costedoat-Chalumeau N, *et al.* Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. *Arthritis Rheum* 2003; 48: 3207–11.
2. Sperber K, *et al.* Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. *Pediatr Rheumatol Online J* 2009; 7: 9.

Interactions

As for Chloroquine, p. 653.2.

Pharmacokinetics

The pharmacokinetics of hydroxychloroquine are similar to those of chloroquine (see p. 653.3).

References.
1. Tett SE, *et al.* Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 1989; 27: 771–9.
2. Miller DR, *et al.* Steady-state pharmacokinetics of hydroxychloroquine in rheumatoid arthritis. *DICP Ann Pharmacother* 1991; 25: 1302–5.
3. Ducharme J, *et al.* Enantioselective disposition of hydroxychloroquine after a single oral dose of the racemate to healthy subjects. *Br J Clin Pharmacol* 1995; 40: 127–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Axokine; Evoquin; Metirel; Narbon; Plaquenil; Polirreumin; ***Austral.***: Plaquenil; ***Belg.***: Plaquenil; ***Braz.***: Plaquinol; Reuquinol; ***Canad.***: Apo-Hydroxyquine; Plaquenil; Pro-Hydroxyquine; ***Chile***: Ilinol; Plaquinol; ***China***: Fen Le (纷乐); Plaquenil (赛能); ***Cz.***: Plaquenil; ***Denm.***: Ercoquin; Plaquenil; ***Fin.***: Oxiklorin; ***Fr.***: Plaquenil; ***Ger.***: Quensyl; ***Gr.***: Plaquenil; ***Hong Kong***: Plaquenil; ***India***: HCQS; HQTor; Hydrocad; Hydroquin; Oxcq; Oxy-Q; ***Irl.***: Plaquenil; ***Israel***: Plaquenil; ***Ital.***: Plaquenil; ***Malaysia***: Plaquenil; ***Mex.***: Plaquenil; ***Neth.***: Plaquenil; ***Norw.***: Plaquenil; ***NZ***: Plaquenil; ***Philipp.***: Plaquenil; ***Port.***: Plaquinol; ***Rus.***: Immard (Иммард); Plaquenil (Плаквенил); ***Singapore***: Plaquenil; ***Spain***: Dolquine; ***Swed.***: Plaquenil; ***Switz.***: Plaquenil; ***Thai.***: HCQS; Hydroquin; Plaquenil; ***Turk.***: Plaquenil; ***UK***: Plaquenil; ***Ukr.***: Immard (Иммард); Plaquenil (Плаквенил); ***USA***: Plaquenil; ***Venez.***: Plaquinol.

Pharmacopoeial Preparations

BP 2014: Hydroxychloroquine Tablets;
USP 36: Hydroxychloroquine Sulfate Tablets.

Lumefantrine *(BAN, USAN, rINN)*

Benflumelol; Benflumetol; Lumefantrin; Lumefantrina; Luméfantrine; Lumefantrinum; Lumefantryna; Лумефантрин.

2,7-Dichloro-9-[(4-chlorophenyl)methylene]-α-[(dibutylamino)methyl]-9*H*-fluorene-4-methanol.

$C_{30}H_{32}Cl_3NO$=528.9

CAS — 82186-77-4.

UNII — F38R0JR742.

Pharmacopoeias. In *Chin.*

Uses and Administration

Lumefantrine is a dichlorobenzylidine derivative given orally with artemether (p. 648.1) for the treatment of uncomplicated falciparum malaria (p. 644.1). In some countries, the combination is also used for the treatment of chloroquine-resistant non-falciparum malaria. Lumefantrine is a blood schizontocide with a relatively slow onset of action but it has a longer duration of action than artemether. The combination is given as a six-dose regimen, with each dose containing lumefantrine 480 mg and artemether 80 mg. The first dose is given at initial diagnosis, with subsequent doses given after 8, 24, 36, 48, and 60 hours; it has been suggested that doses be given after a milky drink or fat-containing food to ensure adequate absorption.

For details of dosing in children, see below.

References.
1. Omari AAA, *et al.* Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 19/07/06).
2. Omari AAA, *et al.* Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 19/07/06).
3. Kokwaro G, *et al.* Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria. *Expert Opin Pharmacother* 2007; 8: 75–94.
4. Adjei GO, *et al.* Artemether-lumefantrine: an oral antimalarial for uncomplicated malaria in children. *Expert Rev Anti Infect Ther* 2009; 7: 669–81.
5. Ngasala BE, *et al.* Efficacy and effectiveness of artemether-lumefantrine after initial and repeated treatment in children < 5 years of age with acute uncomplicated *Plasmodium falciparum* malaria in rural Tanzania: a randomized trial. *Clin Infect Dis* 2011; 52: 873–82.

Administration in children. Lumefantrine may be given orally to infants and children, with artemether, for the treatment of **uncomplicated falciparum malaria**. In some countries, the combination is also used for the treatment of **chloroquine-resistant non-falciparum malaria**. A total of 6 doses are given, starting at diagnosis and repeated after 8, 24, 36, 48, and 60 hours; recommended doses according to body-weight are as follows:

- 5 to 14 kg: lumefantrine 120 mg with artemether 20 mg
- 15 to 24 kg: lumefantrine 240 mg with artemether 40 mg
- 25 to 34 kg: lumefantrine 360 mg with artemether 60 mg
- over 35 kg: as for adults (see above)

It has been suggested that doses be given after a milky drink or fat-containing food to ensure adequate absorption.

Adverse Effects and Precautions

Adverse effects associated with the combination of lumefantrine with artemether commonly include headache, dizziness, sleep disturbance, palpitations, gastrointestinal disturbances, anorexia, pruritus, rash, cough, arthralgia, myalgia, and fatigue.

Lumefantrine-artemether may cause prolongation of the QT interval, and therefore should be avoided in patients with serum-potassium or magnesium disturbances, any clinical condition known to prolong the QT interval (such as congenital long QT syndrome, symptomatic cardiac arrhythmia, or severe heart failure), or a family history of sudden cardiac death.

Lumefantrine-artemether should be given with caution in severe hepatic or renal impairment and ECG and blood potassium monitored.

Effects on the blood. Severe haemolytic anaemia necessitating corticosteroid treatment, blood transfusion, and haemodialysis occurred in a patient after taking 8 lumefantrine-artemether tablets after a malarial attack.[1] It was considered that, given its molecular similarity to other antimalarials known to cause haemolysis, the causative drug was probably lumefantrine.

1. Mérat S, *et al.* Case report: combination artemether-lumefantrine and haemolytic anaemia following a malarial attack. *Trans R Soc Trop Med Hyg* 2003; 97: 433–4.

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

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Interactions

Use of lumefantrine-artemether should be avoided in patients who are using other drugs known to prolong the QT interval (such as halofantrine, quinine, and mefloquine). For patients previously treated with halofantrine, licensed product information recommends that at least a month should pass before starting lumefantrine-artemether. The combination is also considered contra-indicated in patients taking any drugs that are metabolised by the cytochrome enzyme CYP2D6, particularly those with cardiac effects (including amitriptyline, clomipramine, flecainide, imipramine, and metoprolol). Given the long elimination half-life of lumefantrine (see Pharmacokinetics, below), care must also be taken when starting potentially interacting medications soon after lumefantrine has been stopped.

Pharmacokinetics

The bioavailability of lumefantrine after oral doses is variable; absorption begins after a lag-time of up to 2 hours and bioavailability is substantially increased when given with food, particularly meals high in fat. Peak plasma concentrations occur after about 6 to 8 hours. Lumefantrine is almost completely protein bound. It is considered to be metabolised mainly in the liver and is excreted in the faeces. The elimination half-life is reported to be between 4 to 6 days in patients with malaria.

References.

1. White NJ, *et al.* Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 1999; 37: 105–25.
2. Ezzet F, *et al.* Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrob Agents Chemother* 2000; 44: 697–704.
3. Tarning J, *et al.* Population pharmacokinetics of lumefantrine in pregnant women treated with artemether-lumefantrine for uncomplicated *Plasmodium falciparum* malaria. *Antimicrob Agents Chemother* 2009; 53: 3837–46.
4. Djimdé A, Lefèvre G. Understanding the pharmacokinetics of Coartem. *Malar J* 2009; 8 (suppl 1): S4.
5. Hietala SF, *et al.* Population pharmacokinetics and pharmacodynamics of artemether and lumefantrine during combination treatment in children with uncomplicated falciparum malaria in Tanzania. *Antimicrob Agents Chemother* 2010; 54: 4780–8.
6. Mwesigwa J, *et al.* Pharmacokinetics of artemether-lumefantrine and artesunate-amodiaquine in children in Kampala, Uganda. *Antimicrob Agents Chemother* 2010; 54: 52–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Riamet; *Austria*: Riamet; *Belg.*: Co-Artesiane; Riamet; *Cz.*: Riamet†; *Fr.*: Riamet; *Ger.*: Riamet; *Gr.*: Riamet; *India*: Alither; Arh-L; Arlufe; Arsumet-L; Arte Plus; Coartrin; Combither; Falcimax Plus; Falcirid; Lumeart; Lumecap-A; Lumerax; Lumether; Malatrit-EL; *Indon.*: Coartem; *Neth.*: Riamet; *Philipp.*: Coartem; *Port.*: Riamet; *S.Afr.*: Coartem; *Singapore*: Riamet; *Swed.*: Riamet; *Switz.*: Riamet; *Thai.*: Coartem; *UK*: Riamet; *USA*: Coartem.

Mefloquine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de mefloquina; Meflochina Cloridrato; Meflochin-hydrochlorid; Meflokiinihydrokloridi; Meflokin-hidroklorid; Meflokinhydroklorid; Mefloquino hidrochloridas; Mefloquina, hidrocloruro de; Méfloquine, Chlorhydrate de; Mefloquinhydrochlorid; Mefloquini Hydrochloridum; Ro-21-5998 (mefloquine); Ro-21-5998/001 (mefloquine hydrochloride); WR-142490 (mefloquine); Мефлохина Гидрохлорид.

(*RS*)-[2,8-Bis(trifluoromethyl)-4-quinolyl]-(*SR*)-(2-piperidyl) methanol hydrochloride.

$C_{17}H_{16}F_6N_2O,HCl$=414.8

CAS — 53230-10-7 (mefloquine); 51773-92-3 (mefloquine hydrochloride).

ATC — P01BC02.

UNII — 5Y9L3636O3.

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

Ph. Eur. 8: (Mefloquine Hydrochloride). A white or slightly yellow, crystalline powder. It shows polymorphism. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Mefloquine Hydrochloride). A white or slightly yellow, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; soluble in alcohol; freely soluble in methyl alcohol. Store in airtight containers at a temperature between 15 degrees and 30 degrees. Protect from light.

Sorption. For reference to loss of mefloquine hydrochloride from solutions during membrane filtration, see Chloroquine, p. 650.2.

Stability. A report of the photolytic degradation of mefloquine hydrochloride in water.[1]

1. Tønnesen HH, Grislingaas A-L. Photochemical stability of biologically active compounds II: photochemical decomposition of mefloquine in water. *Int J Pharmaceutics* 1990; 60: 157–62.

Uses and Administration

Mefloquine is a 4-methanolquinoline antimalarial related to quinine. It is a blood schizontocide effective against all forms of malaria including chloroquine- or multidrug-resistant strains of *Plasmodium falciparum*, although some strains are naturally resistant to mefloquine. It is used for the treatment of uncomplicated falciparum malaria and chloroquine-resistant vivax malaria, and also for malaria prophylaxis (see below). Mefloquine is also used after treatment with an artemisinin derivative for acute uncomplicated malaria, to reduce the risk of recrudescence.

Mefloquine is given orally as the hydrochloride but variation in the way doses are expressed could lead to confusion. In the UK and elsewhere, doses are expressed in terms of the base and a dose of 250 mg base is equivalent to about 274 mg of mefloquine hydrochloride. In the USA, doses are expressed in terms of the hydrochloride and a dose of 250 mg is therefore equivalent to only about 228 mg of mefloquine base. Doses in the USA could therefore be about 10% less than elsewhere.

For the *treatment of uncomplicated malaria in non-immune travellers*, WHO recommends 25 mg/kg of mefloquine base given in a split-dose regimen of 15 mg/kg initially, followed by 10 mg/kg 6 to 24 hours later. However, the *BNF* notes that mefloquine is rarely used for treatment of falciparum malaria or chloroquine-resistant non-falciparum malarias due to concern about resistance and, in the case of the non-falciparum malarias, the availability of better tolerated treatments.

For the *treatment of uncomplicated falciparum malaria in endemic areas*, WHO recommends that mefloquine 25 mg/kg be given with a 3-day course of artesunate (see p. 648.2); the mefloquine dose may be given as the split-dose regimen above, or as 8.3 mg/kg once daily for 3 days.

For the *prophylaxis* of malaria, a once-weekly dose of 250 mg mefloquine base has been recommended; prophylaxis should start at least 1 week, but preferably 2 to 3 weeks before entering the malarious area and continue for 4 weeks after leaving.

For further information, and for details of dosing in children, see below.

Administration in children. Mefloquine may be given orally to infants and children for malaria prophylaxis, as well as for the treatment of uncomplicated falciparum malaria and chloroquine-resistant vivax malaria, although it is not licensed for use in children under 3 months of age or weighing less than 5 kg.

For the **treatment of uncomplicated malaria in non-immune travellers**, WHO[1] recommends 25 mg/kg of mefloquine base given in a split-dose regimen of 15 mg/kg initially, followed by 10 mg/kg 6 to 24 hours later.

For the **treatment of uncomplicated falciparum malaria in endemic areas**, WHO[2] recommends that mefloquine 25 mg/kg be given with a 3-day course of artesunate (see p. 648.2); the mefloquine dose may be given as the split-dose regimen above, or as 8.3 mg/kg once daily for 3 days.

Recommended doses for **prophylaxis** are generally based on 5 mg/kg of mefloquine base as a single weekly dose in children weighing over 5 kg.[1] Typical once-weekly doses used in the UK[3] for infants and children from 5 kg bodyweight and over 3 months of age are as follows:

- 5 to 15.9 kg (3 months to 3 years 11 months): 62.5 mg
- 16 to 24.9 kg (4 years to 7 years 11 months): 125 mg
- 25 to 44.9 kg (8 years to 12 years 11 months): 187.5 mg
- 45 kg and over: the adult dose (see above)

1. WHO. *International travel and health.* 2011 ed. Available at: http://www.who.int/ith/en/ (accessed 17/06/11)
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

Malaria. The overall treatment and prophylaxis of malaria and the place of mefloquine in current recommendations are discussed on p. 644.1.

TREATMENT. Clinical studies have shown mefloquine to be effective in the treatment of chloroquine- or multidrug-resistant falciparum malaria. It is also effective in non-falciparum malarias, but is not normally required since they usually respond to chloroquine.

Mefloquine has been widely used as an alternative to regimens using quinine for the treatment of chloroquine-resistant or multidrug-resistant strains of *Plasmodium falciparum*. It is now also used with an artemisinin derivative in multidrug resistance (see p. 649.1).

As there is no parenteral formulation of mefloquine currently available it can only be used in patients who can take oral medication and is therefore unsuitable for sole treatment in severe infections. Mefloquine has produced adequate blood concentrations by the nasogastric route, but this route cannot be relied upon in seriously ill patients.[1] If mefloquine is given to patients after parenteral doses of quinine, it is recommended that a period of 12 hours should be allowed after the last dose of quinine to avoid toxicity.

WHO[2] considers that drugs used for the treatment of uncomplicated falciparum malaria may in principle be carried as a *standby* for use in similar doses for the emergency self-treatment of malaria, although mefloquine is not recommended by WHO as a first-line regimen.

PROPHYLAXIS. It had been hoped that mefloquine could be reserved for the treatment of malaria, but increasing drug resistance to chemoprophylactic regimens has led to it being widely used for malaria prophylaxis.[3] WHO recommends[2] that mefloquine should be used where there is a high risk of falciparum malaria and drug resistance or a moderate to low risk but with high drug resistance. The equivalent of 250 mg of mefloquine base is given every week, starting 1 to 3 weeks before departure, and continuing throughout the period of exposure and for 4 weeks after leaving the malarious area. Starting mefloquine prophylaxis 2 to 3 weeks before exposure allows for detection of possible adverse effects before travelling (see Effects on the Nervous System, p. 658.1, for concerns about neurotoxicity). It is now considered that mefloquine prophylaxis can be given for periods of up to one year instead of the previous limit of 3 months.

In the event of breakthrough malaria during malaria prophylaxis there may be a delay of up to several months before the onset of symptoms in contrast to that seen with other forms of prophylaxis.[4] Mefloquine should not be used for treatment if it has been used for prophylaxis.

1. Chanthavanich P, *et al.* Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *Am J Trop Med Hyg* 1985; 34: 1028–36.
2. WHO. *International travel and health.* 2012 ed. Available at: http://www.who.int/ith/en (accessed 29/10/12)
3. Schlagenhauf P, *et al.* The position of mefloquine as a 21st century malaria chemoprophylaxis. *Malar J* 2010; 9: 357.
4. Day JH, Behrens RH. Delay in onset of malaria with mefloquine prophylaxis. *Lancet* 1995; 345: 398.

Schistosomiasis. A combination of mefloquine plus artesunate (p. 648.2) has been investigated for use in the treatment of schistosomiasis (p. 148.1). In a randomised, open-label study,[1] mefloquine 250 mg plus artesunate 100 mg both given orally once daily for 3 days resulted in a cure rate of 61% among schoolchildren infected with *Schistosoma haematobium*; high cure rates and egg reduction rates were also seen in children coinfected with *S. mansoni*.

1. Keiser J, *et al.* Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against *Schistosoma haematobium*: randomized, exploratory open-label trial. *Clin Infect Dis* 2010; 50: 1205–13.

Adverse Effects

Since mefloquine has a long elimination half-life, adverse effects may occur or persist up to several weeks after the last dose.

The most frequent adverse effects of mefloquine are nausea, diarrhoea, vomiting, abdominal pain, anorexia, headache, somnolence, and sleep disorders, notably insomnia and abnormal dreams. Dizziness, vertigo, and loss of balance may also occur, and in rare cases have continued for months after the drug was stopped.

Neurological or psychiatric disturbances have also been reported with mefloquine and include sensory and motor neuropathies, tremor, ataxia, visual disturbances, tinnitus and hearing impairment, convulsions, anxiety, depression, confusion, hallucinations, panic attacks, emotional instability, aggression and agitation, and acute psychosis. There have been rare reports of suicidal ideation.

Other adverse effects include rashes, pruritus and urticaria, hair loss, muscle weakness, myalgia, liver function disturbances, and very rarely thrombocytopenia and leucopenia. There have been rare occurrences of erythema multiforme and Stevens-Johnson syndrome. Anaphylaxis has occurred rarely. Cardiovascular effects have included hypotension, hypertension, tachycardia or palpitations, bradycardia, QT prolongation, and other minor ECG changes. There have been isolated cases of atrioventricular block.

Incidence of adverse effects. The frequencies of adverse effects reported[1] in 134 soldiers given mefloquine hydrochloride 250 mg weekly for malaria chemoprophylaxis were: diarrhoea (48%), nausea (13%), vomiting (2%), headache (13%), and dizziness (7%). All of 7 healthy sub-

jects who received a dose of mefloquine hydrochloride 15 mg/kg had symptoms that included vertigo, nausea, dizziness, and lightheadedness.[2] The manufacturers reported that dizziness occurred in 24% of patients with malaria treated with 750 mg of mefloquine, in 38% treated with 1 g, and in 96% treated with 1.5 g; splitting a dose into two doses given 8 hours apart can reduce the incidence of dizziness.[3] A prospective study involving 3673 patients found that anorexia, nausea, vomiting, dizziness, and sleep disorders were 1.1 to 1.4 times more frequent in patients receiving mefloquine 25 mg/kg for treatment of malaria than in those receiving 15 mg/kg, and that vomiting could be reduced by 40% if the higher dose was split and given as 15 mg/kg followed by a further 10 mg/kg after 16 to 24 hours.[4] The frequency of adverse effects is reported to be higher in subjects who become dehydrated.[5]

There has been concern that the adverse effects of mefloquine, especially neuropsychiatric reactions, might limit its use for the prophylaxis of malaria but, as discussed under Effects on the Nervous System, below, the incidence of adverse effects does not appear to be greater than with other prophylactic schedules.

1. Arthur JD, *et al.* Mefloquine prophylaxis. *Lancet* 1990; 335: 972.
2. Patchen LC, *et al.* Neurologic reactions after a therapeutic dose of mefloquine. *N Engl J Med* 1989; 321: 1415.
3. Stürchler D, *et al.* Neuropsychiatric side effects of mefloquine. *N Engl J Med* 1990; 322: 1752–3.
4. ter Kuile FO, *et al.* Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. *Bull WHO* 1995; 73: 631–42.
5. Perry IC. Malaria prophylaxis. *BMJ* 1995; 310: 1673.

Effects on the blood. Agranulocytosis was reported[1] in a patient with malaria 48 hours after treatment with a 1250-mg course of mefloquine. The patient had previously taken 250 mg of mefloquine weekly for 7 weeks without adverse effects. Thrombotic thrombocytopenic purpura has been reported[2] in a patient after taking two standard weekly doses of mefloquine for malaria prophylaxis. Symptoms improved after plasmapheresis.

1. Hennequin C, *et al.* Agranulocytosis during treatment with mefloquine. *Lancet* 1991; 337: 984.
2. Placcadori E, *et al.* Thrombotic-thrombocytopenic purpura following malaria prophylaxis with mefloquine. *J Antimicrob Chemother* 2006; 57: 160–1.

Effects on the liver. Acute fatty liver was reported[1] in a patient who had recently received mefloquine 250 mg weekly for 5 weeks for malaria prophylaxis. Symptoms resolved with fluid, electrolyte, and albumin replacement, after stopping mefloquine. In another report,[2] acute elevation of liver transaminases, associated with severe acute hepatitis, occurred in a patient with pre-existing mild hepatic impairment after a 6-week course of mefloquine 250 mg weekly.

1. Grieco A, *et al.* Acute fatty liver after malaria prophylaxis with mefloquine. *Lancet* 1999; 353: 295–6.
2. Gotsman I, *et al.* Mefloquine-induced acute hepatitis. *Pharmacotherapy* 2000; 20: 1517–19.

Effects on the lungs. Acute pneumonitis requiring hospitalisation[1] was reported in a patient after a single dose of oral mefloquine 250 mg for malaria prophylaxis. The condition slowly resolved after the drug was stopped but recurred with mefloquine rechallenge 4 months later, leading to intensive care unit admission. A subsequent case of eosinophilic pneumonia associated with mefloquine prophylaxis has also been reported.[2]

Between May 1989 and January 2008, the US FDA received 13 reports of pneumonitis associated with mefloquine use at either treatment or prophylactic doses.[3] Although most of these patients recovered fully after the drug was stopped, one death, in a 4-year old, occurred. Antibacterial treatment was not of benefit in many cases, although one-third of patients improved after treatment with corticosteroids, suggesting a possible allergic aetiology.

1. Soentjens P, *et al.* Mefloquine-induced pneumonitis. *J Travel Med* 2006; 13: 172–4.
2. Katsenos S, *et al.* Mefloquine-induced eosinophilic pneumonia. *Pharmacotherapy* 2007; 27: 1767–71.
3. FDA. Mefloquine Hydrochloride (marketed as Lariam and generics): pneumonitis. *FDA Drug Safety Newsletter* 2008; 1: 41–3. Available at: http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm120613.htm#mefloquine_hydrochloride (accessed 08/09/09)

Effects on the nervous system. Neuropsychiatric reactions have been associated with the use of mefloquine[1] although various figures have been reported for their frequency. The UK CSM has quoted[2] figures of 1 in 10 000 to 1 in 20 000 for severe reactions to *prophylactic* doses and similarly the manufacturers report that 1 in 10 000 patients given mefloquine prophylaxis will have serious problems. Others consider that the incidence of serious reactions is extremely low,[3] with a frequency of about 1 in 80 000. The manufacturers have also reported that most reactions in patients taking mefloquine for prophylaxis appear to occur after the first dose and have suggested that monitoring after the first dose could identify 40% of those at risk of neuropsychiatric effects.[4] Some authorities consider that over 75% of such reactions to mefloquine are apparent by the third dose.[5] This may allow for tolerability problems with mefloquine prophylaxis to be identified before travel. There has been much discussion on the comparative tolerability of antimalarials used for chemoprophylaxis. The incidence of adverse events, including neuropsychiatric events, was comparable for mefloquine and chloroquine in 2 uncontrolled questionnaire studies, one in tourists[6] and one in US Peace Corps volunteers.[7] However, in a more recent questionnaire in travellers,[8] although the incidence of reported adverse events was similar for mefloquine and chloroquine plus proguanil, neuropsychiatric adverse events were significantly more common in mefloquine recipients. In two randomised controlled studies,[9,10] both in military personnel, there was no difference between CNS symptoms in those given weekly mefloquine and those receiving chloroquine (with or without proguanil). In one of these studies,[10] a subgroup receiving a loading dose of mefloquine daily for 3 days initially had a higher incidence of CNS events. A review[11] of 10 controlled studies found no significant difference in the rates of withdrawal and overall incidence of adverse effects for mefloquine and alternative prophylactic regimens, but mefloquine was more likely than other drugs to cause insomnia and fatigue. Women (particularly first-time users of mefloquine, or those with a low BMI)[12] may be at greater risk of adverse effects than men, and WHO has commented that the occurrence of such adverse effects may mean that only highly motivated occupational subgroups or individuals at high risk of infection with chloroquine-resistant malaria will be willing to continue with mefloquine prophylaxis.[13]

Neuropsychiatric reactions are more frequent after the higher doses of mefloquine used for *treatment* than those used for prophylaxis. Some workers have estimated that overall 1 in 8000 mefloquine users have such reactions, with the incidence 60 times higher after treatment than after prophylaxis.[14] Other workers who have used mefloquine in nearly 14 000 treatments calculated that the overall frequency of serious neuropsychiatric reactions was 1 per 1754 treatments; it therefore appeared that serious neuropsychiatric reactions were 10 times more probable after treatment than with prophylactic use of mefloquine.[15]

A severe neurological syndrome associated with mefloquine treatment, with agitation, delirium, stupor, hyperpyrexia, mydriasis, and generalised rigors responded rapidly to treatment with physostigmine, suggesting a central anticholinergic aetiology.[16]

A discrete post-malaria neurological syndrome (including an acute confusional state or acute psychosis, convulsions, and tremor) has been seen on recovery from falciparum malaria and there appeared to be a strong association with mefloquine although it was not the only risk factor.[17] Nevertheless the risk was considered unacceptable and the recommendation made[17] that, where there was an effective alternative drug, mefloquine should not be used after initial treatment of severe malaria.

Emergence delirium during recovery from general anaesthesia after mefloquine prophylaxis has been reported in 3 cases.[18]

There is evidence from a small study[19] in healthy subjects, and from similar results in *animals*, that mefloquine may induce deficits in motor learning skills.

1. Toovey S. Mefloquine neurotoxicity: a literature review. *Travel Med Infect Dis* 2009; 7: 2–6.
2. CSM. Mefloquine (Lariam) and neuropsychiatric reactions. *Current Problems* 1996; 22: 6. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023214 (accessed 18/06/08)
3. Croft AMJ, World MJ. Neuropsychiatric reactions with mefloquine chemoprophylaxis. *Lancet* 1996; 347: 326.
4. Stürchler D, *et al.* Neuropsychiatric side effects of mefloquine. *N Engl J Med* 1990; 322: 1752–3.
5. Bradley DJ, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. *Commun Dis Public Health* 2003; 6: 180–99. Also available at: http://www.hpa.org.uk/cdph/issues/CDPHvol6/No3/6(3)p180-99.pdf (accessed 06/07/06)
6. Steffen R, *et al.* Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* 1993; 341: 1299–1303.
7. Lobel HO, *et al.* Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993; 341: 848–51.
8. Barrett PJ, *et al.* Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996; 313: 525–8. Correspondence. *ibid.*: 1552–4.
9. Croft AMJ, *et al.* Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. *Trans R Soc Trop Med Hyg* 1997; 91: 199–203.
10. Boudreau E, *et al.* Tolerability of prophylactic Lariam regimens. *Trop Med Parasitol* 1993; 44: 257–65.
11. Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. *BMJ* 1997; 315: 1412–16. Correspondence. *ibid.* 1998; 316: 1980–1.
12. van Riemsdijk MM, *et al.* Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine. *Br J Clin Pharmacol* 2004; 57: 506–12.
13. Anonymous. Mefloquine effectiveness impaired by high withdrawal rates. *WHO Drug Inf* 1998; 12: 7–8.
14. Weinke T, *et al.* Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg* 1991; 45: 86–91.
15. Luxemburger C, *et al.* Mefloquine for multidrug-resistant malaria. *Lancet* 1991; 338: 1268.
16. Speich R, Haller A. Central anticholinergic syndrome with the antimalarial drug mefloquine. *N Engl J Med* 1994; 331: 57–8.
17. Mai NTH, *et al.* Post-malaria neurological syndrome. *Lancet* 1996; 348: 917–21.
18. Gullahorn GM, *et al.* Anaesthesia emergence delirium after mefloquine prophylaxis. *Lancet* 1993; 341: 632.
19. van Essen TA, *et al.* Anti-malaria drug mefloquine induces motor learning deficits in humans. *Front Neurosci* 2010; 4: 191.

Effects on the oesophagus. Oesophageal ulceration in one patient and discomfort in another 4 was attributed to swallowing mefloquine tablets with insufficient fluid.[1]

1. Phillips M. Antimalarial mefloquine. *Med J Aust* 1994; 161: 227–8.

Effects on the skin. Isolated cases of Stevens-Johnson syndrome,[1] severe facial lesions,[2,3] exfoliative dermatitis,[3] toxic epidermal necrolysis,[5] psoriasis exacerbation,[6] and cutaneous vasculitis[7] have been associated with use of mefloquine for malaria prophylaxis.

For a comparison of the incidence of pruritus induced by various antimalarials, including mefloquine, see under Chloroquine, p. 652.2.

1. Van den Enden E, *et al.* Mefloquine-induced Stevens-Johnson syndrome. *Lancet* 1991; 337: 683.
2. Shlim DR. Severe facial rash associated with mefloquine. *JAMA* 1991; 266: 2560.
3. Descloux E, *et al.* Mefloquine adverse effects with atypical facial lesions in an overweight patient. *Travel Med Infect Dis* 2010; 8: 318–21.
4. Martin GJ, *et al.* Exfoliative dermatitis during malarial prophylaxis with mefloquine. *Clin Infect Dis* 1993; 16: 341–2.
5. McBride SR, *et al.* Fatal toxic epidermal necrolysis associated with mefloquine antimalarial prophylaxis. *Lancet* 1997; 349: 101.
6. Pace JL. Psoriasis triggered by mefloquine. *Skinmed* 2010; 8: 301–2.
7. White AC, *et al.* Cutaneous vasculitis associated with mefloquine. *Ann Intern Med* 1995; 123: 894.

Overdosage. Cardiac, hepatic, and neurological symptoms have been reported in a patient who inadvertently received 5.25 g of mefloquine over 6 days.[1] All symptoms disappeared rapidly when mefloquine was stopped.

1. Bourgeade A, *et al.* Intoxication accidentelle à la méfloquine. *Presse Med* 1990; 19: 1903.

Precautions

Tasks requiring fine coordination such as driving should not be undertaken during treatment with mefloquine or for at least 3 weeks afterwards; in the case of prophylactic use, care should be exercised while taking mefloquine and for at least 3 weeks after stopping it. The use of mefloquine for malaria prophylaxis is contra-indicated in patients with a history of psychiatric (including depression) or convulsive disorders. Increased plasma concentrations may occur in patients with hepatic impairment. Mefloquine should be stopped should symptoms suggestive of psychiatric disturbance occur during prophylaxis, and an alternative antimalarial substituted.

Mefloquine is teratogenic in *animals* and its use during pregnancy is best avoided; however, in areas of chloroquine-resistant *Plasmodium falciparum*, WHO states that mefloquine may normally be taken for malaria prophylaxis during the second and third trimesters of pregnancy. It is recommended that women should also avoid becoming pregnant during, and for 3 months after, mefloquine use and that mothers should not breast feed while taking mefloquine.

Mefloquine should be used with caution in patients with renal impairment and in those with cardiac conduction disorders.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mefloquine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

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

Pregnancy. Licensed product information for mefloquine reports that it is teratogenic in *rodents*. There is limited information on its effects in humans. One study in Thailand cited by WHO[1] found no difference between mefloquine and quinine in pregnancy outcome, but the numbers of treated patients who were in their first trimester were very small and its use should be kept to a minimum in that stage of pregnancy. Further spontaneous reports of exposure to mefloquine during the first trimester of pregnancy collected by the manufacturer revealed 24 fetal abnormalities and 17 spontaneous or missed abortions in 358 pregnancies, although a causal relationship was not established,[2] and a later study by the manufacturer involving 1627 reports of exposure during pregnancy appeared to show a similar incidence of congenital malformation to

that in offspring of unexposed women.[3] In 53 army service women who inadvertently used mefloquine in pregnancy, and for whom pregnancy outcome was known, there were 17 elective abortions, 12 spontaneous abortions, one molar pregnancy, and 23 healthy live births, with no major congenital malformations.[4] The rate of spontaneous abortions was considered high.[4] A prospective cohort study involving 236 pregnant women who received an antimalarial in the first trimester did not find an increased risk of spontaneous abortion or anomaly in women who took mefloquine compared with other antimalarials, and the rate of spontaneous abortion was comparable with background rates.[5]

Confidence in the safety of mefloquine has increased, and WHO now considers mefloquine suitable for malaria prophylaxis in the second and third trimesters;[6] WHO has stated its use is not recommended in the first trimester because of limited information on its safety. Authorities in the UK consider that use may sometimes be justified in the first trimester in areas of high risk of acquiring falciparum malaria; inadvertent use is not an indication to terminate pregnancy.[7]

Pregnancy should be avoided during and for 3 months after prophylactic use.

1. WHO. Practical chemotherapy of malaria: report of a WHO scientific group. *WHO Tech Rep Ser 805* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_805.pdf (accessed 18/06/05)
2. Palmer KJ, *et al.* Mefloquine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45**: 430–75.
3. Vanhauwere B, *et al.* Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy. *Am J Trop Med Hyg* 1998; **58**: 17–21.
4. Smoak BL, *et al.* The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army service women. *J Infect Dis* 1997; **176**: 831–3.
5. Phillips-Howard PA, *et al.* Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. *J Travel Med* 1998; **5**: 121–6.
6. WHO. *International travel and health.* 2011 ed. Available at: http://www.who.int/ith/en/ (accessed 16/06/11)
7. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

Interactions

Halofantrine should not be given with, or within 15 weeks of the last dose of, mefloquine because of the increased potential to induce hazardous and potentially fatal cardiac arrhythmias, as discussed under Effects on the Heart on p. 654.3. Similarly, ketoconazole given with or after mefloquine may increase serum concentrations and the elimination half-life of mefloquine, potentially increasing the risk of QT-interval prolongation and arrhythmia. There is an increased risk of convulsions when mefloquine is used with chloroquine, quinidine, or quinine.

Alcohol. There has been a case report[1] of a patient who had neuropsychiatric disturbances after consuming a large quantity of alcohol with mefloquine; subsequent abstinence from alcohol led to complete reversal of the reactions.

1. Wittes RC, Saginur R. Adverse reaction to mefloquine associated with ethanol ingestion. *Can Med Assoc J* 1995; **152**: 515–17.

Antibacterials. Studies in healthy subjects have indicated that *ampicillin*[1] or *tetracycline*[2] could increase blood concentrations of mefloquine. Alternatively, concurrent use with *rifampicin* may decrease blood concentrations and reduce the elimination half-life of mefloquine.[3] Convulsions have been precipitated in 3 non-epileptic patients who were given mefloquine and the quinolone antibacterials *ciprofloxacin*, *ofloxacin*, or *sparfloxacin*.[4]

1. Karbwang J, *et al.* Effect of ampicillin on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* 1991; **40**: 631–3.
2. Karbwang J, *et al.* Effect of tetracycline on mefloquine pharmacokinetics in Thai males. *Eur J Clin Pharmacol* 1992; **43**: 567–9.
3. Riddiid W, *et al.* Effect of rifampin on plasma concentrations of mefloquine in healthy volunteers. *J Pharm Pharmacol* 2000; **52**: 1265–9.
4. Mangalvedhekar SS, *et al.* Convulsions in non-epileptics due to mefloquine-fluoroquinolone co-administration. *Natl Med J India* 2000; **13**: 47.

Antidepressants. Licensed product information for mefloquine states that in patients taking tricyclic antidepressants use of mefloquine may theoretically contribute to prolongation of the QT interval.

Antiepileptics. Licensed product information states that mefloquine may reduce seizure control by lowering the plasma concentration of antiepileptics, including carbamazepine, phenobarbital, and phenytoin. For the effect of mefloquine on *valproate*, see p. 557.3. For its effect on *carbamazepine*, see p. 517.2.

Antihistamines. Giving mefloquine with antihistamines may theoretically contribute to the prolongation of QT intervals; however, this is not considered to be an absolute contra-indication.

Antimalarials. It is well established that the use of *halofantrine* with or after mefloquine is contra-indicated because of the risk of hazardous cardiac arrhythmias. Mefloquine and other related compounds such as *quinine*, *quinidine*, and *chloroquine* may be given together only under close medical supervision because of possible additive cardiotoxicity; there is also an increased risk of convulsions.

A study in healthy subjects indicated that use of *primaquine* could increase blood concentrations of mefloquine and might increase the incidence of adverse effects due to mefloquine,[1] but others reported no such interaction.[2]

1. MacLeod CM, *et al.* Interaction of primaquine with mefloquine in healthy males. *J Clin Pharmacol* 1990; **30**: 841.
2. Karbwang J, *et al.* Pharmacokinetics of mefloquine in the presence of primaquine. *Eur J Clin Pharmacol* 1992; **42**: 559–60.

Antipsychotics. The use of mefloquine with *phenothiazines* or *pimozide* may theoretically contribute to prolonged QT intervals, although this is not considered to be an absolute contra-indication.

Cardiovascular drugs. It has been recommended that mefloquine should be used with extreme caution in patients also taking *antiarrhythmics, beta blockers, calcium-channel blockers*, or *digitalis*, until more was known about the risks of cardiotoxicity, since theoretically these drugs might contribute to prolongation of the QT interval. An increased risk of ventricular arrhythmias has been reported when mefloquine is given with *amiodarone*.

Cardiopulmonary arrest has occurred after a single dose of mefloquine in a patient who was taking *propranolol*.[1]

1. Anonymous. Mefloquine for malaria. *Med Lett Drugs Ther* 1990; **32**: 13–14.

Gastrointestinal drugs. Use with *metoclopramide* may increase plasma concentrations of mefloquine.[1]

1. Na Bangchang K, *et al.* The effect of metoclopramide on mefloquine pharmacokinetics. *Br J Clin Pharmacol* 1991; **32**: 640–1.

Vaccines. Unfortunately, conflicting advice has been issued concerning the use of mefloquine after typhoid vaccination, for details see p. 2423.1.

Pharmacokinetics

The pharmacokinetics of mefloquine may be altered by malaria infection in a manner similar to those of quinine, the main effects being reductions in both its volume of distribution and its overall clearance.

Mefloquine is well absorbed from the gastrointestinal tract but there is marked interindividual variation in the time required to achieve peak plasma concentrations. Mefloquine is about 98% bound to plasma proteins and high concentrations have been reported in red blood cells. It is widely distributed throughout the body. Mefloquine has a long elimination half-life; mean values of about 21 days have been reported for some patients, although like other pharmacokinetic data on mefloquine there is considerable variation in reported figures. Subtherapeutic concentrations of mefloquine may persist in the blood for several months. Mefloquine is metabolised in the liver. Little of a dose is excreted in the urine and *animal* studies suggest excretion of mefloquine and its metabolites is mainly in the bile and faeces.

Mefloquine is distributed into breast milk in small amounts.

Reviews of pharmacokinetic studies of mefloquine reveal considerable interindividual variation for several pharmacokinetic parameters and some evidence that there might be pharmacokinetic differences between ethnic groups.[1,2] Mefloquine is well absorbed by healthy subjects and by patients with uncomplicated malaria after oral doses.[3,4] In patients with complicated malaria adequate blood concentrations have been obtained by the nasogastric route but this route cannot be relied upon for seriously ill patients[5] as absorption may be incomplete.[1] Mefloquine has a large apparent volume of distribution but this is reduced in the presence of malaria.[6,7] In children given mefloquine with sulfadoxine and pyrimethamine as tablets crushed and mixed with a glucose syrup, maximum blood-mefloquine concentrations were higher and reached in a shorter time compared with equivalent doses in adults.[8] In pregnant women with uncomplicated malaria, blood concentrations were lower than in non-pregnant women and the apparent volume of distribution was larger.[9] Once-weekly prophylactic doses of mefloquine resulted in steady-state conditions at about 10 doses with no evidence of subsequent accumulation.[10]

Mefloquine is metabolised in the liver[11] largely into 2,8-bis(trifluoromethyl)-4-quinoline carboxylic acid [Ro-21-5104][12] but this metabolite appears to be inactive against *Plasmodium falciparum*.[13] Only a small percentage of a dose is excreted in the urine[14] and *animal* studies suggest excretion of mefloquine and its metabolites is mainly in the bile and faeces.[1] Mefloquine has an extremely long plasma elimination half-life; again there is considerable interindividual variation and mean values ranging from 13.9 to 27.5 days have been quoted, the lower end of the range referring to a formulation that was less well absorbed than the preparation now in use.[1]

Mefloquine is distributed into breast milk, but a single dose study in 2 women[15] indicated that the concentration of mefloquine in milk was only a small proportion of that seen in plasma.

1. Karbwang J, White NJ. Clinical pharmacokinetics of mefloquine. *Clin Pharmacokinet* 1990; **19**: 264–79.
2. Palmer KJ, *et al.* Mefloquine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45**: 430–75.
3. Karbwang J, *et al.* The pharmacokinetics of mefloquine when given alone or in combination with sulphadoxine and pyrimethamine in Thai male and female subjects. *Eur J Clin Pharmacol* 1987; **32**: 173–7.
4. Looareesuwan S, *et al.* Studies of mefloquine bioavailability and kinetics using a stable isotope technique: a comparison of Thai patients with falciparum malaria and healthy caucasian volunteers. *Br J Clin Pharmacol* 1987; **24**: 37–42.
5. Chanthavanich P, *et al.* Intragastric mefloquine is absorbed rapidly in patients with cerebral malaria. *Am J Trop Med Hyg* 1985; **34**: 1028–36.
6. Juma FD, Ogeto JO. Mefloquine disposition in normals and in patients with severe Plasmodium falciparum malaria. *Eur J Drug Metab Pharmacokinet* 1989; **14**: 15–17.
7. Karbwang J, *et al.* A comparison of the pharmacokinetics of mefloquine in healthy Thai volunteers and in Thai patients with falciparum malaria. *Eur J Clin Pharmacol* 1988; **35**: 677–80.
8. Singhasivanon V, *et al.* Pharmacokinetic study of mefloquine in Thai children aged 5-12 years suffering from uncomplicated falciparum malaria treated with MSP or MSP plus primaquine. *Eur J Drug Metab Pharmacokinet* 1994; **19**: 27–32.
9. Na Bangchang K, *et al.* Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1994; **88**: 321–3.
10. Pennie RA, *et al.* Steady state pharmacokinetics of mefloquine in long-term travellers. *Trans R Soc Trop Med Hyg* 1993; **87**: 459–62.
11. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
12. Panisko DM, Keystone JS. Treatment of malaria—1990. *Drugs* 1990; **39**: 160–89.
13. Håkanson A, *et al.* Comparison of the activity in vitro of mefloquine and two metabolites against Plasmodium falciparum. *Trans R Soc Trop Med Hyg* 1990; **84**: 503–4.
14. Schwartz DE, *et al.* Urinary excretion of mefloquine and some of its metabolites in African volunteers at steady state. *Chemotherapy* 1987; **33**: 305–8.
15. Edstein MD, *et al.* Excretion of mefloquine in human breast milk. *Chemotherapy* 1988; **34**: 165–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tropicur; *Austral.*: Lariam; *Austria*: Lariam; *Belg.*: Lariam; *Braz.*: Mephaquin; *Canad.*: Lariam; *Chile*: Lariam; *Cz.*: Lariam; *Denm.*: Lariam; *Fin.*: Lariam; *Fr.*: Lariam; *Ger.*: Lariam; *Gr.*: Lariam; Mephaquin; *Hong Kong*: Lariam; Mephaquin; *Hung.*: Lariam; *India*: Confal; Facital; Falcital; Larimef; Mefact; Mefax; Mefcy; Mefliam; Mefloc; Meflotas; Mefque; Mepalex; MQF; *Irl.*: Lariam; *Israel*: Lariam; Mephaquin†; *Ital.*: Lariam; *Malaysia*: Lariam; Mephaquin; *Neth.*: Lariam; *Norw.*: Lariam; *NZ*: Lariam; *Philipp.*: Lariam; *Port.*: Mefloman†; Mephaquin; *Rus.*: Lariam (Лариам); *S.Afr.*: Lariam; Mefliam; *Singapore*: Lariam; Mephaquin; *Swed.*: Lariam; *Switz.*: Lariam; Mephaquine; *Thai.*: Mequin; *UAE*: Melophar; *UK*: Lariam; *Ukr.*: Lariam (Ларіам); Mephaquin (Мефахин)†; *USA*: Lariam†.

Multi-ingredient Preparations. *India*: Falcigo Plus; Larinate-MF; *Port.*: Falcitrim.

Pharmacopoeial Preparations

USP 36: Mefloquine Hydrochloride Tablets.

Piperaquine Phosphate

Piperaquina, fosfato de; Piperaquini Phosphas; 13228-RP; Пиперахина Фосфат.

1,3-Bis[1-(7-chloro-4-quinolyl)-4′-piperazinyl]propane.

$C_{29}H_{32}Cl_2N_6.4H_3PO_4.4H_2O$=999.6

CAS — 85547-56-4.

UNII — 854D7K8LXB.

Pharmacopoeias. In *Chin.*

Uses and Administration

Piperaquine phosphate is a bisquinoline antimalarial that has traditionally been used in China for the treatment and prophylaxis of falciparum malaria (p. 644.1). It is a structural analogue of chloroquine (p. 650.2) and is thought to have a similar mechanism of action.

A fixed-dose combination product of piperaquine phosphate and artenimol (see Artemisinin Derivatives, p. 648.1) has been developed to improve patient adherence and avoid monotherapy, and thereby decrease the risk of acquired drug resistance. This combination product is used for the treatment of acute uncomplicated malaria caused by *Plasmodium falciparum*; it should not be used to treat severe malaria. The ratio of piperaquine phosphate to artenimol of 8 to 1 has been selected to provide a target daily dose of 18 mg/kg for piperaquine. The combination may be given to patients from 6 months of age and weighing 5 kg or more. It

is given orally once daily for 3 days; no food should be taken within 3 hours of each dose. For those who have difficulties swallowing, the tablets may be crushed and mixed with water. Recommended doses according to body-weight are as follows:

- 5 to less than 7 kg: 80 mg piperaquine phosphate with 10 mg artenimol
- 7 to less than 13 kg: 160 mg piperaquine phosphate with 20 mg artenimol
- 13 to less than 24 kg: 320 mg piperaquine phosphate with 40 mg artenimol
- 24 to less than 36 kg: 640 mg piperaquine phosphate with 80 mg artenimol
- 36 to less than 75 kg: 960 mg piperaquine phosphate with 120 mg artenimol
- 75 to 100 kg: 1280 mg piperaquine phosphate with 160 mg artenimol
- 100 kg or more: no data available on which to make a dose recommendation

Due to the long elimination half-life of piperaquine phosphate a second, 3-day course should not be given within 2 months of the first course; no more than 2 courses should be given within a 12 month period.

Combinations of piperaquine, artenimol, and trimethoprim (*Artecom*) and piperaquine with artemisinin and primaquine (*Artequick*) are available in some countries. Piperaquine is also under investigation for use with a synthetic artemisinin derivative artelolane maleate.

References.

1. Davis TME, *et al.* Piperaquine: a resurgent antimalarial drug. *Drugs* 2005; **65**: 75–87.
2. Ahmed T, *et al.* Safety, tolerability, and single-and multiple-dose pharmacokinetics of piperaquine phosphate in healthy subjects. *J Clin Pharmacol* 2008; **48**: 166–75.
3. Karunajeewa HA, *et al.* A trial of combination antimalarial therapies in children from Papua New Guinea. *N Engl J Med* 2008; **359**: 2545–57.
4. Tangpukdee N, *et al.* Efficacy of Artequick versus artesunate-mefloquine in the treatment of acute uncomplicated falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health* 2008; **39**: 1–8.
5. Chinh NT, *et al.* Pharmacokinetics and bioequivalence evaluation of two fixed-dose tablet formulations of dihydroartemisinin and piperaquine in Vietnamese subjects. *Antimicrob Agents Chemother* 2009; **53**: 828–31.
6. Zwang J, *et al.* Safety and efficacy of dihydroartemisinin-piperaquine in falciparum malaria: a prospective multi-centre individual patient data analysis. *PLoS One* 2009; **4**: e6358.
7. Song J, *et al.* Rapid and effective malaria control in Cambodia through mass administration of artemisinin-piperaquine. *Malar J* 2010; **9**: 57.
8. Mayxay M, *et al.* A phase III, randomized, non-inferiority trial to assess the efficacy and safety of dihydroartemisinin-piperaquine in comparison with artesunate-mefloquine in patients with uncomplicated *Plasmodium falciparum* malaria in southern Laos. *Am J Trop Med Hyg* 2010; **83**: 1221–9.
9. Creek D, *et al.* Increased risk of early vomiting among infants and young children treated with dihydroartemisinin-piperaquine compared with artemether-lumefantrine for uncomplicated malaria. *Am J Trop Med Hyg* 2010; **83**: 873–5.
10. Nambozi M, *et al.* Safety and efficacy of dihydroartemisinin-piperaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Zambian children. *Malar J* 2011; **10**: 50.
11. Menan H, *et al.* Comparative study of the efficacy and tolerability of dihydroartemisinin-piperaquine-trimethoprim versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Cameroon, Ivory Coast and Senegal. *Malar J* 2011; **10**: 185.
12. Yavo W, *et al.* Multicentric assessment of the efficacy and tolerability of dihydroartemisinin-piperaquine compared to artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in sub-Saharan Africa. *Malar J* 2011; **10**: 198.
13. Keating GM. Dihydroartemisinin/Piperaquine: a review of its use in the treatment of uncomplicated *Plasmodium falciparum* malaria. *Drugs* 2012; **72**: 937–61.
14. Valecha N, *et al.* Arterolane maleate plus piperaquine phosphate for treatment of uncomplicated *Plasmodium falciparum* malaria: a comparative, multicenter, randomized clinical trial. *Clin Infect Dis* 2012; **55**: 663–71.

Administration in children. The fixed-dose combination product of piperaquine phosphate and artenimol may be given to children from 6 months of age and weighing 5 kg or more for the treatment of acute uncomplicated infections caused by *Plasmodium falciparum*. For dose recommendations in these children, see p. 659.3.

Adverse Effects and Precautions

Piperaquine phosphate given as monotherapy or with artenimol is generally well tolerated. The most commonly reported adverse effects with piperaquine phosphate alone are dizziness, headache, and gastrointestinal effects such as nausea, vomiting, and abdominal pain.

Commonly reported adverse effects reported with the use of the fixed-dose combination product of piperaquine phosphate and artenimol are anaemia, asthenia, headache, and pyrexia. Prolongation of the QTc interval and tachycardia are also frequent and the combination is contra-indicated in those with a family history of sudden death or cardiovascular disorders such as congenital prolongation of the QTc interval, symptomatic cardiac arrhythmias, severe hypertension, left ventricular hypertrophy, congestive heart failure, and in those with electrolyte disturbances. It is also contra-indicated in those who have recently taken or are taking other drugs known to prolong the QTc interval. ECG and blood potassium monitoring are recommended. Caution is advised when giving the combination product to those with jaundice, and/or moderate or severe renal or hepatic impairment.

Interactions

Piperaquine is metabolised by the cytochrome P450 isoenzyme CYP3A4 and to a lesser extent by CYP2C19 and CYP2C9. It is an inhibitor of the CYP3A4 and CYP2C19 isoenzymes and may inhibit the metabolism of other drugs that are metabolised by this route; it also has the potential to increase the rate of metabolism for CYP2E1 substrates such as paracetamol and theophylline. Drugs that inhibit CYP3A4 may increase plasma concentrations of piperaquine and exacerbate the effect of QTc prolongation. Enzyme inducers may decrease plasma concentrations of piperaquine. Piperaquine should be avoided in patients taking potentially arrhythmogenic drugs including those that prolong the QT interval.

Pharmacokinetics

Piperaquine is slowly absorbed and peak plasma concentrations are generally reached 5 hours after an oral dose. It has a large volume of distribution and is more than 99% bound to plasma protein. *In vitro* studies show that piperaquine is mainly metabolised by the cytochrome P450 isoenzymes CYP3A4. It is eliminated slowly with an elimination half-life of about 22 days in adults and 20 days in children.

References.

1. Tarning J, *et al.* Population pharmacokinetics and pharmacodynamics of piperaquine in children with uncomplicated falciparum malaria. *Clin Pharmacol Ther* 2012; **91**: 497–505.
2. Tarning J, *et al.* Population pharmacokinetics of dihydroartemisinin and piperaquine in pregnant and nonpregnant women with uncomplicated malaria. *Antimicrob Agents Chemother* 2012; **56**: 1997–2007.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *China*: An Li Kang (安立康); Duo-Cotecxin; Ke Tai Fu (科泰复); *Irl.*: Eurartesim; *Neth.*: Eurartesim; *UK*: Eurartesim.

Primaquine Phosphate *(BANM, rINNM)*

Difosfato de Primaquina; Fosfato de primaquina; Primachin difosfát; Primachina Fosfato; Primachini Phosphas; Primakinidifosfaatti; Primakindifosfat; Primakin-difoszfát; Primakvino difosfatas; Primaquina, fosfato de; Primaquinbisdihydrogenphosphat; Primaquine Diphosphate; Primaquine, diphosphate de; Primaquine, Phosphate de; Primaquini diphosphas; Primaquini Phosphas; Primaquinum Phosphoricum; SN-13,272; Примахина Фосфат.

(*RS*)-8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline diphosphate.

$C_{15}H_{21}N_3O.2H_3PO_4$=455.3

CAS — 90-34-6 (primaquine); 63-45-6 (primaquine phosphate).

ATC — P01BA03.

UNII — H0982HF78B.

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

Ph. Eur. 8: (Primaquine Diphosphate). An orange crystalline powder. Soluble in water; practically insoluble in alcohol. Protect from light.

USP 36: (Primaquine Phosphate). An orange-red, odourless, crystalline powder. Soluble 1 in 15 of water; insoluble in chloroform and in ether. Its solutions are acid to litmus. Protect from light.

Uses and Administration

Primaquine is an 8-aminoquinoline antimalarial that is effective as a tissue schizontocide against intrahepatic forms of all types of *Plasmodium*. It is mainly used to produce radical cure of vivax and ovale malarias, but may also be given to reduce transmission of falciparum malaria. It also has some action against *Pneumocystis* and is used with clindamycin in the management of pneumocystis pneumonia. For further information, see below and p. 661.1.

Primaquine phosphate is given orally and doses may be expressed in terms of the base; primaquine phosphate 26.4 mg is equivalent to about 15 mg of primaquine base.

When used for *radical cure* of vivax or ovale malaria, a course of treatment with a blood schizontocide must be given first to kill any erythrocytic parasites. Primaquine phosphate is then given orally, usually in a dose equivalent to 15 mg (or 250 micrograms/kg) of the base daily for 14 days but higher doses or longer courses may be required to overcome resistance in some strains of *P. vivax* (see below); WHO has advised that for uncomplicated malaria acquired in South-East Asia (particularly Indonesia) and Oceania, the dose should be increased to 500 micrograms/kg daily. In the UK, the *BNF* suggests that while 15 mg (or 250 micrograms/kg) daily is appropriate for use in *P. ovale* malaria, 30 mg (or 500 micrograms/kg) daily is necessary or infections caused by *P. vivax*.

For patients with G6PD deficiency the use of up to 45 mg (or 750 micrograms/kg) once every 7 days for 8 weeks has been suggested to minimise haemolysis (but see under Adverse Effects, p. 661.2).

For details of doses in children, see below.

General reviews.

1. Vale N, *et al.* Primaquine revisited six decades after its discovery. *Eur J Med Chem* 2009; **44**: 937–53.
2. Fernando D, *et al.* Primaquine in vivax malaria: an update and review on management issues. *Malar J* 2011; **10**: 351–62.

Administration in children. Primaquine may be used orally in children for **radical cure** of **malaria** caused by *P. ovale* or *P. vivax*. Doses are expressed in terms of primaquine base, and WHO[1,2] has suggested a dose of 250 micrograms/kg (to a maximum of 15 mg) once daily for 14 days; in South-East Asia and Oceania, the dose should be increased to 500 micrograms/kg (maximum 30 mg) daily. In the UK, the *BNFC* has recommended that, although the lower dose is appropriate for treatment of *P. ovale* malaria, the higher dose regimen should be used for all infections caused by *P. vivax*.

Although a lower age limit for the use of primaquine has not been formally established,[2] the *BNFC* suggests that it may be used in children over 6 months of age, but that specialist advice should be sought for younger children. Primaquine should be avoided in patients with severe G6PD deficiency, however in milder deficiency, a dose of 500 to 750 micrograms/kg once every 7 days for 8 weeks has been found to be without harmful effects.[3] (The *BNFC* also comments that this regimen is safe but suggests that the total daily dose should not exceed 45 mg.)

For a discussion on the use of primaquine to reduce transmission of falciparum malaria, see below.

1. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 27/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/manual_treatchild_revised.pdf (accessed 20/05/11)
2. WHO. *International travel and health*. 2011 ed. Available at: http://www.who.int/ith/en (accessed 17/06/11)
3. WHO. *WHO model formulary for children: based on the second model list of essential medicines for children 2009*. Geneva: WHO, 2010. Available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf (accessed 27/07/10)

Malaria. The overall treatment and prophylaxis of malaria and the place of primaquine in current recommendations are described on p. 644.1.

Despite the generally successful use of oral primaquine for **radical cure** of benign (non-falciparum) malarias, resistance of vivax (but not ovale) malaria is a known problem in some areas of the world,[1,2] and failures have occurred. The suggestion has been made that higher doses of primaquine (15 mg twice daily for 14 days, to give a total dose of 6 mg/kg assuming a body-weight of 70 kg) should be considered wherever the vivax malaria was acquired,[1-4] and this is the standard recommendation in the UK (see above). A systematic review[5] concluded that when used with chloroquine, a 14-day course of primaquine 15 mg daily was more effective than a 5-day course in preventing relapses of vivax malaria. The 5-day course of primaquine plus chloroquine appeared to be no better than chloroquine alone.

Variable responses to primaquine in the Amazonian region were attributed to considerable variation in the content of primaquine both between and within batches of tablets; primaquine content ranged from 19 to 168% of the labelled content.[6]

In the USA, the CDC[7] have suggested presumptive antirelapse therapy (or terminal prophylaxis) with primaquine at the end of prophylaxis to prevent relapses due to *Plasmodium vivax* or *P. ovale* in persons returning from prolonged exposure in areas where relapsing malaria is endemic. In those who have taken chloroquine, doxycycline, or mefloquine as prophylaxis, primaquine is usually given during the last 2 weeks of prophylaxis, but, when necessary, may also be taken immediately after prophylaxis is completed. When atovaquone plus proguanil is taken as prophylaxis, primaquine is preferably given during the last 7 days and then for an additional 7 days, but may also be given for 14 days after atovaquone plus proguanil prophylaxis is completed. The recommended daily oral dose of primaquine for terminal prophylaxis is 30 mg for adults and 500 micrograms/kg for children.

Primaquine has also been tried for **prophylaxis** of falciparum and vivax malaria; use for a year produced effective cover and was well tolerated by Javanese men without G6PD deficiency.[8] It was also effective for prophylaxis in Colombian military personnel; it was noted that primaquine prophylaxis could be stopped 1 week after departing the endemic area.[9]

The use of primaquine as a gametocytocide has the potential to **reduce the transmission** of falciparum malaria in low transmission areas and to help contain the

spread of artemisinin-resistant falciparum malaria.[10,11] WHO therefore initially suggested that primaquine be given as a single dose of 750 micrograms/kg (to a maximum of 45 mg) with an artemisinin derivative-based combination regimen for the treatment of uncomplicated *P. falciparum* malaria, provided the risk for G6PD deficiency was considered low or testing for deficiency was available.[10] However, testing for G6PD is not widely available in malaria endemic areas and concerns over primaquine's potential for haemolysis have limited its use. Following a review of safety and efficacy data, WHO has subsequently suggested that a lower dose of 250 micrograms/kg would be safer and equally effective and should be given on the first day of treatment (except in pregnant women and infants less than 1 year of age) without the need for G6PD testing.[10,12]

1. Ajdukiewicz KM, Ong EL. Management of vivax malaria with low sensitivity to primaquine. *J Infect* 2007; **54:** 209–11.
2. Beeching NJ, *et al.* Management of vivax malaria with primaquine. *J Infect* 2007; **55:** 282.
3. Doherty JF, *et al.* Treatment of Plasmodium vivax malaria—time for a change? *Trans R Soc Trop Med Hyg* 1997; **91:** 76.
4. Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis* 2004; **39:** 1336–45.
5. Galappaththy GNL, *et al.* Primaquine for preventing relapses in people with Plasmodium vivax malaria. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2007 (accessed 14/03/08).
6. Petralanda I. Quality of antimalarial drugs and resistance to Plasmodium vivax in Amazonian region. *Lancet* 1995; **345:** 1433.
7. CDC. Malaria. In: *The Yellow Book: CDC Health Information for International Travel*; 2012. Also available at: http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm (accessed 12/09/11)
8. Fryauff DJ, *et al.* Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. *Lancet* 1995; **346:** 1190–3.
9. Soto J, *et al.* Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. *Ann Intern Med* 1998; **129:** 241–4.
10. White NJ, *et al.* Rationale for recommending a lower dose of primaquine as a *Plasmodium falciparum* gametocytocide in populations where G6PD deficiency is common. *Malar J* 2012; **11:** 418.
11. Sutanto I, *et al.* The effect of primaquine on gametocyte development and clearance in the treatment of uncomplicated falciparum malaria with dihydroartemisinin-piperaquine in South Sumatra, Western Indonesia: an open-label, randomized, controlled trial. *Clin Infect Dis* 2013; **56:** 685–93.
12. WHO. Single dose Primaquine as a gametocytocide in *Plasmodium falciparum* malaria: updated WHO policy recommendation (Issued October 2012). Available at: http://www.who.int/malaria/pq_updated_policy_recommendation_en_102012.pdf (accessed 06/06/13)

Pneumocystis pneumonia. Primaquine with clindamycin is used in the treatment of pneumocystis pneumonia as an alternative to co-trimoxazole[1] (see p. 567.2). Treatment has usually lasted 3 weeks, and US experts suggest primaquine be given orally in daily doses equivalent to 15 to 30 mg of the base, and clindamycin be given in doses of 600 to 900 mg intravenously or 300 to 450 mg orally every 6 to 8 hours.[2,3] In the UK, the *BNF* suggests clindamycin 600 mg orally every 8 hours with oral primaquine 30 mg daily for mild to moderate disease, but notes that the combination may cause considerable toxicity.

A randomised multicentre study[4] compared this latter regimen (primaquine 30 mg daily and clindamycin 600 mg three times daily) with co-trimoxazole and with a combination of dapsone and trimethoprim in 181 AIDS patients who had confirmed mild to moderate pneumocystis pneumonia. Primaquine-clindamycin was as effective as the other two regimens, although the authors suggested that the combination might be best avoided in patients with severe myelosuppression.

Primaquine with clindamycin is not normally recommended for prophylaxis although there are reports of it being tried.[5] A retrospective examination[6] of the records of patients who had received prophylaxis found that clindamycin with primaquine was less effective than co-trimoxazole or dapsone, although this could have been due in part to underdosing.

1. Benfield T, *et al.* Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr* 2008; **48:** 63–7.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 2nd ed. New Rochelle NY: The Medical Letter 2010.
3. 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 09/09/09)
4. Safrin S, *et al.* Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS: a double-blind, randomized trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. *Ann Intern Med* 1996; **124:** 792–802.
5. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against Pneumocystis carinii pneumonia in patients with AIDS. *South Med J* 1990; **83:** 403–4.
6. Barber BA, *et al.* Clindamycin/primaquine as prophylaxis for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1996; **23:** 718–22.

Adverse Effects

Adverse effects with therapeutic doses of primaquine are usually minimal but abdominal pain and gastric distress are more common if taken on an empty stomach. Larger doses may cause nausea and vomiting. Methaemoglobinaemia may occur occasionally. Haemolytic anaemia can occur in persons with G6PD deficiency (see below). Other uncommon effects include mild anaemia and leucocytosis. Hypertension and cardiac arrhythmias have been reported on rare occasions. Primaquine may rarely produce leucopenia or agranulocytosis, usually after overdosage. Other effects associated with overdosage include gastrointestinal symptoms, haemolytic anaemia, and methaemoglobinaemia with cyanosis.

Many adverse effects have been reported after use of primaquine[1] but some, including pruritus and disturbances of visual accommodation, are considered to be inadequately documented or doubtfully attributed to the drug.

Acute intravascular haemolysis is the most serious toxic hazard of primaquine, especially in people with G6PD deficiency, other defects of the erythrocytic pentose phosphate pathway of glucose metabolism, or some types of haemoglobinopathy. In individuals with G6PD deficiency the severity of haemolysis is directly related to the degree of deficiency and to the quantity of primaquine given. In patients with the African variant the standard course of primaquine generally produces a moderate and self-limiting anaemia, while in those with the Mediterranean and related Asian variants, haemolysis can result in progressive haemoglobinaemia and haemoglobinuria which can be fatal. Whenever possible, therapy with primaquine should be delayed until the acute stage of malaria has been brought under control by a blood schizontocide because of the risk of inducing haemolysis and compromising the gastrointestinal tolerance of therapy.

1. Clyde DF. Clinical problems associated with the use of primaquine as a tissue schizontocidal and gametocytocidal drug. *Bull WHO* 1981; **59:** 391–5.

Precautions

Primaquine should be used cautiously in acutely ill patients with any serious systemic disease characterised by a tendency to granulocytopenia such as rheumatoid arthritis or lupus erythematosus. It should also be used with care in patients with G6PD deficiency. Primaquine should be withdrawn if signs of haemolysis or methaemoglobinaemia occur and the blood count should be monitored periodically.

Breast feeding. Primaquine should not be used in nursing women, unless the breast-fed infant has been determined not to be G6PD-deficient.

Pregnancy. Primaquine should not be given during pregnancy; radical cure of vivax or ovale malarias with primaquine should be delayed in pregnant women until after delivery.[1]

1. Panisko DM, Keystone JS. Treatment of malaria—1990. *Drugs* 1990; **39:** 160–89.

Interactions

Primaquine should not be used with drugs liable to induce haemolysis or bone marrow depression. Theoretically, mepacrine may increase the plasma concentrations of primaquine resulting in a higher risk of toxicity, and it has been recommended that these drugs should not be used together.

Antimalarials. The pharmacokinetics of primaquine were not altered by *mefloquine* in healthy subjects,[1] although the effect of primaquine on mefloquine pharmacokinetics is uncertain (see under Mefloquine, p. 659.2). In a study in patients with malaria, *quinine* reduced the plasma concentrations of primaquine, although the clinical importance of the interaction was unclear.[1]

1. Edwards G, *et al.* Interactions among primaquine, malaria infection and other antimalarials in Thai subjects. *Br J Clin Pharmacol* 1993; **35:** 193–8.

Pharmacokinetics

Primaquine is readily absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after a dose and then rapidly diminish with a reported elimination half-life of 3 to 6 hours. It is widely distributed into body tissues.

Primaquine is rapidly metabolised in the liver. Its major metabolite carboxyprimaquine accumulates in the plasma on repeated dosage. Little unchanged drug is excreted in the urine.

References.

1. Fletcher KA, *et al.* Studies on the pharmacokinetics of primaquine. *Bull WHO* 1981; **59:** 407–12.
2. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
3. Mihaly GW, *et al.* Pharmacokinetics of primaquine in man. I: studies of the absolute bioavailability and effects of dose size. *Br J Clin Pharmacol* 1985; **19:** 745–50.
4. Ward SA, *et al.* Pharmacokinetics of primaquine in man. II: comparison of acute vs chronic dosage in Thai subjects. *Br J Clin Pharmacol* 1985; **19:** 751–5.
5. Bhatia SC, *et al.* Pharmacokinetics of primaquine in patients with P. vivax malaria. *Eur J Clin Pharmacol* 1986; **31:** 205–10.
6. Rønn A, Bygbjerg I. Unexpected high primaquine concentrations in acutely ill malaria patients. *Lancet* 1993; **341:** 305.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Primacin; *Braz.*: Primakinder†; *India*: Malirid; Malquine; PMQ-INGA; Primacip.

Pharmacopoeial Preparations

USP 36: Primaquine Phosphate Tablets.

Proguanil Hydrochloride

(BANM, rINNM)

Bigumalum; Chloriguane Hydrochloride; Chloroguanide Hydrochloride; Chlorowodorek Prokwanilu; Hidrocloruro de proguanil; Proguanide Hydrochloride; Proguanilihydrokloridi; Proguanil, chlorhydrate de; Proguanil, hidrocloruro de; Proguanil hydrochlorid; Proguanil-hidroklorid; Proguanilhydrochlorid; Proguanilhydroklorid; Proguanil hydrochloridum; Proguanilo hidrochloridas; RP-3359; SN-12,837; Прогуанила Гидрохлорид.

1-(4-Chlorophenyl)-5-isopropylbiguanide hydrochloride.

$C_{11}H_{16}ClN_5HCl=290.2$

CAS — 500-92-5 (proguanil); 637-32-1 (proguanil hydrochloride).

ATC — P01BB01.

UNII — R71Y86M0WT.

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

Ph. Eur. 8: (Proguanil Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in dichloromethane. Protect from light.

USP 36: (Proguanil Hydrochloride). A white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

Stability. Although the Ph. Eur. 8 directs that proguanil hydrochloride should be protected from light, stability studies[1,2] suggest that it is a very stable compound with only small amounts of its major decomposition product 4-chloroaniline being formed during thermal and photochemical stress.

1. Owoyale JA, Elmarakby ZS. Effect of sunlight, ultraviolet irradiation and heat on proguanil. *Int J Pharmaceutics* 1989; **50:** 219–21.
2. Taylor RB, *et al.* A chemical stability study of proguanil hydrochloride. *Int J Pharmaceutics* 1990; **60:** 185–90.

Uses and Administration

Proguanil is a biguanide compound that has little antimalarial activity until metabolised in the body to the active antimalarial drug cycloguanil. Cycloguanil, like pyrimethamine, inhibits plasmodial dihydrofolate reductase and thus disrupts synthesis of nucleic acids in the parasite. Cycloguanil is active against pre-erythrocytic forms and is a slow-acting blood schizontocide. It also has some sporontocidal activity, rendering the gametocytes non-infective to the mosquito vector.

The value of proguanil is limited by the rapid development of resistance.

Proguanil is used orally as the hydrochloride for the chemoprophylaxis of malaria, with chloroquine or atovaquone. The schizontocidal activity of cycloguanil on erythrocytic forms is too slow for cycloguanil or proguanil to be used alone for the treatment of malaria, but proguanil hydrochloride is given with atovaquone for the treatment of uncomplicated falciparum malaria (p. 644.1).

For *prophylaxis* of malaria in combination with chloroquine, the usual adult daily dose of proguanil hydrochloride is 200 mg taken after food. For prophylaxis in combination with atovaquone 250 mg, the daily dose of proguanil hydrochloride is 100 mg. It is generally recommended that chemoprophylaxis for travellers should start 1 week before exposure to malaria, but if this is not possible it can be started 1 to 2 days before travel. Use should continue throughout exposure and for at least 4 weeks (1 week when proguanil is given with atovaquone) after leaving a malarious area.

In the *treatment* of uncomplicated falciparum malaria, adult doses are proguanil hydrochloride 400 mg with atovaquone 1 g, each orally as a single dose for 3 consecutive days.

For children's doses in the prophylaxis and treatment of malaria, see p. 662.1.

Cycloguanil was also formerly given by intramuscular injection as an oily suspension of the embonate.

Reviews.

1. McKeage K, Scott LJ. Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. *Drugs* 2003; **63:** 597–623.
2. Matta P, *et al.* Atovaquone-proguanil for prophylaxis and treatment of malaria. *Ann Pharmacother* 2003; **37:** 1266–75.

3. Nakato H, *et al.* A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (Malarone) for chemoprophylaxis against malaria. *J Antimicrob Chemother* 2007; 60: 929–36.

Administration in children. Dosage recommendations for proguanil with **chloroquine** for **malaria prophylaxis** in children have varied. UK malaria experts[1] have suggested the following prophylactic oral doses of proguanil hydrochloride for children based on fractions of the adult dose of 200 mg daily:

- under 6.0 kg (up to 12 weeks of age): one-eighth the adult dose
- 6 to 9.9 kg (3 to 11 months): one-quarter the adult dose
- 10 to 15.9 kg (1 year to 3 years 11 months): three-eighths the adult dose
- 16 to 24.9 kg (4 years to 7 years 11 months): half the adult dose
- 25 to 44.9 kg (8 years to 12 years 11 months): three-quarters the adult dose
- 45 kg and over (13 years or more): the adult dose

They noted that body-weight was a better guide to dosage than age for children over 6 months.

Children may be given proguanil with **atovaquone** for the **prophylaxis** of malaria.[1] A daily dose based on either a paediatric tablet containing 25 mg of proguanil hydrochloride plus 62.5 mg of atovaquone *or* an adult tablet containing 100 mg of proguanil hydrochloride plus 250 mg of atovaquone is as follows:

- children weighing 5 to 8 kg: half of a paediatric tablet
- > 8 to 10 kg: three-quarters of a paediatric tablet
- > 10 to 20 kg: one paediatric tablet or one-quarter of the adult tablet
- > 20 to 30 kg: two paediatric tablets or half of the adult tablet
- > 30 to 40 kg: three paediatric tablets or three-quarters of the adult tablet
- > 40 kg: four paediatric tablets or one adult tablet

Doses of proguanil with atovaquone for the **treatment** of malaria, based on the adult dose of 400 mg of proguanil hydrochloride daily, are:

- children weighing 5 to 8 kg: one-eighth the adult dose
- 9 to 10 kg: three-sixteenths the adult dose
- 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- 40 kg and over: the adult dose

1. Public Health England. Guidelines for malaria prevention in travellers from the UK (issued August 2013). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1203496943523 (accessed 24/10/13)

Administration in renal impairment. Proguanil is excreted by the kidneys and should be given in reduced dosage or avoided in patients with renal impairment. The following oral doses have been recommended based on creatinine clearance (CC):

- CC 20 to 59 mL/minute: 100 mg daily
- CC 10 to 19 mL/minute: 50 mg every other day
- CC less than 10 mL/minute: 50 mg once weekly

Adverse Effects and Precautions

Apart from mild gastric intolerance, diarrhoea, and some reports of aphthous ulceration there appear to be few adverse effects associated with usual doses of proguanil hydrochloride. There have been rare reports of hypersensitivity reactions including urticaria and angioedema. Rare cases of seizures and psychotic events have also been reported. Haematological changes have been reported in patients with severe renal impairment. Overdosage may produce epigastric discomfort, vomiting, and renal irritation leading to haematuria.

Proguanil should be used with caution in patients with renal impairment; dosage should be reduced accordingly (see under Uses and Administration, above).

Proguanil may be taken during pregnancy, but UK guidelines recommend that folate supplements (folic acid 5 mg daily) should also be given; however, the combination of proguanil with atovaquone should be avoided as data regarding the safety of atovaquone are lacking.

For information on the adverse effects and precautions associated with the use of proguanil with atovaquone, see under p. 929.1.

Until 1985 proguanil was generally taken in a dose of 100 mg daily for malaria prophylaxis with few adverse effects. Although there was no increase in serious adverse effects when the dose was increased to 200 mg daily, and it began to be used with chloroquine, there were an increasing number of reports of reversible aphthous ulceration.[1] Chloroquine may exacerbate this effect.[2] There has also been a report of reversible alopecia in women and scaling of the skin in both men and women using proguanil.[3] More severe skin reactions have been coupled with symptoms such as acute eosinophilic pneumonia as part of a hypersensitivity reaction.[4]

Megaloblastic anaemia and pancytopenia have been associated with proguanil accumulation in patients with renal impairment.[5,6]

1. Peto TEA. Toxicity of antimalarial drugs. *J R Soc Med* 1989; 82 (suppl 17): 30–4.
2. Drysdale SF, *et al.* Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990; 335: 164.
3. Hanson SN, *et al.* Hairloss and scaling with proguanil. *Lancet* 1989; i: 225.
4. Just N, *et al.* Severe hypersensitivity reaction as acute eosinophilic pneumonia and skin eruption induced by proguanil. *Eur Respir J* 2011; 37: 1526–8.
5. Boots M, *et al.* Megaloblastic anemia and pancytopenia due to proguanil in patients with chronic renal failure. *Clin Nephrol* 1982; 18: 106–8.
6. Jolink H, *et al.* Pancytopenia due to proguanil toxicity in a returning traveller with fever. *Eur J Clin Pharmacol* 2010; 66: 811–12.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pyrimethamine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Interactions

Antidepressants. *Fluvoxamine* can virtually abolish[1] the metabolism of proguanil to its active metabolite cycloguanil via an inhibitory effect on the cytochrome P450 isoenzyme CYP2C19.

1. Jeppesen U, *et al.* The CYP2C19 catalyzed bioactivation of proguanil is abolished during fluvoxamine intake. *Eur J Clin Pharmacol* 1997; 52 (suppl): A134.

Warfarin. For a report of haematuria and high prothrombin ratio in a patient stabilised on warfarin who took proguanil for malaria prophylaxis, see p. 1532.2.

Pharmacokinetics

Proguanil is readily absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about 4 hours. It is about 75% bound to plasma proteins. Proguanil is metabolised in the liver to the active metabolite cycloguanil. Peak plasma concentrations of cycloguanil occur about 1 hour after those of the parent drug. The elimination half-lives of both proguanil and cycloguanil are about 20 hours. About 40 to 60% of proguanil is eliminated in the urine, of which 60% is unchanged and 30% cycloguanil. There is also some elimination via the faeces. Proguanil is distributed into breast milk in small amounts (which are not adequate to provide chemoprophylaxis for the infant).

Early studies found proguanil to be well absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 4 hours.[1] In more recent studies, peak plasma concentrations of proguanil have been achieved within 2 to 4 hours.[2-4] Plasma protein binding for proguanil is 75%.[5] Proguanil is metabolised in the liver[3] to the active metabolite cycloguanil and to *p*-chlorophenylbiguanide which is inactive. Peak plasma concentrations of cycloguanil occur about 5.3 hours after doses of proguanil.[4] Unlike proguanil and *p*-chlorophenylbiguanide, cycloguanil is not concentrated in erythrocytes and thus concentrations of cycloguanil in plasma and whole blood are similar.[4] The elimination half-lives for proguanil and cycloguanil are about 20 hours.[3,4] A review of early studies states that 40 to 60% of a dose of proguanil is excreted in the urine, 60% of this as the unchanged drug, 30% as cycloguanil, and 8% as *p*-chlorophenylbiguanide.[1] About 10% of a dose is excreted in the faeces.[1] However, these values can vary greatly and wide interindividual variations in the ability to metabolise proguanil to cycloguanil have been reported.[3,6,7] Malaria prophylaxis with proguanil might be less effective in poor metabolisers although this has not been proved conclusively[8] and, anyway, other factors such as lack of protection against mosquitoes and sensitivity of the malaria parasite might be more important.[9]

Plasma concentrations of cycloguanil may be reduced in the third trimester of pregnancy.[10]

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; 10: 187–215.
2. Kelly JA, *et al.* The kinetics of proguanil during prophylaxis. *Trans R Soc Trop Med Hyg* 1986; 80: 338.
3. Watkins WM, *et al.* Variability in the metabolism of proguanil to the active metabolite cycloguanil in healthy Kenyan adults. *Trans R Soc Trop Med Hyg* 1990; 84: 492–5.
4. Wattanagoon Y, *et al.* Single dose pharmacokinetics of proguanil and its metabolites in healthy subjects. *Br J Clin Pharmacol* 1987; 24: 775–80.
5. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; 2: 242–73.
6. Ward SA, *et al.* Inter-subject variability in the metabolism of proguanil to the active metabolite cycloguanil in man. *Br J Clin Pharmacol* 1989; 27: 781–7.
7. Helsby NA, *et al.* The multiple dose pharmacokinetics of proguanil. *Br J Clin Pharmacol* 1993; 35: 653–6.
8. Mberu EK, *et al.* Japanese poor metabolizers of proguanil do not have an increased risk of malaria chemoprophylaxis breakthrough. *Trans R Soc Trop Med Hyg* 1995; 89: 658–9.
9. Skjelbo E, *et al.* Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians. *Clin Pharmacol Ther* 1996; 59: 304–11.
10. Wangboonskul J, *et al.* Single dose pharmacokinetics of proguanil and its metabolites in pregnancy. *Eur J Clin Pharmacol* 1993; 44: 247–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Paludrine†; ***Austria***: Paludrine†; ***Belg.***: Paludrine; ***Fr.***: Paludrine; ***Ger.***: Paludrine; ***Gr.***: Paludrine; ***India***: Laveran; ***Irl.***: Paludrine†; ***Ital.***: Paludrine†; ***Neth.***: Paludrine; ***Singapore***: Paludrine; ***Swed.***: Paludrine†; ***UK***: Paludrine.

Multi-ingredient Preparations. ***Austral.***: Malarone; ***Austria***: Malarone; ***Belg.***: Malarone; ***Canad.***: Malarone; ***Chile***: Malarone; ***Cz.***: Malarone; ***Denm.***: Malarone; ***Fin.***: Malarone; ***Fr.***: Malarone; Nopalu; Savarine; ***Ger.***: Malarone; ***Gr.***: Malarone; Savarine; ***Hong Kong***: Malarone; ***Hung.***: Malarone; ***Irl.***: Malarone; ***Israel***: Malarone; ***Ital.***: Malarone; ***Jpn***: Malarone; ***Malaysia***: Malarone; ***Neth.***: Malarone; ***Norw.***: Malarone; ***NZ***: Malarone; ***Pol.***: Malarone; ***Port.***: Malarone; ***S.Afr.***: Malanil; ***Singapore***: Malarone; ***Spain***: Malarone; ***Swed.***: Malarone; ***Switz.***: Malarone; ***Thai.***: Malanil; ***UK***: Malarone; Reprapog; ***USA***: Malarone.

Pharmacopoeial Preparations

BP 2014: Proguanil Tablets.

Pyrimethamine *(BAN, rINN)*

BW-50-63; Pirimetamin; Pirimetamina; Pirimetaminas; Pyrimetamina; Pyrimetamiini; Pyrimetamin; Pyrimethamine; Pyriméthamine; Pyrimethaminum; RP-4753; Пириметамин.

5-(4-Chlorophenyl)-6-ethylpyrimidine-2,4-diyldiamine.

$C_{12}H_{13}ClN_4$=248.7

CAS — 58-14-0.

ATC — P01BD01.

UNII — Z3614QOX8W.

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

Ph. Eur. 8: (Pyrimethamine). An almost white crystalline powder or colourless crystals. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Pyrimethamine). A white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 200 of alcohol and 1 in 125 of chloroform; slightly soluble in acetone. Store in airtight containers. Protect from light.

Uses and Administration

Pyrimethamine is a diaminopyrimidine antimalarial used with a sulfonamide in the treatment of malaria (see p. 644.1) and toxoplasmosis (see p. 663.1). Pyrimethamine with sulfadoxine has also been used in the treatment of actinomycetoma (p. 663.1), for prophylaxis of pneumocystis pneumonia (p. 663.1), and in the treatment of isosporiasis (p. 663.1).

Pyrimethamine exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase, thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is active against pre-erythrocytic forms and is also a slow-acting blood schizontocide. It also has some sporontocidal activity; it does not prevent the formation of gametocytes but renders them non-infective to the mosquito vector. It is mainly effective against *Plasmodium falciparum* but has some activity against *P. vivax*.

The development of plasmodial resistance has rendered obsolete the use of pyrimethamine on its own in malaria. Combinations of pyrimethamine with long-acting sulfonamides, such as sulfadoxine or sulfametopyrazine, are now used, although resistance has also developed to them.

For the *treatment* of uncomplicated falciparum **malaria**, pyrimethamine is given orally with sulfadoxine in a fixed dose ratio of 1 to 20 (*Fansidar*). WHO recommends that a single dose of pyrimethamine 1.25 mg/kg plus sulfadoxine 25 mg/kg be used with a 3-day course of artesunate.

For details of doses in children, see below.

A combination of pyrimethamine with sulfametopyrazine has also been used in the treatment of malaria.

Pyrimethamine and pyrimethamine combinations are no longer recommended for *prophylaxis* of malaria. Combined preparations of pyrimethamine with sulfadoxine (*Fansidar*, and with dapsone in a fixed ratio of 1 to 8 (*Maloprim*), have been used in areas of chloroquine or multidrug resistance, although other antimalarials are now preferred.

Pyrimethamine given with a sulfonamide such as sulfadiazine is used in the treatment of **toxoplasmosis**. Alternatively, pyrimethamine may be given with clindamycin in AIDS patients with toxoplasmosis unable to tolerate a sulfonamide. For details of dosage regimens used, see p. 663.1.

Administration in children. Pyrimethamine may be used orally with sulfadoxine (as the fixed-dose combination

product *Fansidar*) in infants and children 2 months of age and older for the treatment of **uncomplicated falciparum malaria.** WHO[1] recommends a single oral dose of pyrimethamine 1.25 mg/kg (with sulfadoxine 25 mg/kg) be given with a 3-day regimen of artesunate.

Alternatively, US licensed product information provides the following dosing recommendations based on body-weight for children 2 months of age and older:

- 5 to 10 kg: 12.5 mg with sulfadoxine 250 mg
- 11 to 20 kg: 25 mg with sulfadoxine 500 mg
- 21 to 30 kg: 37.5 mg with sulfadoxine 750 mg
- 31 to 45 kg: 50 mg with sulfadoxine 1 g
- over 45 kg: as for adults

In infants and children, pyrimethamine may also be used with sulfadiazine for the management of toxoplasmosis. For further details and doses, see under Uses and Administration of Sulfadiazine, p. 362.1.

1. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Isosporiasis. Isosporiasis (p. 921.3) usually responds well to treatment with co-trimoxazole, but there is a high incidence of recurrence in immunocompromised patients, such as those with AIDS, and some form of maintenance therapy is generally required. Oral therapy with co-trimoxazole 960 mg given three times weekly or pyrimethamine 25 mg with sulfadoxine 500 mg given weekly were found to be equally effective maintenance regimens.[1] Pyrimethamine given alone in daily doses of 50 to 75 mg with folate therapy may be of use in the treatment of patients sensitive to sulfonamides.[2]

1. Pape JW, *et al.* Treatment and prophylaxis of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **320**: 1044–7.
2. Weiss LM, *et al.* Isospora belli infection: treatment with pyrimethamine. *Ann Intern Med* 1988; **109**: 474–5.

Malaria. The overall treatment and prophylaxis of malaria and the place of pyrimethamine-sulfadoxine (Fansidar) in current recommendations are discussed on p. 644.1.

Mycetoma. For reference to the use of pyrimethamine as part of the treatment of actinomycetoma, see under Mycetoma, p. 193.1.

Pneumocystis pneumonia. For a mention of pyrimethamine with either dapsone or sulfadoxine for the prophylaxis of pneumocystis pneumonia, and a discussion of conventional prophylaxis and treatment, see p. 567.2. For details of doses used, see under Uses and Administration of Dapsone, p. 282.1.

Toxoplasmosis. Pyrimethamine is given, usually with sulfadiazine or another appropriate sulphonamide, in the treatment of toxoplasmosis (p. 924.2), including the management of congenital toxoplasmosis in neonates (see Administration in Children, under Sulfadiazine, p. 362.1, for doses), although the management of maternal and fetal infection may vary considerably from country to country. Folinic acid is also given to counteract the megaloblastic anaemia associated with these regimens.

In the US, guidelines for the treatment of opportunistic infections in HIV-infected adults and adolescents[1] consider pyrimethamine plus sulfadiazine to be the initial therapy of choice for *Toxoplasma gondii* encephalitis and recommend the following doses, based on body-weight, be given for at least 6 weeks:

- less than 60 kg: pyrimethamine 200 mg orally, followed by 50 mg daily plus sulfadiazine 1 g orally every 6 hours
- 60 kg or more: pyrimethamine 200 mg orally, followed by 75 mg daily plus sulfadiazine 1.5 g orally every 6 hours

Pyrimethamine with clindamycin is an alternative in patients unable to tolerate a sulfonamide, for further information see under Clindamycin, p. 271.1.

Other drugs that have been tried with pyrimethamine include azithromycin,[2] clarithromycin,[3] and doxycycline.[4,5]

For *long-term maintenance* therapy, US guidelines[1] recommend that pyrimethamine 25 to 50 mg be given orally once daily with sulfadiazine 2 to 4 g daily divided in 2 or 4 oral doses; clindamycin may be used as an alternative to sulfadiazine if necessary. Alternatively, pyrimethamine 25 mg daily has been used with atovaquone 750 mg orally every 6 to 12 hours.

Although not typically considered first-line therapy, pyrimethamine may also be used for *primary prevention* of toxoplasmosis with either atovaquone or dapsone in the following regimens:[1]

- 25 mg daily with atovaquone 1.5 g daily
- 50 mg once weekly with dapsone 50 mg daily
- 75 mg once weekly with dapsone 200 mg once weekly (although this regimen may be poorly tolerated[6])

Pyrimethamine with sulfadoxine, also given once weekly, was of benefit in bone marrow transplant recipients.[7]

1. 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 15/09/09)
2. Saba J, *et al.* Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis* 1993; **12**: 853–6.
3. Fernandez-Martin J, *et al.* Pyrimethamine-clarithromycin combination therapy of acute Toxoplasma encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1991; **35**: 2049–52.
4. Morris JT, Kelly JW. Effective treatment of cerebral toxoplasmosis with doxycycline. *Am J Med* 1992; **93**: 107–8.
5. Hagberg L, *et al.* Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis* 1993; **25**: 157–60.
6. Opravil M, *et al.* Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1995; **20**: 531–41.
7. Foot ABM, *et al.* Prophylaxis of toxoplasmosis infection with pyrimethamine/sulfadoxine (Fansidar) in bone marrow transplant recipients. *Bone Marrow Transplant* 1994; **14**: 241–5.

Adverse Effects and Treatment

Use of pyrimethamine for prolonged periods, as used to be the case when it was **given alone** for the prophylaxis of malaria, can cause depression of haematopoiesis due to interference with folic acid metabolism. Rashes and hypersensitivity reactions also occurred.

Larger doses, such as those used in the treatment of toxoplasmosis, may cause gastrointestinal symptoms such as atrophic glossitis, abdominal pain, and vomiting; haematological effects such as megaloblastic anaemia, leucopenia, thrombocytopenia, and pancytopenia are also more likely to occur. CNS effects including headache, dizziness, and insomnia have also been reported.

Pulmonary eosinophilia has been reported in patients taking pyrimethamine **with other antimalarials.** Severe and sometimes fatal reactions have occurred when pyrimethamine has been used with sulfadoxine (*Fansidar*), including erythema multiforme and the Stevens-Johnson syndrome, and toxic epidermal necrolysis; there have also been isolated reports of hepatotoxicity. Agranulocytosis occurs more frequently when pyrimethamine is used with dapsone (*Maloprim*) and fatalities have been reported.

Acute overdosage with pyrimethamine can cause gastrointestinal effects and CNS stimulation with vomiting, excitability, and convulsions. Tachycardia, respiratory depression, circulatory collapse, and death may follow. Treatment of overdosage is symptomatic.

Adverse effects with dapsone. Between 1972 and 1988, the UK CSM received 76 reports of reactions that were attributed to the use of pyrimethamine with dapsone (*Maloprim*), of which 40 (53%) were considered to be serious, including 6 deaths.[1] The incidence was estimated to be 1 in 9100 for serious reactions and 1 in 60 200 for fatalities. Serious blood disorders including agranulocytosis, granulocytopenia, or leucopenia occurred in 15 patients (estimated incidence of 1 in 20 000), five of whom died. The other death was in a patient with myocarditis. Three patients had cyanosis due to methaemoglobinaemia. Respiratory disorders such as pulmonary eosinophilia, flu-like syndrome, and dyspnoea occurred in 6 patients. In 4 patients skin disorders were the principal effect and included epidermal necrolysis, angioedema, and bullous eruptions. Hepatic disorders were also reported in 4 patients. Three women using pyrimethamine-dapsone during pregnancy delivered malformed babies, one of them being stillborn. Other effects in 4 patients included convulsions, exacerbated epilepsy, pancreatitis, or a generalised allergic reaction.

A review[2] of 21 cases of agranulocytosis associated with pyrimethamine-dapsone concluded that, although agranulocytosis can occur very rarely in patients taking pyrimethamine or dapsone alone, agranulocytosis due to the combination appears to be caused by an idiosyncratic reaction to dapsone exacerbated by pyrimethamine. Of the 18 individuals for whom dosage was certain, 12 had been taking one tablet of pyrimethamine-dapsone twice weekly, twice the recommended dose of one tablet once weekly. Of the 9 patients who died, 6 had been taking one tablet twice weekly and one patient had taken one tablet once weekly; the dosage was uncertain in the remaining patients. The time of onset of symptoms had been 7 to 9 weeks after starting therapy in 16 of 19 of the patients.

Some consider that pyrimethamine with dapsone may produce some degree of immunosuppression and render users more susceptible to common infections. A higher incidence of non-specific upper respiratory-tract infections occurred in military recruits taking the combination than in those not given antimalarial prophylaxis.[3]

Pulmonary eosinophilia has also occurred in patients taking pyrimethamine with dapsone but, as there have also been similar reports of pulmonary toxicity in patients taking pyrimethamine with sulfadoxine (see below) or pyrimethamine with chloroquine, it has been suggested that pyrimethamine is probably the causative agent.[4]

1. Phillips-Howard PA. West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83**: 82–5.
2. Hutchinson DBA, *et al.* Agranulocytosis associated with Maloprim: review of cases. *Hum Toxicol* 1986; **5**: 221–7.
3. Lee PS, Lau EYL. Risk of acute non-specific upper respiratory tract infections in healthy men taking dapsone–pyrimethamine for prophylaxis against malaria. *BMJ* 1988; **296**: 893–5.
4. Davidson AC, *et al.* Pulmonary toxicity of malaria prophylaxis. *BMJ* 1988; **297**: 1240–1.

Adverse effects with sulfonamides. Severe and potentially fatal cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been associated with the combined use of pyrimethamine with sulfadoxine (*Fansidar*) for malaria prophylaxis. The reported incidence of these reactions has varied with surveys in the UK,[1] USA,[2] and Sweden[3] yielding similar results and a survey from Switzerland[4] finding a much lower incidence. The overall rate of serious reactions to pyrimethamine-sulfadoxine in the UK has been estimated to be 1 in 2100. The estimates for severe cutaneous reactions were 1 in 4900 in the UK, 1 in 5000 to 1 in 8000 in the USA, 1 in 10 000 in Sweden, and 1 in 150 000 in Switzerland, and the death rates were 1 in 11 100 in the UK, 1 in 11 000 to 1 in 25 000 in the USA, and 1 in 35 000 in Sweden; no fatalities were reported in Switzerland. Workers on the Swiss survey had suggested that the high incidence of cutaneous reactions reported in the USA might have been due to concurrent therapy with chloroquine but this has been disputed.[5] The authors of the UK survey[1] suggested that the lower incidence reported in Switzerland may have been due to the different methods used to estimate the amount of drug usage. Whether this toxicity is due to the combined use of pyrimethamine and sulfadoxine is unclear as the estimated frequency of fatal reactions associated with the use of sulfadoxine alone in Mozambique[6] was 1 in 50 000.

There have been isolated reports of other severe or life-threatening reactions associated with the use of pyrimethamine-sulfadoxine when used alone or with chloroquine, including hepatotoxicity[7-9] (estimated incidence of 1 in 11 100 in the UK[1]), fatal multisystem toxicity,[10] drug fever and photodermatitis,[11] agranulocytosis,[11] and erythroderma resembling Sézary syndrome.[12] Severe pulmonary reactions have also occurred[3,13] but, as similar reactions have also been reported when pyrimethamine has been used with other antimalarials, including dapsone, it has been suggested that pyrimethamine is the causative agent (see Adverse Effects with Dapsone, above). Hyperammonaemia and carnitine deficiency with deterioration in mental status has been reported in a patient given pyrimethamine and sulfadiazine for the treatment of toxoplasmosis.[14]

Severe megaloblastic anaemia in a patient taking pyrimethamine and sulfadiazine for toxoplasmosis of the CNS[15] was treated by withdrawing pyrimethamine and giving folinic acid orally with a single platelet infusion.

For a comparison of the incidence of pruritus induced by various antimalarials including pyrimethamine with sulfadoxine, see Effects on the Skin under Chloroquine, p. 652.2.

1. Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83**: 82–5.
2. Miller KD, *et al.* Severe cutaneous reactions among American travelers using pyrimethamine–sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986; **35**: 451–8.
3. Hellgren U, *et al.* Adverse reactions to sulphadoxine–pyrimethamine in Swedish travellers: implications for prophylaxis. *BMJ* 1987; **295**: 365–6.
4. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine–pyrimethamine in Switzerland. *Lancet* 1986; **i**: 610.
5. Rombo L, *et al.* Does chloroquine contribute to the risk of serious adverse reactions to Fansidar? *Lancet* 1985; **ii**: 1298–9.
6. Hernborg A. Stevens-Johnson syndrome after mass prophylaxis with sulfadoxine for cholera in Mozambique. *Lancet* 1985; **ii**: 1072–3.
7. Lazar HP, *et al.* Fansidar and hepatic granulomas. *Ann Intern Med* 1985; **102**: 722.
8. Wejstal R, *et al.* Liver damage associated with Fansidar. *Lancet* 1986; **i**: 854–5.
9. Zitelli BJ, *et al.* Fatal hepatic necrosis due to pyrimethamine–sulfadoxine (Fansidar). *Ann Intern Med* 1987; **106**: 393–5.
10. Selby CD, *et al.* Fatal multisystemic toxicity associated with prophylaxis with pyrimethamine and sulfadoxine (Fansidar). *BMJ* 1985; **290**: 113–14.
11. Olsen VV, *et al.* Serious reactions during malaria prophylaxis with pyrimethamine–sulfadoxine. *Lancet* 1982; **ii**: 994.
12. Langtry JAA, *et al.* Erythroderma resembling Sézary syndrome after treatment with Fansidar and chloroquine. *BMJ* 1986; **292**: 1107–8.
13. Svanbom M, *et al.* Unusual pulmonary reaction during short term prophylaxis with pyrimethamine–sulfadoxine (Fansidar). *BMJ* 1984; **288**: 1876.
14. Sekas G, Harbhajan PS. Hyperammonemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med* 1993; **95**: 112–13.
15. Chute JP, *et al.* Severe megaloblastic anemia complicating pyrimethamine therapy. *Ann Intern Med* 1995; **122**: 884–5.

Overdosage. Reports of overdosage with pyrimethamine in infants.

1. Akinyanju O, *et al.* Pyrimethamine poisoning. *BMJ* 1973; **4**: 147–8.

2. Elmalem J, *et al.* Les accidents graves lors de la prescription de pyriméthamine chez les nourrissons traités pour une toxoplasmose. *Therapie* 1985; 40: 357–9.
3. Duveau E, *et al.* Convulsion liée à un surdosage en pyriméthamine. *Arch Pediatr* 1996; 3: 286–7.

Precautions

Pyrimethamine may aggravate subclinical folic acid deficiency and it should not be given to patients with conditions associated with folate deficiency such as megaloblastic anaemia. Blood counts are required with prolonged treatment, and when large doses of pyrimethamine are used, as in the treatment of toxoplasmosis, blood counts should be checked twice weekly. Folinic acid, which does not interfere with the action of pyrimethamine against malaria or toxoplasmosis, has been given to prevent haematological toxicity due to pyrimethamine and its use is especially recommended if pyrimethamine is given during pregnancy. (Folic acid may be used as an alternative to folinic acid in malaria, but it interferes with the action of pyrimethamine against toxoplasmosis). For further information concerning use during pregnancy, see below.

Pyrimethamine should be given with caution to patients with renal or hepatic impairment. When patients with convulsive disorders need to receive large doses, as in the treatment of toxoplasmosis, it is recommended that small starting doses should be used.

When pyrimethamine is used with sulfonamides or dapsone, the general precautions applicable to those drugs should also be taken (see under Sulfamethoxazole, p. 366.1 and under Dapsone, p. 283.2) and treatment should be stopped immediately if any skin reactions, sore throat, or shortness of breath occurs.

Breast feeding. Pyrimethamine is distributed into breast milk[1] but as no adverse effects have been reported in breast-fed infants, the most recent guidance from the American Academy of Pediatrics considered breast feeding to be compatible with the use of pyrimethamine for malaria prophylaxis.[2] However, exposure of the infant to other folate antagonists should be avoided. The large doses of pyrimethamine used for treating toxoplasmosis may distribute into breast milk in sufficient quantities to interfere with folic acid metabolism in nursing infants.

1. Edstein MD, *et al.* Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; 22: 733–5.
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 19/04/04)

Porphyria. For a discussion of the use of antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

Pregnancy. There have been concerns over the use of pyrimethamine during pregnancy as it has been shown to be teratogenic in *animal* studies.[1] In one report, severe congenital defects in a stillborn infant were attributed to the use of pyrimethamine in early pregnancy,[2] but the association was considered to be questionable.[3] Other instances of congenital malformations with pyrimethamine and dapsone are given under Adverse Effects with Dapsone, p. 663.2.

Others[4] suggest that intermittent preventive therapy for malaria with pyrimethamine-sulfadoxine has a favourable safety profile in pregnancy. WHO considers that pyrimethamine combinations may be used after the first trimester of pregnancy in the treatment of toxoplasmosis,[5] but that pyrimethamine-sulfadoxine although considered safe for malaria treatment in the second or third trimesters, is likely to be ineffective because of increasing resistance.[6]

1. Anonymous. Pyrimethamine combinations in pregnancy. *Lancet* 1983; ii: 1005–7. Correction. *ibid.*; 1378.
2. Harpey J-P, *et al.* Teratogenicity of pyrimethamine. *Lancet* 1983; ii: 399.
3. Smithells RW, Sheppard S. Teratogenicity of Debendox and pyrimethamine. *Lancet* 1983; ii: 623–4.
4. Peters PJ, *et al.* Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Safety* 2007; 30: 481–501.
5. WHO. *WHO model formulary.* Geneva: WHO,2008. Also available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 19/10/09)
6. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update issued April 2011 available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Interactions

Use of pyrimethamine with other folate antagonists such as co-trimoxazole, trimethoprim, methotrexate, proguanil, phenytoin, or zidovudine may exacerbate bone marrow depression. The absorption of pyrimethamine may be reduced by use with antacid salts or kaolin.

Pyrimethamine may displace other drugs from protein-binding sites, causing elevated concentrations of unbound drug; this may be of particular clinical concern for drugs (such as quinine and warfarin) that are both highly protein bound and have a narrow therapeutic index.

Lorazepam. Signs of mild liver toxicity in 2 of 5 subjects who received lorazepam and pyrimethamine appeared to confirm earlier suspicions that giving these drugs together could cause hepatotoxicity. Both patients tolerated each drug when given separately.[1]

1. Briggs M, Briggs M. Pyrimethamine toxicity. *BMJ* 1974; 1: 40.

Zidovudine. Studies *in vitro* and in *animals* suggest that zidovudine could reduce the efficacy of pyrimethamine in the treatment of toxoplasmic encephalitis.[1] Furthermore, the dose of zidovudine may need to be altered if these drugs are used together as there has been a report that pyrimethamine with sulfadoxine (*Fansidar*) prolonged the serum half-life of zidovudine.[2]

1. Israelski DM, *et al.* Zidovudine antagonizes the action of pyrimethamine in experimental infection with Toxoplasma gondii. *Antimicrob Agents Chemother* 1989; 33: 30–4.
2. Klein RS. Prophylaxis of opportunistic infections in individuals infected with HIV. *AIDS* 1989; 3 (suppl 1): S161–S173.

Pharmacokinetics

Pyrimethamine is almost completely absorbed from the gastrointestinal tract. Peak-plasma concentrations generally occur 2 to 4 hours after a dose and can vary widely between individuals; concentrations ranging from 260 to 1411 nanograms/mL may occur after daily oral doses of 25 mg. It is mainly concentrated in the kidneys, lungs, liver, and spleen; in AIDS patients given daily dose of pyrimethamine, concentrations of about one-fifth of those in the serum occur in the CSF. About 80 to 90% is bound to plasma proteins.

It is metabolised in the liver and slowly excreted via the kidney, the average half-life in plasma being about 4 days. Several metabolites have been detected in the urine. Pyrimethamine crosses the placenta. It is distributed into breast milk (see under Breast Feeding in Precautions, above).

References.
1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; 10: 187–215.
2. Cook IF, *et al.* Race-linked differences in serum concentrations of dapsone, monoacetyldapsone and pyrimethamine during malaria prophylaxis. *Trans R Soc Trop Med Hyg* 1986; 80: 897–901.
3. Weiss LM, *et al.* Pyrimethamine concentrations in serum and cerebrospinal fluid during treatment of acute toxoplasma encephalitis in patients with AIDS. *J Infect Dis* 1988; 157: 580–3.
4. Hellgren U, *et al.* Plasma concentrations of sulfadoxine-pyrimethamine, mefloquine and its main metabolite after regular malaria prophylaxis for two years. *Trans R Soc Trop Med Hyg* 1991; 85: 356–7.
5. Winstanley PA, *et al.* The disposition of oral and intramuscular pyrimethamine/sulphadoxine in Kenyan children with high parasitaemia but clinically non-severe falciparum malaria. *Br J Clin Pharmacol* 1992; 33: 143–8.
6. Newton CRJC, *et al.* A single dose of intramuscular sulfadoxine-pyrimethamine as an adjunct to quinine in the treatment of severe malaria: pharmacokinetics and efficacy. *Trans R Soc Trop Med Hyg* 1993; 87: 207–10.
7. Jacobson JM, *et al.* Pyrimethamine pharmacokinetics in human immunodeficiency virus-positive patients seropositive for Toxoplasma gondii. *Antimicrob Agents Chemother* 1996; 40: 1360–5.
8. Klinker H, *et al.* Plasma pyrimethamine concentrations during long-term treatment for cerebral toxoplasmosis in patients with AIDS. *Antimicrob Agents Chemother* 1996; 40: 1623–7.
9. Trenque T, *et al.* Human maternofoetal distribution of pyrimethamine-sulphadoxine. *Br J Clin Pharmacol* 1998; 45: 179–80.
10. Trenque T, *et al.* Population pharmacokinetics of pyrimethamine and sulfadoxine in children with congenital toxoplasmosis. *Br J Clin Pharmacol* 2004; 57: 735–41.
11. Barnes KI, *et al.* Sulfadoxine-pyrimethamine pharmacokinetics in malaria: pediatric dosing implications. *Clin Pharmacol Ther* 2006; 80: 582–96.
12. Karunajeewa HA, *et al.* Pharmacokinetic properties of sulfadoxine-pyrimethamine in pregnant women. *Antimicrob Agents Chemother* 2009; 53: 4368–76.
13. Nyunt MM, *et al.* Pharmacokinetics of sulfadoxine and pyrimethamine in intermittent preventive treatment of malaria in pregnancy. *Clin Pharmacol Ther* 2010; 87: 226–34.
14. Salman S, *et al.* Pharmacokinetic properties of conventional and double-dose sulfadoxine-pyrimethamine given as intermittent preventive treatment in infancy. *Antimicrob Agents Chemother* 2011; 55: 1693–1700.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Daraprim; *Austral.*: Daraprim; *Belg.*: Daraprim; *Braz.*: Daraprim; *Canad.*: Daraprim; *Chile*: Daraprim; *Fr.*: Malocide; *Ger.*: Daraprim; *Gr.*: Daraprim; *Hong Kong*: Daraprim†; *Malaysia*: Fansidar; *Mex.*: Daraprim; *Neth.*: Daraprim; *Pol.*: Daraprim; *S.Afr.*: Daraprim; *Spain*: Daraprim; *Switz.*: Daraprim; *UK*: Daraprim; *USA*: Daraprim.

Multi-ingredient Preparations. *Austral.*: Fansidar†; Maloprim†; *Belg.*: Co-Arinate; Dafrafin†; *Braz.*: Fansidar; *Fr.*: Fansidar; *Gr.*: Fansidar; *India*: Amalar; Croydoxin-FM; Domine; Laridox; Larinate Kit; Malarwin; Malasulf; Malcidal; Malocide; Masunate; Metakelfin; Metasulfin; Onli-2; Pyralfin; Pyramet; Rimodar; *Indon.*: Fansidar; Plasmodin; Suldox; *Irl.*: Fansidar†; *Israel*: Fansidar†; *Ital.*: Metakelfin; *Malaysia*: Madomine; Malafon; *Philipp.*: Fansidar; *Rus.*: Fansidar (Фансидар); *S.Afr.*: Fansidar; *Singapore*: Pyrisone; *Switz.*: Fansidar†; *Thai.*: Vinsilar; *UK*: Fansidar; *Ukr.*: Fansidar (Фансидар)†; *USA*: Fansidar†.

Pharmacopoeial Preparations
BP 2014: Pyrimethamine Tablets;
USP 36: Pyrimethamine Oral Suspension; Pyrimethamine Tablets; Sulfadoxine and Pyrimethamine Tablets.

Pyronaridine Phosphate *(rINNM)*

Fosfato de pironaridina; Malaridine Phosphate; Pironaridina, fosfato de; Pyronaridine, Phosphate de; Pyronaridini Phosphas; Пиронаридина Фосфат.

4-[(7-Chloro-2-methoxybenzo[*b*]-1,5-naphthyridin-10-yl)amino]-2,6,-bis[(pyrrolidin-1-yl)methyl]phenol phosphate.

$C_{29}H_{32}ClN_5O_3.4H_3PO_4$=910.0

CAS — 74847-35-1 *(pyronaridine)*; 76748-86-2 *(pyronaridine phosphate).*

UNII — 2T289F9ACO.

Pharmacopoeias. In *Chin.*

Uses and Administration

Pyronaridine is a naphthyridine derivative that has traditionally been used in China in the treatment of malaria (p. 644.1). Its use has also been investigated in Africa and in Thailand. It is a blood schizontocide active against *Plasmodium vivax* and against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*. The drug produced in China has been given as the phosphate orally or by intramuscular or intravenous injection.

A fixed-dose combination product of pyronaridine phosphate and artesunate has been developed to improve patient adherence and avoid monotherapy, and thereby decrease the risk of acquired drug resistance. This combination product is used for the treatment of acute uncomplicated infections caused by *P. vivax* and *P. falciparum* in areas of low transmission with evidence of artemisinin resistance; it should not be used to treat severe malaria. The ratio of pyronaridine phosphate to artesunate of 3 to 1 has been selected to provide the current dose recommendations for each of the individual drugs when given as monotherapy. The combination is given orally, as a single, 3-day treatment course, to children and adults weighing 20 kg or more. Recommended doses are given once daily for 3 days according to body-weight as follows:

- 20 to less than 24 kg: 180 mg pyronaridine phosphate with 60 mg artesunate
- 24 to less than 45 kg: 360 mg pyronaridine phosphate with 120 mg artesunate
- 45 to less than 65 kg: 540 mg pyronaridine phosphate with 180 mg artesunate
- 65 kg or more: 720 mg pyronaridine phosphate with 240 mg artesunate

References.
1. Anonymous. Pyronaridine: yet another promising antimalarial substance from China. *WHO Drug Inf* 1996; 10: 9–10.
2. Looareesuwan S, *et al.* Clinical study of pyronaridine for the treatment of acute uncomplicated falciparum malaria in Thailand. *Am J Trop Med Hyg* 1996; 54: 205–9.
3. Ringwald P, *et al.* Efficacy of oral pyronaridine for the treatment of acute uncomplicated falciparum malaria in African children. *Clin Infect Dis* 1998; 26: 946–53.
4. Vivas L, *et al.* Anti-malarial efficacy of pyronaridine and artesunate in combination in vitro and in vivo. *Acta Trop* 2008; 105: 222–8.
5. Ramharter M, *et al.* Fixed-dose pyronaridine-artesunate combination for treatment of uncomplicated falciparum malaria in pediatric patients in Gabon. *J Infect Dis* 2008; 198: 911–9.
6. Tshefu AK, *et al.* Pyronaridine-artesunate Study Team. Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated Plasmodium falciparum malaria: a randomised non-inferiority trial. *Lancet* 2010; 375: 1457–67.
7. Poravuth Y, *et al.* Pyronaridine-artesunate versus chloroquine in patients with acute *Plasmodium vivax* malaria: a randomized, double-blind, non-inferiority trial. *PLoS One* 2011; 6: e14501.
8. Kurth F, *et al.* Pyronaridine: a new 'old' drug on the verge of entering the antimalarial armamentarium. *Expert Rev Anti Infect Ther* 2011; 9: 393–6.
9. Rueangweerayut R, *et al.* Pyronaridine-artesunate versus mefloquine plus artesunate for malaria. *N Engl J Med* 2012; 366: 1298–1309.
10. Croft SL, *et al.* Review of pyronaridine anti-malarial properties and product characteristics. *Malar J* 2012; 11: 270.

Administration in children. The fixed-dose combination product of pyronaridine phosphate and artesunate may be given to children weighing 20 kg or more for the treatment of acute uncomplicated infections caused by *Plasmodium vivax* and *P. falciparum* in areas of low transmission with evidence of artemisinin resistance. For dose recommendations in these children, see above.

Adverse Effects and Precautions

Adverse effects of pyronaridine are usually mild and resolve within 2 days of starting treatment. The most commonly reported adverse effects are dizziness, headache, pruritus, and gastrointestinal effects such as diarrhoea, nausea, vomiting, and abdominal pain. There have also been some reports of allergic skin reactions, palpitations, and transient ECG changes with the use of higher doses.

The most common adverse effects associated with the use of a fixed-dose combination product of pyronaridine

phosphate and artesunate are abdominal pain, bradycardia, headache, hypoglycaemia, vomiting, and haematological changes such as eosinophilia, neutropenia, anaemia, and an increased platelet count; abnormal laboratory test results include transient raises of serum transaminases (mostly ALT). Syncope, isolated prolongation of the QTc interval, and hypersensitivity reactions occur rarely.

Pyronaridine phosphate-artesunate should not be used for malaria prophylaxis. It is also contra-indicated in those with underlying hepatic injury or significant hepatic abnormalities; liver function tests should be carried out before and after a treatment course. The combination should be used with caution in those with cardiovascular disorders such as congenital prolongation of QTc interval, cardiac arrhythmia, and heart failure. Caution is also advised in patients with hypokalaemia, in those being treated with other drugs that block potassium channels, and in those who have recently taken medicines known to prolong the QTc interval.

Pregnancy. Data on the use of pyronaridine phosphate in pregnant women are not available, although *animal* studies have not reported any teratogenic effects. The safety of pyronaridine phosphate-artesunate in pregnancy has also not been established and the potential risk is unknown. For further information on the use of artesunate in pregnancy see under Artemisinin Derivatives, p. 649.2.

Interactions

In vitro studies have shown that pyronaridine phosphate is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and of P-glycoprotein. It should therefore be used with caution in patients taking drugs that are metabolised by the cytochrome P450 isoenzyme CYP2D6 and that are substrates for P-glycoprotein.

Pharmacokinetics

Peak plasma concentrations for pyronaridine are generally reached between 2 and 8 hours after an oral dose. Pyronaridine and its metabolites are extensively distributed into tissues. It is about 92 to 95% bound to plasma protein and may also bind to melanin in the eye. *In vitro* studies show that the cytochrome P450 isoenzymes CYP1A2, CYP2D6, and CYP3A4 could be involved in the metabolism of pyronaridine and that it inhibits the activity of CYP2D6. Pyronaridine is eliminated slowly with an elimination half-life of between 14 and 18 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Kor.*: Pyramax.

Quinine *(BAN)*

Chinin; Chinina; Chininum; Kiniini; Kinin; Kinine; Kuinina; Quinina; Хинин.

(8*S*,9*R*)-6′-Methoxycinchonan-9-ol; (α*R*)-α-(6-Methoxy-4-quinolyl)-α-[(2*S*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

$C_{20}H_{24}N_2O_2$=324.4

CAS — 130-95-0 (anhydrous quinine).

ATC — P01BC01.

UNII — A7V27PHC7A.

Description. Quinine is the chief alkaloid of various species of *Cinchona* (Rubiaceae). It is an optical isomer of quinidine.

Quinine Bisulfate *(BANM)*

Chininum Bisulfuricum; Neutral Quinine Sulphate; Quinina, bisulfato de; Quinine Acid Sulphate; Quinine Bisulphate; Quinini Bisulfas; Двусернокислый Хинин; Хинина бисульфат.

$C_{20}H_{24}N_2O_2H_2SO_4.7H_2O$=548.6

CAS — 549-56-4 (anhydrous quinine bisulfate).

ATC — P01BC01.

UNII — M201HC068W (anhydrous quinine bisulfate); GNS01V2R3N (quinine bisulfate heptahydrate).

Pharmacopoeias. In *Br., Int.*, and *Viet.*

BP 2014: (Quinine Bisulphate). Colourless crystals or a white crystalline powder. It effloresces in dry air. Freely soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 2.8 to 3.4. Protect from light.

Quinine Dihydrochloride *(BANM)*

Chinini Dihydrochloridum; Neutral Quinine Hydrochloride; Quinina, dihidrocloruro de; Quinine Acid Hydrochloride; Quinini Dihydrochloridum; Двухлористоводородный Хинин; Хинина Дигидрохлорид.

$C_{20}H_{24}N_2O_2.2HCl$=397.3

CAS — 60-93-5.

ATC — P01BC01.

UNII — 8C3EMH7D9X.

Pharmacopoeias. In *Br., Chin.*, and *Int.*

Viet. includes the injection.

BP 2014: (Quinine Dihydrochloride). A white or almost white powder. Very soluble in water; soluble in alcohol. A 3% solution in water has a pH of 2.0 to 3.0. Protect from light.

Quinine Etabonate

Euquinina; Euquinine; Quinina, etilcarbonato de; Quinine Ethyl Carbonate; Хинина Этабонат.

$C_{23}H_{28}N_2O_4$=396.5

CAS — 83-75-0.

ATC — P01BC01.

UNII — L2V8911157.

Pharmacopoeias. In *Jpn.*

Quinine Hydrobromide *(BANM)*

Basic Quinine Hydrobromide; Chinini Bromidum; Quinina, hidrobromuro de; Quinine Monohydrobromide; Хинина Гидробромид.

$C_{20}H_{24}N_2O_2HBr.H_2O$=423.4

CAS — 549-49-5 (anhydrous quinine hydrobromide).

ATC — P01BC01.

UNII — VWF36Q4G6V.

Pharmacopoeias. In *Fr.*

Quinine Hydrochloride *(BANM)*

Basic Quinine Hydrochloride; Chinin hydrochlorid dihydrát; Chininhydrochlorid; Chinini Hydrochloridum; Chininii Chloridum; Chininium Chloratum; Chinino hidrochloridas; Chininum Hydrochloricum; Chininy chlorowodorek; Kiniini-hydrokloridi; Kinin-hidroklorid; Kininhydroklorid; Quinina, hidrocloruro de; Quinine, chlorhydrate de; Quinine Monohydrochloride; Quinini Hydrochloridum; Quinini Hydrochloridum Dihydricum; Хинина Гидрохлорид.

$C_{20}H_{24}N_2O_2HCl.2H_2O$=396.9

CAS — 130-89-2 (anhydrous quinine hydrochloride); 6119-47-7 (quinine hydrochloride dihydrate).

ATC — P01BC01.

UNII — 71158Y0T33 (quinine hydrochloride dihydrate); 7CS0WNO31M (anhydrous quinine hydrochloride).

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

Ph. Eur. 8: (Quinine Hydrochloride). White or almost white, or colourless, fine, silky needles, often grouped in clusters. Soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

Quinine Sulfate *(BANM)*

Basic Quinine Sulphate; Chinin sulfát dihydrát; Chinini sulfas; Chinino sulfatas; Chininsulfat; Chininum Sulfuricum; Chininy siarczan; Kiniinisulfaatti; Kininsulfat; Kinin-szulfát; Quinina, sulfato de; Quinine, sulfate de; Quinine Sulphate; Quinini Sulfas; Quinini Sulfas Dihydricus; Хинина Сульфат.

$(C_{20}H_{24}N_2O_2)_2.H_2SO_4.2H_2O$=783.0

CAS — 804-63-7 (anhydrous quinine sulfate); 6119-70-6 (quinine sulfate dihydrate).

ATC — P01BC01.

UNII — KF7Z0E0Q2B.

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

Ph. Eur. 8: (Quinine Sulfate). A white or almost white, crystalline powder or fine, colourless needles. Slightly soluble in water; sparingly soluble in boiling water and in alcohol. A 1% suspension in water has a pH of 5.7 to 6.6. Protect from light.

USP 36: (Quinine Sulfate). It is the sulfate of an alkaloid obtained from the bark of species of *Cinchona*. White, odourless, fine needle-like crystals, usually lusterless, making a light and readily compressible mass. It darkens on exposure to light. Soluble 1 in 500 of water and 1 in 120 of alcohol; sparingly soluble in water at 100 degrees; slightly soluble in chloroform; freely soluble in alcohol at 80 degrees and in a mixture of 2 parts of chloroform and one part of dehydrated alcohol; very slightly soluble in ether. Its saturated solution in water is neutral or alkaline to litmus. Protect from light.

Sorption. For reference to loss of quinine sulfate from solutions during membrane filtration, see Chloroquine, p. 650.2.

Uses and Administration

Quinine is a cinchona alkaloid and a 4-methanolquinoline antimalarial that is a rapid-acting blood schizontocide with activity against *Plasmodium falciparum, P. vivax, P. ovale*, and *P. malariae*. It is active against the gametocytes of *P. malariae* and *P. vivax*, but not against mature gametocytes of *P. falciparum*. The precise mechanism of action of quinine is unclear but it may interfere with lysosome function or nucleic acid synthesis in the malaria parasite. Since it has no activity against exoerythrocytic forms, quinine does not produce a radical cure in vivax or ovale malarias. The increasing spread of resistance to chloroquine has been responsible for the re-emergence of quinine as an important drug in the treatment of falciparum malaria (p. 666.1). Quinine is not generally used for malaria prophylaxis.

Quinine is also used to treat the protozoal infection babesiosis (p. 666.1) and for the relief of nocturnal leg cramps (p. 666.2).

Quinine has mild analgesic and antipyretic properties and is sometimes included in preparations used for the symptomatic relief of the common cold and influenza; additional salts that have been used for this purpose include the camsilate and the gluconate.

Quinine is also used as a bitter and a flavour (p. 666.1).

Quinine is used as several salts and 100 mg of anhydrous quinine is equivalent to about:

- 169 mg of quinine bisulfate
- 122 mg of quinine dihydrochloride
- 122 mg of quinine etabonate
- 130 mg of quinine hydrobromide
- 122 mg of quinine hydrochloride
- 121 mg of quinine sulfate

For the treatment of **malaria** quinine is given orally, usually as the sulfate, hydrochloride, or dihydrochloride, or parenterally as the dihydrochloride; quinine etabonate is sometimes used orally because unlike other quinine salts, which are intensely bitter, it is tasteless. They all contain about the same amount of quinine and any of them can be used when the dose is cited in terms of "quinine salt"; this is not the case for the bisulfate, which contains a correspondingly smaller amount of quinine. Quinine formate is sometimes given parenterally.

A course of treatment with quinine for falciparum malaria usually lasts 7 days and is accompanied by follow-on treatment with clindamycin, tetracycline, or doxycycline; in uncomplicated infections treatment should preferably be given by the oral route. The usual *oral* dose is 600 mg of quinine salt given every 8 hours for 7 days.

In severe or complicated falciparum malaria, or when the patient is unable to take oral medication, quinine should be given parenterally by slow intravenous infusion, but this can be hazardous and patients generally need monitoring, particularly for signs of cardiotoxicity. Therapy should be changed to the oral route as soon as possible to complete the course. To obtain therapeutic concentrations rapidly with parenteral therapy, quinine is often given in an initial loading dose followed by maintenance doses. A recommended *intravenous* dosage regimen suggested by WHO is an initial loading dose of 20 mg/kg of quinine dihydrochloride (up to a maximum of 1.4 g) given over 4 hours with maintenance infusions being started 8 hours later, calculated from the start of the previous infusion. Alternatively, in intensive care units, an initial loading dose of 7 mg/kg may be given over 30 minutes followed immediately by the first of the maintenance infusions. Maintenance infusions consist of 10 mg/kg (up to a maximum of 700 mg) given over 4 hours every 8 hours. A loading dose should not be given if the patient has received quinine, quinidine, mefloquine, or halofantrine, during the previous 12 hours. If parenteral therapy is required for more than 48 hours the maintenance dose of quinine dihydrochloride should be reduced to 5 to 7 mg/kg.

If intravenous infusion is not possible, quinine dihydrochloride has been given *intramuscularly*. Doses, including the loading dose, are the same as those used intravenously; the drug should be diluted in sodium chloride 0.9% to a concentration of 60 to 100 mg of the dihydrochloride per mL and the loading dose should be divided between two injection sites, preferably each anterior thigh (not the buttock). However, intramuscular injection can be irritant and there have been concerns regarding its safety and efficacy (see under Malaria, p. 666.1).

For details of doses in children and advice on dosing in renal or hepatic failure, see below and p. 666.1, respectively.

When used for the relief of nocturnal **leg cramps**, quinine is given at night in an oral dose of 200 to 300 mg of the sulfate or bisulfate. Quinine benzoate has also been used.

Administration in children. Quinine may be used orally in children for the treatment of **uncomplicated falciparum malaria**, or parenterally when malaria is severe or oral

therapy is not possible. Doses are expressed in terms of quinine salt.

For treatment of uncomplicated malaria a dose of 10 mg/kg orally every 8 hours[1] for 7 days may be used, along with clindamycin for follow-on treatment.[2] When parenteral therapy is required, quinine may be given by slow intravenous infusion at a rate not exceeding 5 mg/kg per hour, but if this is not possible the intramuscular route may be considered.[2] Parenteral doses and administration are as for adults (see p. 665.3).

1. WHO. *WHO model formulary for children: based on the second model list of essential medicines for children 2009*. Geneva: WHO, 2010. Available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf (accessed 19/07/10)
2. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 19/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Administration in hepatic impairment. Quinine may accumulate in patients with hepatic impairment, and WHO[1] has therefore suggested that quinine doses for severe malaria be reduced by one-third after the first 48 hours of treatment in patients with severe hepatic impairment. Similarly, in the UK the *BNF* suggests that when *intravenous* quinine is used in patients with severe hepatic impairment, the maintenance dose should be reduced to 5 to 7 mg/kg of quinine salt every 8 hours.

1. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 07/07/11) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 07/07/11)

Administration in renal impairment. Quinine may accumulate in severe renal impairment, and WHO[1] has suggested that quinine doses for severe malaria should be reduced by one-third in such patients if severe renal failure persists after 48 hours of treatment. Some licensed product information also gives recommendations: when *oral* quinine is required for malaria treatment in patients with chronic, severe renal impairment, the usual dose may be given as an initial loading dose, followed at 12-hour intervals by half the usual dose. In the UK, the *BNF* suggests that when *intravenous* quinine is used in severe renal failure, the maintenance dose should be reduced to 5 to 7 mg/kg of quinine salt every 8 hours.

No dose adjustment is required for patients undergoing haemodialysis or haemofiltration.

1. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)

Babesiosis. Although there is no established specific treatment for babesiosis (p. 920.2), a combination of quinine and clindamycin has been used.[1,2] For suggested doses see under Clindamycin, p. 270.3. Quinine with azithromycin was reported to be effective in a patient who had not responded to quinine with clindamycin.[3]

1. Abramowicz M., ed. *Drugs for parasitic infections*. 2nd ed. New Rochelle NY: The Medical Letter. 2010.
2. Wormser GP, *et al*. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 43: 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 17/06/08)
3. Shalo MF, Yang KD. Response of babesiosis to a combined regimen of quinine and azithromycin. *Trans R Soc Trop Med Hyg* 1997; 91: 214–15.

Flavouring. The Joint FAO/WHO Expert Committee on Food Additives concluded that quinine levels in soft drinks of up to 100 mg/litre (as quinine base) were not of toxicological concern.[1] However, because of the possibility of hypersensitivity reactions in some individuals, the committee recommended that consumers be informed of the presence of quinine in food or beverages.

1. FAO/WHO. Evaluation of certain food additives and contaminants: forty-first report of the Joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 837 1993. Also available at: http://libdoc.who.int/trs/WHO_TRS_837.pdf (accessed 12/09/11)

Malaria. Quinine has had an important role in the treatment of falciparum malaria (see p. 644.1). Quinine salts are normally given orally (any quinine lost through vomiting within one hour of an oral dose should be replaced by additional doses)[1] or in severe infection by slow intravenous infusion of the dihydrochloride.[2] If intravenous formulations of quinine are unavailable quinidine may be used as an alternative; for further details, see under the Uses and Administration of Quinidine, p. 1481.3.

If facilities for intravenous infusion, including monitoring, are not available quinine may be given by deep intramuscular injection.[2] The use of the intramuscular route has been controversial because of concerns over safety and efficacy but there is some evidence of benefit.[3–6] Intramuscular injections of quinine can be irritant and have caused pain, focal necrosis, and abscess formation; fatal tetanus has developed in some patients.[7] It has been suggested that some such reactions may be related to the use of preparations formulated in urethane or other irritant substances. Diluted solutions of quinine dihydrochloride 60 mg/mL adjusted to neutral pH appear to be less painful than the usual undiluted preparation of 300 mg/mL.

If facilities do not exist to give quinine parenterally then patients with severe malaria should receive quinine by mouth or nasogastric tube.

Quinine as formerly standardised used to contain a higher concentration of cinchona alkaloids and there might be synergy between mixtures of these alkaloids.[8] In practice no advantage has been shown by such mixtures over quinine alone in the treatment of chloroquine-resistant falciparum malaria.[9]

1. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 07/04/09)
2. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. Wattanagoon Y, *et al*. Intramuscular loading dose of quinine for falciparum malaria: pharmacokinetics and toxicity. *BMJ* 1986; 293: 11–13. Correction. *ibid.*; 362.
4. Mansor SM, *et al*. The safety and kinetics of intramuscular quinine in Malawian children with moderately severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; 84: 482–7.
5. Waller D, *et al*. The pharmacokinetic properties of intramuscular quinine in Gambian children with severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; 84: 488–91.
6. Schapira A, *et al*. Comparison of intramuscular and intravenous quinine for the treatment of severe and complicated malaria in children. *Trans R Soc Trop Med Hyg* 1993; 87: 299–302.
7. Yen LM, *et al*. Role of quinine in the high mortality of intramuscular injection tetanus. *Lancet* 1994; 344: 786–7.
8. Druilhe P, *et al*. Activity of a combination of three cinchona bark alkaloids against Plasmodium falciparum in vitro. *Antimicrob Agents Chemother* 1988; 32: 250–4.
9. Bunnag D, *et al*. A combination of quinine, quinidine and cinchonine (LA 40221) in the treatment of chloroquine resistant falciparum malaria in Thailand: two double-blind trials. *Trans R Soc Trop Med Hyg* 1989; 83: 66.

Muscle spasm. Quinine (usually as quinine sulfate or bisulfate) has traditionally been used for nocturnal cramps (p. 2014.1) but there has been concern over its efficacy and potential for adverse effects, especially in the elderly. In the USA, for example, the FDA ruled that quinine products should no longer be used for the management of nocturnal cramps.[1,2] A similar ban has been imposed in Australia.[3] Meta-analyses[4,5] concluded that although quinine was effective in the treatment of nocturnal cramps in ambulatory patients the risk of serious adverse effects should be borne in mind. It was recommended that patients should be closely monitored while the efficacy of quinine is assessed over a period of at least 4 weeks. In contrast, a later Cochrane review[6] found moderate quality evidence to suggest that when quinine was used to treat muscle cramps for up to 60 days, the incidence of serious adverse effects was not significantly different than with placebo. Some[7] have recommended that treatment be stopped every 3 months to see whether it is still needed.

Haemodialysis-induced cramp (p. 1781.3) has been reported to respond to treatment with quinine[8,9] but similar concerns apply.

1. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; 59: 43234–52.
2. Nightingale SL. Quinine for nocturnal leg cramps. *ACP J Club* 1995; 123: 86.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Quinine indications—cramps deleted. *Aust Adverse Drug React Bull* 2004; 23: 20. Also available at: http://www.tga.gov.au/hp/aadrb-0410.htm (accessed 12/09/11)
4. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; 310: 13–17.
5. Man-Son-Hing M, *et al*. Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; 13: 600–606.
6. El-Tawil S, *et al*. Quinine for muscle cramps. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 08/07/11).
7. Anonymous. Quinine for nocturnal leg cramps? *Drug Ther Bull* 1996; 34: 7–8.
8. Kaji DM, *et al*. Prevention of muscle cramps in haemodialysis patients by quinine sulphate. *Lancet* 1976; ii: 66–7.
9. Roca AO, *et al*. Dialysis leg cramps; efficacy of quinine versus vitamin E. *ASAIO J* 1992; 38: M481–M485.

Adverse Effects

Quinine or its salts given in usual therapeutic doses may give rise to a train of symptoms known as cinchonism, characterised in its mild form by tinnitus, impaired hearing, headache, nausea, and disturbed vision, with, in its more severe manifestations, vomiting, abdominal pain, diarrhoea, and vertigo.

Cinchonism may also occur after small doses in patients hypersensitive to quinine, but urticaria and flushing of the skin with intense pruritus are the most frequent reactions seen in these patients. Other effects include fever, rashes, and dyspnoea. Angioedema may also occur and asthma can be precipitated. Thrombocytopenia and other blood disorders have been reported. Thrombocytopenic purpura has been associated with quinine hypersensitivity. Haemoglobinuria occurs rarely.

Other adverse effects of quinine include hypoglycaemia, hypoprothrombinaemia, and renal failure.

The main symptoms of overdosage, which can be fatal, include gastrointestinal effects, oculotoxicity, CNS disturbances, and cardiotoxicity. Visual disturbances including sudden blindness are usually slowly reversible but there may be residual damage. Overdosage is discussed in detail p. 667.2. Quinine can produce cardiovascular toxicity similar to that seen with quinidine, including conduction disturbances, arrhythmias, anginal symptoms, and hypotension leading to cardiac arrest and circulatory failure. Severe or even fatal cardiovascular toxicity can result from rapid intravenous dosage of quinine.

Large amounts of quinine can induce abortion; congenital malformations, particularly of the optic and auditory nerves, have been reported after failure to induce abortion with quinine. However, quinine should not be withheld from pregnant women with life-threatening malaria (see also under Pregnancy in Precautions, p. 668.1).

Intramuscular injections of quinine can be irritant and have caused pain, focal necrosis, and abscess formation; tetanus has developed in some patients (see under Malaria in Uses and Administration, above).

Effects on the blood. Between 1966 and 1975 the Swedish Adverse Drug Reaction Committee received 43 reports of *thrombocytopenia* attributable to quinine or quinidine[1] and the Boston Collaborative Drug Surveillance Program had 11 similar reports in patients studied between 1972 and 1981.[2] Up to October 2004, there had also been 228 cases of thrombocytopenia reported to the Australian Adverse Drug Reactions Advisory Committee, including 6 fatalities.[3] In the USA, the FDA has continued to receive reports of serious adverse events, including fatalities, despite efforts to restrict the use of quinine in response to existing toxicity concerns. Between April 2005 and October 2008, 24 domestic reports of serious haematological adverse events were received, of which 87.5% were thrombocytopenia requiring hospitalisation. The median time to onset of toxicity, and median reported quinine dose were 13.5 days and 325 mg daily respectively.[4] A similar analysis by Health Canada[5] of 71 reports of serious adverse effects suspected of being associated with quinine sulfate up to September 2010 included 43 cases where the indication had been leg cramps, for which the drug was not licensed; in 20 of these the adverse effect had been thrombocytopenia, often severe, while other adverse effects had included Stevens-Johnson syndrome, vasculitis, and arrhythmias. Quinine-induced thrombocytopenia appears to be a hypersensitivity reaction and beverages containing quinine as a bitter in concentrations as low as 20 micrograms/mL have precipitated thrombocytopenic purpura in previously sensitised individuals.[6]

Although quinine can cause *haemolysis*, there is some doubt over the traditional view that irregular dosage with quinine predisposes patients with malaria to *blackwater fever*, a syndrome of severe haemolytic anaemia, haemoglobinuria, oliguria, and renal failure.[7] Some of the patients affected may have had G6PD deficiency.[7] Haemolytic-uraemic syndrome[8–10] and pancytopenia with coagulopathy and renal impairment[11,12] have also been associated with the use of quinine.

There have also been reports of *disseminated intravascular coagulation*, including one fatality, after use of quinine by patients with quinine hypersensitivity.[13–15] In one case[15] the hypersensitivity reaction closely mimicked septic shock.

There have been isolated reports of *agranulocytosis* due to quinine.[16]

1. Böttiger LE, *et al*. Drug-induced blood dyscrasias. *Acta Med Scand* 1976; 205: 457–61.
2. Danielson DA, *et al*. Drug-induced blood disorders. *JAMA* 1984; 252: 3257–60.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Quinine indications—cramps deleted. *Aust Adverse Drug React Bull* 2004; 23: 20. Also available at: http://www.tga.gov.au/hp/aadrb-0410.htm (accessed 12/09/11)
4. FDA. Quinine sulfate (marketed as Qualaquin): off-label (not approved by FDA) use of quinine. *FDA Drug Safety Newsletter* 2009; 2: 11–13. Also available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/UCM168579.pdf (accessed 10/09/09)
5. Health Canada. Quinine sulfate and serious adverse reactions. *Can Adverse React News* 2011; 21 (2): 5. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v21n2-eng.pdf (accessed 02/08/11)
6. Murray JA, *et al*. Bitter lemon purpura. *BMJ* 1979; 2: 1531–2.
7. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; 84 (suppl 2): 1–65.
8. Hagley MT, *et al*. Hemolytic-uremic syndrome associated with ingestion of quinine. *Am J Nephrol* 1992; 12: 192–5.
9. Gottschall JL, *et al*. Quinine-induced immune thrombocytopenia with hemolytic uremic syndrome: clinical and serological findings in nine patients and review of literature. *Am J Hematol* 1994; 47: 283–9.
10. McDonald SP, *et al*. Quinine-induced hemolytic uremic syndrome. *Clin Nephrol* 1997; 47: 397–400.
11. Maguire RB, *et al*. Recurrent pancytopenia, coagulopathy, and renal failure associated with multiple quinine-dependent antibodies. *Ann Intern Med* 1993; 119: 215–17.

12. Schmitt SK, Tomford JW. Quinine-induced pancytopenia and coagulopathy. *Ann Intern Med* 1994; 120: 90–1.
13. Spearing RL, *et al.* Quinine-induced disseminated intravascular coagulation. *Lancet* 1990; 336: 1535–7.
14. Barr E, *et al.* Recurrent acute hypersensitivity to quinine. *BMJ* 1990; 301: 323.
15. Schattner A. Quinine hypersensitivity simulating sepsis. *Am J Med* 1998; 104: 488–90.
16. Sutherland R, *et al.* Quinine-induced agranulocytosis: toxic effect of quinine bisulphate on bone marrow cultures in vitro. *BMJ* 1977; 1: 605–7.

Effects on the ears. Although ototoxicity such as tinnitus or deafness is known to be a possible adverse effect of quinine, reversible hearing loss may also occur. While one group of workers[1] found the reduction in auditory acuity to be greatest at higher frequencies, another group[2] have found that hearing loss was generally equal across the range of frequencies tested and appeared to be related to the plasma concentration of quinine.

1. Roche RJ, *et al.* Quinine induces reversible high-tone hearing loss. *Br J Clin Pharmacol* 1990; 29: 780–2.
2. Karlsson KK, *et al.* Audiometry as a possible indicator of quinine plasma concentration during treatment of malaria. *Trans R Soc Trop Med Hyg* 1990; 84: 765–7.

Effects on the eyes. Oculotoxicity after overdosage with quinine is well recognised (see below), but there has also been a report of blindness in two patients occurring during supposedly routine therapy.[1]

1. Waddell K. Blindness from quinine as an antimalarial. *Trans R Soc Trop Med Hyg* 1996; 90: 331–2.

Effects on glucose metabolism. Hypoglycaemia is now recognised to be a frequent complication of falciparum malaria and it is often associated with a poor prognosis. Children, pregnant women, and patients with severe disease appear to be particularly at risk. It is important to recognise that hypoglycaemia rather than cerebral malaria may be the cause of coma. Hypoglycaemia may also be induced by antimalarial therapy; first episodes of hypoglycaemia have been detected after patients received quinine[1-3] or quinidine[4] intravenously, although others have not found that quinine led to the development of hypoglycaemia.[5,6]

Quinine has also been reported to induce hypoglycaemia during treatment for leg cramps.[7]

1. White NJ, *et al.* Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983; 309: 61–6.
2. Okitolonda W, *et al.* High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria. *BMJ* 1987; 295: 716–18.
3. Looareesuwan S, *et al.* Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; ii: 4–8.
4. Phillips RE, *et al.* Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *BMJ* 1986; 292: 1319–21.
5. Taylor TE, *et al.* Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. *N Engl J Med* 1988; 319: 1040–7.
6. Kawo NG, *et al.* The metabolic effects of quinine in children with severe and complicated Plasmodium falciparum malaria in Dar es Salaam. *Trans R Soc Trop Med Hyg* 1991; 85: 711–13.
7. Limburg PJ, *et al.* Quinine-induced hypoglycemia. *Ann Intern Med* 1993; 119: 218–19.

Effects on the heart. Cardiotoxicity after overdosage with quinine is well recognised, and prolongation of the QT interval has been noted with therapeutic doses. There has also been a report[1] of fatal ventricular fibrillation with QT prolongation in an elderly patient who received standard doses of quinine by slow intravenous infusion for falciparum malaria. It was noted that the patient had some prolongation of the QT interval before starting quinine and also that her free quinine concentrations were unusually high despite total quinine concentrations considered to be within the therapeutic range.

1. Bonington A, *et al.* Fatal quinine cardiotoxicity in the treatment of falciparum malaria. *Trans R Soc Trop Med Hyg* 1996; 90: 305–7.

Effects on the kidneys. See Effects on the Blood, p. 666.3.

Effects on the liver. Although hepatitis has been associated with quinidine therapy (see p. 1482.2), there appear to be few reports of hepatotoxicity due to quinine usage. Granulomatous hepatitis has been reported in 2 patients taking quinine,[1,2] but the diagnosis in the first of these cases was challenged as the histological findings were considered to be more indicative of non-specific reactive hepatitis.[3] Hepatotoxicity due to quinine hypersensitivity has been reported in another patient.[4] Symptoms of hepatotoxicity occurred within 24 hours in a further patient taking quinine for nocturnal leg cramps.[5]

1. Katz B, *et al.* Quinine-induced granulomatous hepatitis. *BMJ* 1983; 286: 264–5.
2. Mathur S, *et al.* Quinine induced granulomatous hepatitis and vasculitis. *BMJ* 1990; 300: 613.
3. Mirodi NS. Quinine induced granulomatous hepatitis. *BMJ* 1983; 286: 647.
4. Punukollu RC, *et al.* Quinine hepatotoxicity: an underrecognized or rare phenomenon? *Arch Intern Med* 1990; 150: 1112–13.
5. Parver DK, Lavin MN. Quinine-induced hepatotoxicity. *Ann Pharmacother* 1999; 33: 32–4.

Effects on the skin. Urticaria, cutaneous flushing, various rashes, and pruritus are the commonest symptoms of hypersensitivity reactions to quinine.

Topical contact with quinine may cause contact as well as photocontact allergy, but quinine can also induce photosensitivity reactions after systemic dosage.[1-3] Photosensitivity associated with quinine intake from excessive consumption of tonic water has been reported;[4] fixed drug eruptions due to quinine in tonic water have also occurred.[5] There have also been reports of eczematous dermatitis,[1] oedema and erythema,[6] hyperpigmentation,[7] and lichen planus.[6] Both phototoxic[6] and photoallergic[1] mechanisms have been suggested. Fatal cutaneous vasculitis related to quinine treatment for nocturnal cramps has been reported.[8]

For a comparison of the incidence of pruritus induced by various antimalarials, see under Chloroquine, p. 652.2.

1. Ljunggren B, Sjövall P. Systemic quinine photosensitivity. *Arch Dermatol* 1986; 122: 909–11.
2. Ljunggren B, *et al.* Systemic quinine photosensitivity with photoepicutaneous cross-reactivity to quinidine. *Contact Dermatitis* 1992; 26: 1–4.
3. Hickey JR, *et al.* Photoallergic reaction to systemic quinine sulphate. *Contact Dermatitis* 2007; 57: 384–6.
4. Wagner GH, *et al.* I'll have mine with a twist of lemon': quinine photosensitivity from excessive intake of tonic water. *Br J Dermatol* 1994; 131: 734–5.
5. Bel B, *et al.* Fixed eruption due to quinine contained in tonic water: positive patch-testing. *Contact Dermatitis* 2009; 61: 242–4.
6. Ferguson J, *et al.* Quinine induced photosensitivity: clinical and experimental studies. *Br J Dermatol* 1987; 117: 631–40.
7. Rosen T, Aponte C. Cutaneous hyperpigmentation due to chronic quinine ingestion. *Cutis* 2005; 75: 114–6.
8. Price EJ, *et al.* Quinine-induced cutaneous vasculitis. *Br J Clin Pract* 1992; 46: 138–9.

Hypersensitivity. For reference to hypersensitivity reactions associated with quinine, see Effects on the Blood (p. 666.3), Effects on the Liver (above), and Effects on the Skin (above).

Overdosage. Cinchonism may occur with therapeutic doses of quinine and symptoms include nausea, vomiting, tinnitus, deafness, headache, vasodilatation, and slightly disturbed vision. These symptoms may also occur in acute overdosage, but the visual disorders may be severe and there may be CNS disturbances and cardiotoxicity. A lethal dose or lethal plasma-quinine concentration has not been established but fatalities have been reported[1] in adults after doses of 2 to 8 g and in children after 1 g.

An analysis[2] of 165 cases of acute quinine poisoning revealed that: 21% had no symptoms, nausea with or without vomiting occurred in 47%, visual disturbances in 42%, tinnitus in 38%, other auditory disturbances in 23%, sinus tachycardia in 23%, and other ECG abnormalities in 8%. Mild impairment of consciousness was reported in 14% of the patients while 7 (4%) patients had deeper grades of coma. Of the 5 patients who died, 4 developed intractable ventricular arrhythmias and the fifth had a Jacksonian seizure followed by cardiac arrest. Another analysis,[3] of 96 cases of quinine intoxication reported in Scotland between 1997 and 2002, noted that there had been no changes in the pattern of poisoning from that in older studies; 6 cases involved moderate to serious toxicity after ingestion of 10 g or more. Intentional overdose was most common in patients aged between 11 and 30; children aged 10 or less were at greatest risk of accidental ingestion but toxicity was often not severe because the quantities were smaller. Both auditory and ocular toxicity appeared to be dose-related.

The effects of oculotoxicity may include blurred vision, defective colour perception, visual field constriction, and total blindness.[2,4] The onset of symptoms may vary from a few hours to a day or more after ingestion.[2,4] Suggested mechanisms for the oculotoxicity of quinine include an action on the retinal vasculature to produce ischaemia or a direct toxic effect on the retina.[1] Visual loss in one group of patients[4] was associated with plasma-quinine concentrations in excess of 10 micrograms/mL. However, in another group plasma-quinine concentrations were considered to be an imprecise guide to predicting visual disturbances.[2] The speed and degree of visual recovery varies. Of 70 patients with visual disturbances after quinine poisoning, 39 subsequently had a period of total blindness.[2] Permanent visual deficits remained in 19 of these but no patient had permanent bilateral blindness. All of the 31 patients who had blurred vision recovered full visual acuity.

It is considered that the actions of quinine on the myocardium are similar to those of quinidine but that it is less potent.[1] Sinus tachycardia and minor ECG changes are the most common cardiovascular effects. Conduction abnormalities and ventricular dysrhythmias may occur with severe poisoning. Ventricular tachycardia is mostly associated with cardiogenic shock or circulatory collapse. Hypokalaemia may also occur.[1]

1. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; 2: 242–73.
2. Boland ME, *et al.* Complications of quinine poisoning. *Lancet* 1985; i: 384–5.
3. Langford NJ, *et al.* Quinine intoxications reported to the Scottish Poisons Information Bureau 1997-2002: a continuing problem. *Br J Clin Pharmacol* 2003; 56: 576–8.
4. Dyson EH, *et al.* Death and blindness due to overdose of quinine. *BMJ* 1985; 291: 31–3.

Treatment of Adverse Effects

In acute overdosage with quinine or its salts multiple doses of activated charcoal (p. 1537.3) may be given to adults or children who present within one hour of ingesting more than the equivalent of 30 mg/kg of quinine base or any amount in a child under 5 years of age; gastric lavage may also be considered for use in adults. Other measures aimed at enhancing the elimination of quinine are largely ineffective. Treatment is mostly symptomatic with attention being given to maintaining blood pressure, respiration, and renal function, and to treating arrhythmias (for further information, see Acute Poisoning, p. 1537.1).

Vasodilators and stellate ganglion block have been used to prevent or reverse visual impairment but there is little evidence to support their use.

It has been suggested that, as quinine has antimuscarinic effects, gastric emptying may be delayed and considerable amounts of drug might be removed from the stomach beyond the usual 4 hours.[1] Others consider that gastric lavage is of doubtful value as quinine is rapidly absorbed and vomiting has often occurred before admission.[2] However, studies in healthy subjects and poisoned patients suggest that oral activated charcoal may increase the elimination of quinine.[3,4] Other methods of increasing elimination are probably ineffective. In a study involving 16 patients with quinine poisoning forced acid diuresis, haemodialysis, haemoperfusion, or plasma exchange were all found to be ineffective in increasing quinine elimination.[5]

Stellate ganglion block has been recommended to prevent or reverse retinal damage, the rationale being that quinine-induced oculotoxicity might arise from retinal arteriolar constriction. However, clinical studies have failed to find sufficient improvement to justify its use.[6,7] Intravenous nitrates produced beneficial responses in 2 patients.[8]

1. Boland M, Volans G. ABC of poisoning: miscellaneous drugs. *BMJ* 1984; 289: 1361–5.
2. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; 2: 242–73.
3. Lockey D, Bateman DN. Effect of oral activated charcoal on quinine elimination. *Br J Clin Pharmacol* 1989; 27: 92–4.
4. Prescott LF, *et al.* Treatment of quinine overdosage with repeated oral charcoal. *Br J Clin Pharmacol* 1989; 27: 95–7.
5. Bateman DN, *et al.* Pharmacokinetics and clinical toxicity of quinine overdosage: lack of efficacy of techniques intended to enhance elimination. *Q J Med* 1985; 54: 125–31.
6. Boland ME, *et al.* Complications of quinine poisoning. *Lancet* 1985; i: 384–5.
7. Dyson EH, *et al.* Quinine amblyopia: is current management appropriate? *J Toxicol Clin Toxicol* 1985–6; 23: 571–8.
8. Moore D, *et al.* Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; 76: 703.

Precautions

Quinine and its salts are contra-indicated in patients with a history of hypersensitivity to quinine or quinidine and in patients with tinnitus or optic neuritis. They should not be used in the presence of haemolysis. They should be used with caution in patients with atrial fibrillation, cardiac conduction defects, or heart block. Quinine should be avoided in patients with myasthenia gravis as it may aggravate their condition.

Pregnancy in a patient with malaria is not generally regarded as a contra-indication to the use of quinine.

As quinine has been implicated in precipitating blackwater fever it is generally contra-indicated in patients who have already suffered an attack. Quinine may also cause haemolysis in some types of G6PD deficiency and should be used with care (but see also below).

It is important that when quinine is given intravenously it should be given by slow infusion and the patient observed closely for signs of cardiotoxicity. Blood-glucose concentrations should also be monitored. Problems that have been associated with intramuscular use are discussed under Malaria in Uses and Administration, p. 666.1.

Breast feeding. Although quinine is distributed into breast milk in small amounts,[1] the most recent guidance from the American Academy of Pediatrics considered that the use of quinine was probably compatible with breast feeding.[2]

1. Phillips RE, *et al.* Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. *Br J Clin Pharmacol* 1986; 21: 677–83.
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 19/04/04)

Glucose-6-phosphate deficiency. Although licensed product information has noted that quinine may cause hae-

molysis in G6PD deficient patients (and in some countries, contra-indicates its use by such patients), a review[1] noted that haemolysis has not been seen in published studies, and re-affirmed an earlier conclusion[2] that full therapeutic doses may be safely administered to G6PD-deficient patients.

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; 33: 713–26.
2. Beutler E. Glucose-6-phosphate dehydrogenase deficiency. *N Engl J Med* 1991; 324: 169–74.

Liver disease. See under Pharmacokinetics, below.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

For a discussion of the use of other antimalarials in patients with porphyria, see under Precautions for Chloroquine, p. 653.1.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Pregnancy. The use of quinine in large doses as an abortifacient in the past has led to concern over its use during pregnancy, but no evidence of an oxytocic effect was found when it was used to treat severe falciparum malaria in women in the third trimester of pregnancy.[1]

Congenital abnormalities including damage to the auditory and optic nerves have been seen, usually after attempted abortions, but WHO[2] considers quinine to be safe when used in normal therapeutic doses during pregnancy (although the problem of hypoglycaemia in the second and third trimesters may mean that artemisinin derivatives are preferred). Jitteriness attributed to quinine withdrawal has been reported in an infant whose mother had drunk large quantities of tonic water containing quinine during the last 17 weeks of pregnancy.[3]

As malaria is potentially serious during pregnancy and poses a threat to the mother and fetus, there appears to be little justification for withholding treatment in the absence of a suitable alternative. However, pregnant patients treated for malaria are at special risk from hypoglycaemia exacerbated or caused by quinine-induced hyperinsulinaemia (see under Effects on Glucose Metabolism in Adverse Effects, p. 667.1) and should be managed appropriately.

1. Looareesuwan S, *et al.* Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; ii: 4–8.
2. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 09/07/10) Update (issued April 2011) available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
3. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; 224: 315–19.

Renal impairment. See under Pharmacokinetics, below.

Interactions

As quinine shares many of the actions of quinidine, interactions seen between quinidine and other drugs (see p. 1483.1) might also occur with quinine. Both have actions on skeletal muscle and may potentiate the effects of drugs with neuromuscular-blocking activity (see under Antiarrhythmics on p. 2031.3). There is an increased risk of inducing ventricular arrhythmias if quinine is given with halofantrine (see p. 655.1) or other drugs that prolong the QT-interval such as amiodarone, the antihistamines astemizole and terfenadine, cisapride, moxifloxacin, and the antipsychotics pimozide and thioridazine. There may be an increased risk of convulsions when quinine is given with mefloquine. Quinine may also potentiate the effects of hypoglycaemic drugs.

Antibacterials. Elimination of quinine has been reported to increase in patients also receiving *rifampicin*.[1]

1. Wanwimolruk S, *et al.* Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man. *Br J Clin Pharmacol* 1995; 40: 87–91.

Amantadine. For a report of quinine reducing renal clearance of amantadine, see Antiarrhythmics, p. 892.2.

Anticoagulants. Quinine can cause hypoprothrombinaemia and thereby enhance the effect of anticoagulants. In one report, reductions in *warfarin* dosage were necessary after ingestion of large amounts of tonic water containing quinine (see p. 1532.2).

Antimalarials. Quinine and *chloroquine* may be antagonistic when used for falciparum malaria (see p. 653.2). For a report of quinine reducing plasma concentrations of *primaquine*, see p. 661.2.

Antivirals. In a pharmacokinetic study,[1] co-administration with *ritonavir* (in an oral dose of 200 mg twice daily) led to increases of about fourfold in the AUC and peak-plasma concentration of quinine; a modest, but significant increase in plasma concentrations of ritonavir was also noted. The authors of the study suggest that a downward dose adjustment of quinine may be necessary, given the magnitude of the plasma-concentration increase possible for the drug, and the seriousness of its adverse effects.

Although there appears to be no evidence regarding potential interaction with other HIV-protease inhibitors, they all have the potential to affect cytochrome P450 isoenzyme CYP3A4 (although to a lesser extent than ritonavir) and therefore might be expected to raise serum-concentrations of quinine (a substrate of CYP3A4); therefore, such combinations should be used with caution. UK licensed product information for *saquinavir* suggests its use (ritonavir-boosted) with quinine is contra-indicated, due to a potential risk for cardiac arrhythmia.

1. Soyinka JO, *et al.* Pharmacokinetic interactions between ritonavir and quinine in healthy volunteers following concurrent administration. *Br J Clin Pharmacol* 2010; 69: 262–70.

Cardiovascular drugs. Quinidine has been reported to increase serum-digoxin concentrations (see Quinidine under Antiarrhythmics, p. 1356.2) and quinine has reduced total body clearance of digoxin (see Antimalarials, p. 1357.1).

For a report of quinine inhibiting the metabolism of *flecainide*, see p. 1384.3.

Histamine H_2-antagonists. *Cimetidine* has been reported to reduce the clearance of quinine and prolong its elimination half-life in a study in healthy subjects; no significant effect was seen with *ranitidine*.[1]

1. Wanwimolruk S, *et al.* Effects of cimetidine and ranitidine on the pharmacokinetics of quinine. *Br J Clin Pharmacol* 1986; 22: 346–50.

Immunosuppressants. For a report of quinine decreasing plasma concentrations of *ciclosporin*, see p. 1957.1.

Tobacco smoking. A single-dose study in healthy subjects has suggested that blood concentrations of quinine are lower in heavy smokers than in non-smokers, potentially impairing efficacy.[1]

1. Wanwimolruk S, *et al.* Cigarette smoking enhances the elimination of quinine. *Br J Clin Pharmacol* 1993; 36: 610–14.

Pharmacokinetics

The pharmacokinetics of quinine are altered significantly by malaria infection, the major effects being reductions in both its apparent volume of distribution and its clearance.

Quinine is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations in the circulation occur about 1 to 3 hours after oral doses of the sulfate or bisulfate. Plasma protein binding is about 70% in healthy subjects and rises to 90% or more in patients with malaria. Quinine is widely distributed throughout the body. Concentrations attained in the CSF of patients with cerebral malaria have been reported to be about 2 to 7% of those in the plasma.

Quinine is extensively metabolised in the liver and rapidly excreted mainly in the urine. Estimates of the proportion of unchanged quinine excreted in the urine vary from less than 5 to 20%. Excretion is increased in acid urine. The elimination half-life is about 11 hours in healthy subjects but may be prolonged in patients with malaria. Small amounts of quinine also appear in the bile and saliva.

Quinine crosses the placenta and is distributed into breast milk (see Breast Feeding, p. 667.3).

References.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; 10: 187–215.
2. Supanaranond W, *et al.* Disposition of oral quinine in acute falciparum malaria. *Eur J Clin Pharmacol* 1991; 40: 49–52.
3. Wanwimolruk S, *et al.* Pharmacokinetics of quinine in young and elderly subjects. *Trans R Soc Trop Med Hyg* 1991; 85: 714–17.
4. Dyer JR, *et al.* The pharmacokinetics and pharmacodynamics of quinine in the diabetic and non-diabetic elderly. *Br J Clin Pharmacol* 1994; 38: 205–12.
5. Sowunmi A, Salako LA. Effect of dose size on the pharmacokinetics of orally administered quinine. *Eur J Clin Pharmacol* 1996; 49: 383–6.
6. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine: clinical implications. *Clin Pharmacokinet* 1996; 30: 263–99.
7. Boele van Hensbroek M, *et al.* Quinine pharmacokinetics in young children with severe malaria. *Am J Trop Med Hyg* 1996; 54: 237–42.
8. Zhang H, *et al.* Evidence for involvement of human CYP3A in the 3-hydroxylation of quinine. *Br J Clin Pharmacol* 1997; 43: 245–52.
9. Viriyayudhakorn S, *et al.* Pharmacokinetics of quinine in obesity. *Trans R Soc Trop Med Hyg* 2000; 94: 425–8.
10. Pukrittayakamee S, *et al.* Quinine pharmacokinetic-pharmacodynamic relationships in uncomplicated falciparum malaria. *Antimicrob Agents Chemother* 2003; 47: 3458–63.
11. Abdelrahim IL *et al.* Pharmacokinetics of quinine and its metabolites in pregnant Sudanese women with uncomplicated Plasmodium falciparum malaria. *J Clin Pharm Ther* 2007; 32: 15–9.
12. Mirghani RA, *et al.* Effects of *Plasmodium falciparum* infection on the pharmacokinetics of quinine and its metabolites in pregnant and non-pregnant Sudanese women. *Eur J Clin Pharmacol* 2010; 66: 1229–34.

Administration in liver disease. Reduced clearance of quinine and prolonged elimination half-life have been reported in patients with acute hepatitis B given a single intravenous dose.[1] The results suggested that quinine accumulation after multiple doses could be greater in patients with hepatitis, even once hepatic function had returned to normal. In another study[2] patients with moderate chronic liver disease were given quinine orally the half-life was prolonged but total clearance was not affected.

1. Karbwang J, *et al.* The pharmacokinetics of quinine in patients with hepatitis. *Br J Clin Pharmacol* 1993; 35: 444–6.
2. Auprayoon P, *et al.* Pharmacokinetics of quinine in chronic liver disease. *Br J Clin Pharmacol* 1995; 40: 494–7.

Administration in renal impairment. As urinary clearance comprises only 20% of total clearance of quinine, it appears that high plasma concentrations reported in patients with severe falciparum malaria and acute renal failure may be related more to the severity of the malaria, and associated pharmacokinetic changes, rather than to any reduction in the glomerular filtration rate.[1]

Continuous veno-venous high-volume haemofiltration appeared to have little effect on the pharmacokinetics of quinine,[2] suggesting that no dose supplementation would be needed in anuric patients undergoing this procedure. There were significant changes in the pharmacokinetics of quinine in 6 patients with chronic renal failure after a single oral dose.[3] The changes included a prolonged half-life, but there was no clear relationship between severity of renal failure and the degree of impairment of quinine clearance.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; 10: 187–215.
2. Lioter J, *et al.* Quinine clearance during continuous veno-venous high-volume hemofiltration. *Intensive Care Med* 2008; 34: 1925–6.
3. Rimchala P, *et al.* Pharmacokinetics of quinine in patients with chronic renal failure. *Eur J Clin Pharmacol* 1996; 49: 497–501.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Circonyl; *Austral.*: Biquinate†; Quinate; Quinbisul; Quinsul†; *Braz.*: Palukin†; *Denm.*: Kinin; *Fr.*: Quinoforme†; Surquina; *Ger.*: Limptar N; *Gr.*: Kinin; *Hong Kong*: Q200†; Q300†; Quinbisul†; *India*: Cinkona; Falcimax-Q; Foquin; Kwinil; Malgo; Mosgard; Nine; Quinarsol; Quininga; *Indon.*: Euchinin; *Malaysia*: Malakin; *NZ*: Q200; Q300; *Philipp.*: Malarin; *Swed.*: Kinin; *Thai.*: Alquinn; Genin; *USA*: Qualaquin.

Multi-ingredient Preparations. *Austria*: Iromin-Chinin-C†; Seltoc†; *Braz.*: Monotrean B6; Monotrean; *Fin.*: Crampiton; Pelapamil†; *Fr.*: Hexaquine; Okimus; Quinimax; *Ger.*: Togal Classic†; *Hung.*: Nicobrevin; *Irl.*: Anadin; Nicobrevin†; *Neth.*: Aflukin C†; *NZ*: Nicobrevin; *Rus.*: Analgin-Chinin (Анальгин-Хинин); *S.Afr.*: Ilvico†; *Spain*: Brota Rectal Balsamico†; *UK*: Nicobrevin.

Homoeopathic Preparations. *Canad.*: Pertudoron 1†; *Fr.*: Selenium Complexe No 99; *Ger.*: Otio-cyl Ho-Len-Complex; Otio-cyl Ho-Len-Complex.

Pharmacopoeial Preparations

BP 2014: Quinine Bisulphate Tablets; Quinine Dihydrochloride Infusion; Quinine Sulphate Tablets;
USP 36: Quinine Sulfate Capsules; Quinine Sulfate Tablets.

Tafenoquine *(BAN, rINN)*

SB-252263; Tafenoquin; Tafenoquina; Tafénoquine; Tafenoquinum; WR-238605; Тафенохин.

(±)-8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[(α,α,α-trifluoro-*m*-tolyl)oxy]quinoline; (*RS*)-N^4-[2,6-Dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-8-yl]pentane-1,4-diamine.

$C_{24}H_{28}F_3N_3O_3$=463.5

CAS — 106635-80-7.

UNII — 262P8GS9L9.

Profile

Tafenoquine is an 8-aminoquinoline antimalarial and more lipophilic derivative of primaquine. It acts as a tissue schizontocide and is under investigation as the succinate for the radical cure and prevention of relapse in vivax malaria. It may also have a role in the prophylaxis of falciparum malaria. Although it has been suggested to be better tolerated than primaquine, tafenoquine still carries a risk of haemolysis in G6PD-deficient patients.

References.

1. Walsh DS, *et al.* Randomized dose-ranging study of the safety and efficacy of WR 238605 (tafenoquine) in the prevention of relapse of Plasmodium vivax malaria in Thailand. *J Infect Dis* 1999; 180: 1282–7.
2. Lell B, *et al.* Malaria chemoprophylaxis with tafenoquine: a randomised study. *Lancet* 2000; 355: 2041–5.
3. Shanks GD, *et al.* A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. *Clin Infect Dis* 2001; 33: 1968–74.
4. Nasveld P, *et al.* Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. *Trans R Soc Trop Med Hyg* 2002; 96: 683–4.

5. Hale BR, *et al.* A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against Plasmodium falciparum. *Clin Infect Dis* 2003; **36**: 541–9.
6. Walsh DS, *et al.* Randomized trial of 3-dose regimens of tafenoquine (WR238605) versus low-dose primaquine for preventing Plasmodium vivax malaria relapse. *Clin Infect Dis* 2004; **39**: 1095–1103.
7. Walsh DS, *et al.* Efficacy of monthly tafenoquine for prophylaxis of Plasmodium vivax and multidrug-resistant P. falciparum malaria. *J Infect Dis* 2004; **190**: 1456–63.
8. Charles BG, *et al.* Population pharmacokinetics of tafenoquine during malaria prophylaxis in healthy subjects. *Antimicrob Agents Chemother* 2007; **51**: 2709–15.
9. Elmes NJ, *et al.* The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of Plasmodium vivax malaria in the Southwest Pacific. *Trans R Soc Trop Med Hyg* 2008; **102**: 1095–101.
10. Leary KJ, *et al.* A randomized, double-blind, safety and tolerability study to assess the ophthalmic and renal effects of tafenoquine 200 mg weekly versus placebo for 6 months in healthy volunteers. *Am J Trop Med Hyg* 2009; **81**: 356–62.
11. Nasveld PE, *et al.* Tafenoquine Study Team. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrob Agents Chemother* 2010; **54**: 792–8.

The symbol † denotes a preparation no longer actively marketed

Antimigraine Drugs

Cluster headache, p. 670
Medication-overuse headache, p. 670
Migraine, p. 670
Post-dural puncture headache, p. 671
Tension-type headache, p. 671

This chapter reviews the management of headache, in particular migraine and cluster headache, and the drugs used mainly for their treatment. The mechanisms of head pain or headache are not fully understood but may involve neurovascular changes (as in migraine and cluster headache), muscle contraction (tension headache), nerve lesions (neuralgias), direct head injury, infection (meningitis), or referred pain (sinusitis, toothache, eye disorders). Headache is also an adverse effect of many drugs including, paradoxically, those used to treat it. The International Headache Society has published guidelines to aid the diagnosis of the various headache types. Patients may have more than one headache disorder simultaneously and require separate treatment for each.

References.

1. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; **24** (suppl 1): 9–160. Also available at: http://ihs-classification.org/en/01_einleitung/ (accessed 14/06/11)

Cluster headache

Cluster headache (migrainous neuralgia, histaminic cephalalgia, Horton's syndrome) is of unknown aetiology but may be neurovascular in origin.[1-5] Patients have one or more short-lived attacks of intense unilateral head pain, usually at the same time of day (often at night). These are associated with autonomic symptoms such as conjunctival injection or lachrymation, miosis or ptosis, nasal congestion or rhinorrhoea, forehead or facial sweating, and eyelid oedema. Restlessness during the attacks is characteristic. The period during which attacks occur is called a cluster period; it may last several weeks or months. In the typical episodic form of cluster headache, cluster periods are followed by periods of remission lasting for months or years but in the more rare chronic form, patients may have cluster periods lasting for more than a year, or with short periods of remission in between. Substances such as alcohol, histamine, or glyceryl trinitrate can precipitate headache attacks during cluster periods, but not during periods of remission. There is speculation that sleep-disordered breathing[6] and increased body heat[7] may also trigger cluster headaches.

The **treatment** of individual acute attacks during a cluster period is difficult because the headache is short-lived and oral analgesics are unlikely to be absorbed fast enough to produce much benefit.[1,3,4] Inhalation of 100% oxygen should be considered in all patients.[8-11] It is rapid and effective in aborting attacks, but has practical difficulties. Some consider subcutaneous sumatriptan to be the acute therapy of choice in cluster attacks;[4,5,8-13] intranasal sumatriptan or zolmitriptan are possible alternatives, although less effective.[1,4,8,12] Oral zolmitriptan may be considered for patients who cannot tolerate subcutaneous or intranasal triptans and oxygen, or who prefer oral medication.[4] Intranasal instillation of lidocaine may be considered in patients who have still not responded.[8-11] It has been reported to be of some benefit but most patients do not obtain complete pain relief.[1,3,4,9] Intranasal dihydroergotamine[1,4] and inhaled ergotamine have also been used to treat acute attacks; injectable dihydroergotamine has usually been reserved for emergency settings.[4]

Since individual attacks are difficult to treat it is probably more effective to manage cluster headache by **prophylaxis** once a cluster period has started. The changing or combining of prophylactic treatment has also been advised by some.[12] If patients do not respond to the maximum possible dose of a drug within a week, Verapamil is usually considered the preventive therapy of choice,[1,4,8-13] particularly in patients with chronic long-lasting cluster periods.[5] Lithium may also be useful for the episodic or chronic form of the disorder.[9-13] Despite a lack of studies, oral corticosteroids are considered by some to be effective in the prophylaxis of cluster headache,[8,10,12] including those with short-lasting cluster periods (less than 2 months).[5] Methysergide, pizotifen, and valproate have also been tried.[1,3,5,9-11] Ergotamine may be used rectally in the short-term management of episodic cluster headache, if attacks are predictable;[10,12] it should not be used for prolonged periods. Other drugs under investigation include gabapentin, melatonin, and topiramate.[4,9-11,13]

Paroxysmal hemicrania is a rare variant of cluster headache and differs mainly in the high frequency and shorter duration of individual attacks. One of its features, which may be diagnostic, is its invariable response to indometacin.[10]

1. Dodick DW, Capobianco DJ. Treatment and management of cluster headache. *Curr Pain Headache Rep* 2001; **5**: 83–91.
2. Zakrzewska JM. Cluster headache: review of literature. *Br J Oral Maxillofac Surg* 2001; **39**: 103–13.
3. Ekbom K, Hardebo JE. Cluster headache: aetiology, diagnosis and management. *Drugs* 2002; **62**: 61–9.
4. Matharu MS, *et al*. Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003; **63**: 1637–77.
5. May A. Cluster headache: pathogenesis, diagnosis, and management. *Lancet* 2005; **366**: 843–55.
6. Chervin RD, *et al*. Sleep disordered breathing in patients with cluster headache. *Neurology* 2000; **54**: 2302–6.
7. Blau JN, Engel HO. A new cluster headache precipitant: increased body heat. *Lancet* 1999; **354**: 1001–2.
8. Scottish Intercollegiate Guidelines Network. Diagnosis and management of headache in adults (issued November 2008). Available at: http://www.sign.ac.uk/pdf/sign107.pdf (accessed 26/01/09)
9. Halker R, *et al*. Cluster headache: diagnosis and treatment. *Semin Neurol* 2010; **30**: 175–85.
10. Evers S, *et al*. Cluster headache and other trigemino-autonomic cephalgias. In: Gilhus NE, *et al*., eds. *European Handbook of Neurological Management: volume 1*. 2nd ed. Chichester: Wiley-Blackwell, 2011: 179–90. Also available at: http://www.efns.org/fileadmin/user_upload/guidline_papers/EFNS_guideline_2011_Cluster_headache_and_other_trigemino-autonomic_cephalgias.pdf (accessed 14/06/11)
11. Ashkenazi A, Schwedt T. Cluster headache—acute and prophylactic therapy. *Headache* 2011; **51**: 272–86.
12. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (issued 18th January, 2007; 1st revision, September 2010). Available at: http://217.174.249.183/upload/NS_BASH/2010_BASH_Guidelines.pdf (accessed 01/12/10)
13. Francis GJ, *et al*. Acute and preventive pharmacologic treatment of cluster headache. *Neurology* 2010; **75**: 463–73.

Medication-overuse headache

Overuse of drugs such as ergotamine, triptans, and analgesics (including opioids and combination preparations containing caffeine or butalbital) to treat headache or migraine can lead to dependence and paradoxical chronic daily headache in headache-prone patients.[1-5] Such headaches do not appear to occur with regular use of analgesics to treat other disorders except occasionally in patients with a history of migraine.[1] Medication-overuse headaches, also referred to as rebound, analgesic abuse, or analgesic-induced headaches, can be difficult to treat and are relieved by withdrawal of the offending drug, but the primary headache may still persist and revert to its previous pattern of occurrence. Furthermore, stopping abruptly can exacerbate headache and produce other symptoms of withdrawal. This may then lead the patient to resume treatment to relieve the headache thereby setting up a vicious circle.

Options for outpatient **treatment** include either abrupt or gradual withdrawal of the overused drug. Abrupt withdrawal has been suggested if the headache has been caused by the use of simple analgesics, ergot derivatives, or triptans, and gradual withdrawal if it is due to opioids.[6,7] Aggravation of symptoms may be managed by the use of naproxen, prednisolone, or amitriptyline.[6,7] Substitution with long-acting NSAID or intramuscular dihydroergotamine has been tried in withdrawal from ergotamine or analgesics;[8,9] However, withdrawal symptoms may persist for up to 2 weeks and detoxification from ergotamine or analgesics may require hospitalisation; intravenous metoclopramide and repetitive intravenous dihydroergotamine may be required to control nausea and vomiting and intractable headache, respectively.[8] Withdrawal from triptans has been reported to be of shorter duration with no intensive withdrawal symptoms; however, triptan overuse produces headaches at a faster rate and at lower dosages compared with ergotamine and analgesics, and is associated with an increase in migraine attack frequency.[1]

General advice on the **prevention** of medication-overuse headache has included limiting the frequency of use of such drugs,[1,3,4,8] and starting prophylactic therapy in migraine patients having more than 2 headache days a week.[3]

1. Limmroth V, Katsarava Z. Medication overuse headache. *Curr Opin Neurol* 2004; **17**: 301–6.
2. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; **24** (suppl 1): 9–160. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/cha.2004.24.issue-s1/issuetoc (accessed 12/08/10)
3. Smith TR, Stoneman J. Medication overuse headache from antimigraine therapy: clinical features, pathogenesis and management. *Drugs* 2004; **64**: 2503–14.
4. Anonymous. Management of medication overuse headache. *Drug Ther Bull* 2010; **48**: 2–6.
5. Bigal ME, Lipton RB. Excessive acute migraine medication use and migraine progression. *Neurology* 2008; **71**: 1821–8.
6. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (issued 18th January, 2007; 1st revision, September 2010). Available at: http://217.174.249.183/upload/NS_BASH/2010_BASH_Guidelines.pdf (accessed 01/12/10)
7. Scottish Intercollegiate Guidelines Network. Diagnosis and management of headache in adults (issued November 2008). Available at: http://www.sign.ac.uk/pdf/sign107.pdf (accessed 26/01/09)
8. Silberstein SD, Young WB. Analgesic rebound headache. *Drug Safety* 1995; **13**: 133–44.
9. Zed PJ, *et al*. Medication-induced headache: overview and systematic review of therapeutic approaches. *Ann Pharmacother* 1999; **33**: 61–7.

Migraine

Migraine is characterised by recurrent attacks of headache that typically last 4 to 72 hours. Attacks persisting for longer than 72 hours are referred to as status migrainosus. The headache is usually a unilateral pulsating pain that is aggravated by movement and is usually of sufficient severity to disturb or prevent daily activities. It is frequently accompanied by nausea, vomiting, or other gastrointestinal disturbances and there may be photophobia and phonophobia. Migraine with aura (classic migraine) is characterised by an aura consisting of visual or sensory symptoms that lasts less than an hour. The headache usually follows the aura directly, or within 1 hour, but may begin simultaneously with the aura. In addition, aura can occur without headache. Migraine without aura (common migraine) is the more common form occurring in about 75% of patients with migraine. Premonitory symptoms may occur before a migraine attack (with or without aura). Familial hemiplegic migraine is a rare syndrome in which migraine with aura may be preceded or accompanied by dysphasia, confusion, and hemiparesis. Basilar-type migraine is another rare form of migraine with aura in which there may be disturbances of the brain stem or occipital lobes accompanied by symptoms such as decreased level of consciousness, vertigo, ataxia, dysarthria, and diplopia.

Migraine is described as a neurovascular headache. Traditionally, intracranial vasoconstriction was considered responsible for the aura and extracranial vasodilatation for the headache. However, it appears that vascular events may be secondary to neuropathic changes and the liberation of vasoactive substances including serotonin (5-HT), catecholamines, histamine, kinins, neuropeptides such as calcitonin gene-related peptide (CGRP), and prostaglandins.

There are several factors that may precipitate migraine attacks. These include anxiety, physical and emotional stress, a change in sleep pattern, bright lights, fasting, some foods, and menstruation. Menstrual migraine is characterised by attacks without aura which are most likely to occur within 2 days of the start of menstruation. Migraine may also be precipitated by drugs including combined oral contraceptives and oestrogens, and glyceryl trinitrate. The frequency of migraine attacks can be reduced if such precipitating factors can be identified and avoided. Quiet, darkness, and sleep can ease an attack, with sleep heralding recovery.

The drug **treatment** of migraine may be tailored to the severity of individual disease from the outset (stratified care) or may begin with simple analgesics and be subsequently adjusted according to response (step strategy); in the UK stepped care seems to be increasingly preferred. Acute treatment of menstrual migraine is the same as for migraine however, as menstrual migraine may be of longer duration treatment may need to be repeated over several consecutive days.

Simple **analgesics** (paracetamol or NSAIDs including aspirin) are effective if taken at the earliest signs of an attack; weak opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations. However, the frequent use of analgesics is best avoided to decrease the risk of medication-overuse headaches. Other drugs used with analgesics in antimigraine preparations have included caffeine and the sympathomimetic vasoconstrictor isometheptene. Dispersible and effervescent analgesic preparations are preferable because of their more rapid absorption.

If the initial treatment of migraine is delayed, absorption of oral drugs may be compromised by development of gastric stasis and nausea and vomiting. The addition of **antiemetics** such as buclizine and cyclizine, and the **prokinetic** drugs metoclopramide and domperidone is recommended if needed; they are often included in compound antimigraine preparations. Prokinetic drugs also

have the advantage of promoting gastric emptying and normal peristalsis. If nausea and vomiting are prominent rectal administration may be necessary.

Attacks not responding to simple analgesics such as NSAIDs may be treated with specific antimigraine drugs such as the selective serotonin (5-HT_1) agonists (e.g. sumatriptan) or the ergot derivatives ergotamine and dihydroergotamine; poor absorption and adverse effects limit the use of ergot derivatives and selective serotonin (5-HT_1) agonists are preferred.

Serotonin (5-HT_1) agonists are highly effective in relieving the pain and nausea of a migraine attack. There are a number of **triptans** available; patient characteristics and preferences vary in response to use and can sometimes be unpredictable. Some patients experience recurrence of the headache within 24 to 48 hours and often respond to a second dose. Finding the best triptan to suit the individual patient may involve trial and error; a change in formulation should also be considered. Triptans should not be used in patients with major risk factors for, or suffering from, cardiovascular disease. The main concern with all triptans is their potential for coronary vasoconstriction and no triptan appears to be safer than the others. Medication-overuse headaches have also been noted with triptan use.

Ergot derivatives are rarely needed now in the treatment of migraine. If **ergotamine** is used it should be given at the first warning of an attack; the earlier it is given, the more effective the treatment. Since its oral bioavailability is poor and may be reduced further during a migraine attack, ergotamine has sometimes been given in sublingual or rectal preparations. Ergotamine can also exacerbate nausea and vomiting; metoclopramide or domperidone, or in severe cases the phenothiazines chlorpromazine or prochlorperazine, may be given. Dihydroergotamine may be of use if parenteral treatment is required; it can also be given intranasally but there is less experience with this route. Patients who fail to respond to monotherapy may find combination treatment, such as a simple analgesic with a triptan, helpful particularly in prolonged attacks.

Patients who rapidly develop severe migraine may be given **parenteral** dihydroergotamine or sumatriptan. Some consider parenteral metoclopramide to be suitable first-line treatment. Intramuscular diclofenac has also been recommended. If there is no response to these drugs, dopamine antagonists, such as chlorpromazine or prochlorperazine, given parenterally may be effective in relieving the pain of acute migraine attacks. Prolonged attacks (status migrainosus) may require intravenous administration of dihydroergotamine with metoclopramide. The NSAIDs naproxen or diclofenac are better than specific antimigraine drugs for long duration attacks that are really migraine with a superseding tension-type headache.

Other drugs that may be given alone or in combination include corticosteroids or pethidine. Lidocaine has been given intravenously for the emergency treatment of migraine; intranasal lidocaine has also been tried. The opioid agonist-antagonist butorphanol, given by nasal spray, has been advocated, but its place in therapy, if any, remains to be established. Other drugs that have been investigated include CGRP antagonists; intravenous valproic acid has also shown promise in aborting acute attacks.

Guidelines have been issued for the treatment of migraine in **children and adolescents**. For acute treatment, ibuprofen and paracetamol were found to be effective in children aged 6 years and over; sumatriptan nasal spray should be considered in those aged 12 years and over.

Prophylactic treatment should be considered for patients in whom abortive measures are ineffective or migraine attacks occur frequently, or for those with less frequent but severe or prolonged attacks. Some recommend prophylaxis if attacks occur more often than once or twice a month. Prophylaxis can reduce the severity and/or frequency of attacks but does not eliminate them completely and patients still need additional abortive or symptomatic treatment. Drugs suggested for prophylaxis have a range of actions which reflects uncertainty over the pathogenesis of migraine. It is important to give prophylactic drugs for an adequate period before assessing their efficacy; a general guide of 6 to 8 weeks is advisable. Once an optimum effect has been achieved the need for continuing prophylaxis should be reviewed at intervals of about 3 to 6 months. Treatment is best withdrawn gradually, over 2 to 3 weeks.

The main prophylactic drugs are **beta blockers**, tricyclic **antidepressants**, and the **antiepileptics**, topiramate and valproate. Propranolol is considered by many to be the prophylactic drug of choice. Lethargy appears to be the most common adverse effect. Other beta blockers reported to be effective are those that, like propranolol, possess no intrinsic sympathomimetic activity; these include atenolol, metoprolol, nadolol, and timolol. The potential for beta blockers to interact with some serotonin (5-HT_1) agonists and ergotamine should be borne in mind. Tricyclic antidepressants, particularly amitriptyline, given in gradually increasing doses at night are useful for preventing migraine, especially in patients who also have depression or tension-type headache, although antimuscarinic adverse effects may occur. Valproate is also used for preventing migraine. Nausea appears to be the most common adverse effect. Topiramate is the main alternative to valproate. Weight loss and paraesthesia are commonly reported adverse effects. Topiramate or valproate are particularly useful in patients who also have epilepsy or bipolar disorder. Gabapentin may also be used for the prophylaxis of migraine.

Other drugs have been used for the prophylaxis of migraine. Of the drugs with calcium-channel blocking activity, flunarizine appears to be effective, and has been suggested for use in children, and verapamil may be useful, but evidence for the efficacy of other calcium-channel blockers such as diltiazem, nifedipine, or nimodipine is less convincing; NSAIDs may be worth trying. Pizotifen, an antihistamine and serotonin antagonist, has been widely used but evidence for its efficacy is limited; it may be tried in children. The use of methysergide, a potent serotonin antagonist, has declined because of serious adverse effects, in particular retroperitoneal fibrosis. MAOIs such as phenelzine have been used occasionally but are best reserved for severe cases refractory to other forms of prophylactic treatment. Cyproheptadine, an antihistamine and serotonin antagonist, has been used for migraine prophylaxis, particularly in children. Botulinum A toxin is used for the prophylaxis of headaches in adults with chronic migraine. Other drugs used for the prophylaxis of migraine have included butterbur, clonidine, cyclandelate, indoramin, feverfew, and the ergot derivative metergoline. Positive results have been seen with magnesium and riboflavin. Investigated drugs which have shown potential for prevention of migraine attacks include: baclofen, candesartan, lisinopril, montelukast, and venlafaxine. Despite promising initial results, there is limited evidence to support the use of SSRIs.

References.

1. Ferrari MD. Migraine. *Lancet* 1998; 351: 1043–51.
2. Anonymous. Managing migraine. *Drug Ther Bull* 1998; 36: 41–4.
3. Diener H-C, *et al.* A practical guide to the management and prevention of migraine. *Drugs* 1998; 56: 811–24.
4. Bartleson JD. Treatment of migraine headaches. *Mayo Clin Proc* 1999; 74: 702–8.
5. Tfelt-Hansen P, *et al.* Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs* 2000; 60: 1259–87.
6. Lipton RB, *et al.* Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) study, a randomised trial. *JAMA* 2000; 284: 2599–2605.
7. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review)— report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000; 55: 754–62. Correction. *Ibid.* 2001; 56: 142. Also available at http://www.neurology.org/cgi/reprint/55/6/754 (accessed 31/05/06)
8. Ferrari MD, *et al.* Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; 358: 1668–75.
9. Rapaport AM, Tepper SJ. Triptans are all different. *Arch Neurol* 2001; 58: 1479–80.
10. Jamieson DG. The safety of triptans in the treatment of patients with migraine. *Am J Med* 2002; 112: 135–40.
11. Goadsby PJ, *et al.* Migraine—current understanding and treatment. *N Engl J Med* 2002; 346: 257–70.
12. Cady R, Dodick DW. Diagnosis and treatment of migraine. *Mayo Clin Proc* 2002; 77: 255–61.
13. Steiner TJ, Fontebasso M. Headache. *BMJ* 2002; 325: 881–6.
14. Snow V, *et al.* Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med* 2002; 137: 840–9.
15. Silberstein SD. Migraine. *Lancet* 2004; 363: 381–91.
16. Anonymous. Managing migraine in children. *Drug Ther Bull* 2004; 42: 25–8.
17. Colman I, *et al.* Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* 2004; 329: 1369–72.
18. Lewis D, *et al.* Practice parameter: pharmacological treatment of migraine headache in children and adolescents—report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology* 2004; 63: 2215–24. Also available at: http://www.neurology.org/cgi/reprint/63/12/2215.pdf (accessed 11/04/05)
19. Chronicle E, Mulleners W. Anticonvulsant drugs for migraine prophylaxis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 15/05/06).
20. Moja L, *et al.* Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 27/01/09).
21. Goadsby PJ. Recent advances in the diagnosis and management of migraine. *BMJ* 2006; 332: 25–9.
22. Tozer BS, *et al.* Prevention of migraine in women throughout the life span. *Mayo Clin Proc* 2006; 81: 1086–91.
23. Biland LS, *et al.* Pediatric migraine: pharmacologic agents for prophylaxis. *Ann Pharmacother* 2007; 41: 1181–90.
24. Suthisisang C, *et al.* Efficacy of low-dose ibuprofen in acute migraine treatment: systematic review and meta-analysis. *Ann Pharmacother* 2007; 41: 1782–91.
25. Colman I, *et al.* Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. *BMJ* 2008; 336: 1359–61.
26. Goadsby PJ, *et al.* Migraine in pregnancy. *BMJ* 2008; 336: 1502–4.
27. Scottish Intercollegiate Guidelines Network. Diagnosis and management of headache in adults (issued November 2008). Available at: http://www.sign.ac.uk/pdf/sign107.pdf (accessed 26/01/09)
28. Pringsheim T, *et al.* Acute treatment and prevention of menstrually related migraine headache: evidence-based review. *Neurology* 2008; 70: 1555–63.
29. Evers S, *et al.* European Federation of Neurological Societies. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. *Eur J Neurol* 2009; 16: 968–81. Also available at: http://www.efns.org/fileadmin/user_upload/guidline_papers/EFNS_guideline_2009_drug_treatment_of_migraine.pdf (accessed 28/07/10)
30. Loder E. Triptan therapy in migraine. *N Engl J Med* 2010; 363: 63–70.
31. MacGregor EA. Prevention and treatment of menstrual migraine. *Drugs* 2010; 70: 1799–1818.
32. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (issued 18th January, 2007; 1st revision, September 2010). Available at: http://217.174.249.183/upload/NS_BASH/2010_BASH_Guidelines.pdf (accessed 01/12/10)
33. Penstermacher N, *et al.* Pharmacological prevention of migraine. *BMJ* 2011; 342: 540–3.

Post-dural puncture headache

For the management of headache associated with lumbar puncture or spinal anaesthesia, see Post-dural Puncture Headache under Local Anaesthetics, p. 1983.1.

Tension-type headache

Tension-type headaches, also referred to as muscle-contraction headaches, are probably the commonest form of headache. They are characterised by bilateral pain, which unlike migraine is continuous and non-pulsatile. The pain is often described by the patient as feeling like a tight band pressed around the head. Headaches of this type may be precipitated by many factors including psychosocial stress or muscular stress. Many patients also have associated symptoms of anxiety or depression. Tension-type headaches and migraine often co-exist and may then be referred to as combination or mixed headaches. Some patients only experience isolated acute attacks of tension-type headache (episodic tension-type headache), but others may develop chronic tension-type headache which is difficult to treat.

Treatment is aimed at removing the underlying causes where these can be identified. Simple massage may help if muscle contraction is a prominent component of the pain. Non-opioid analgesics, such as aspirin or other NSAIDs and paracetamol, may be tried for individual acute attacks of headache, but analgesic overuse must be avoided as this can lead to chronic headache resistant to other measures (see Medication-overuse Headache, p. 670.2). Opioids alone or in combination preparations with other analgesics should also be avoided. Hypnotics or sedatives have sometimes been used in combination preparations with analgesics in the management of tension-type headache that disrupts sleep but, because of the potential for abuse, they should be avoided in chronic headaches. Muscle relaxants appear to have little place in the management of tension-type headache; although some patients may respond, results are generally disappointing. Other drugs that have been tried include valproate and botulinum A toxin. **Prophylaxis** is preferable to regular short-term use of analgesics in controlling chronic tension-type headache. Tricyclic antidepressants, particularly amitriptyline, are generally considered as first choice, although benefit is rarely complete. The mode of action is unclear and appears to be independent of any antidepressant action. In most cases, improvement is seen with low doses, but full antidepressant doses are necessary in the presence of underlying depression. Addition of a beta blocker such as propranolol may sometimes be of benefit for patients with some migraine features. The antiepileptic topiramate has also been tried with some success.

References.

1. Silberstein SD. Tension-type and chronic daily headache. *Neurology* 1993; 43: 1644–9.
2. Kumar KL, Cooney TG. Headaches. *Med Clin North Am* 1995; 79: 261–86.
3. Anonymous. Management of tension-type headache. *Drug Ther Bull* 1999; 37: 41–4.
4. Lenaerts ME. Pharmacoprophylaxis of tension-type headache. *Curr Pain Headache Rep* 2005; 9: 442–7.
5. Schulte-Mattler WJ, Martinez-Castrillo JC. Botulinum toxin therapy of migraine and tension-type headache: comparing different botulinum toxin preparations. *Eur J Neurol* 2006; 13 (suppl 1): 51–4.
6. Anttila P. Tension-type headache in childhood and adolescence. *Lancet Neurol* 2006; 5: 268–74.
7. Mathew NT. Tension-type headache. *Curr Neurol Neurosci Rep* 2006; 6: 100–105.
8. Loder E, Rizzoli P. Tension-type headache. *BMJ* 2008; 336: 88–92.
9. Scottish Intercollegiate Guidelines Network. Diagnosis and management of headache in adults (issued November 2008). Available at: http://www.sign.ac.uk/pdf/sign107.pdf (accessed 26/01/09)
10. Bendtsen L, *et al.* European Federation of Neurological Societies. EFNS guideline on the treatment of tension-type headache — report of an EFNS task force. *Eur J Neurol* 2010; 17: 1318–25. Also available at: http://www.efns.org/fileadmin/user_upload/guidline_papers/EFNS_guideline_2010_treatment_of_tension-type_headache.pdf (accessed 15/12/10)
11. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (issued 18th January 2007; 1st revision, September 2010). Available at: http://217.174.249.183/upload/NS_BASH/2010_BASH_Guidelines.pdf (accessed 01/12/10)

Almotriptan Malate *(BANM, USAN, rINNM)*

Almotriptán, Malate d'; Almotriptán, malato de; Almotriptani Malas; LAS-31416 (almotriptan); Malato de almotriptán; PNU-180638E; Альмотриптана Малат.

1-[(3-[2-(Dimethylamino)ethyl]indol-5-yl]methyl)sulfonyl] pyrrolidine malate (1:1).

$C_{17}H_{25}N_3O_2S,C_4H_6O_5$=469.6

CAS — 154323-57-6 (almotriptan); 181183-52-8 (almotriptan malate).

ATC — N02CC05.

ATC Vet — QN02CC05.

UNII — PJP312605E.

Uses and Administration

Almotriptan malate is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Almotriptan is given orally as the malate, and doses are expressed in terms of the base; almotriptan malate 8.75 mg is equivalent to about 6.25 mg of almotriptan.

The recommended dose of almotriptan is 12.5 mg in the UK and 6.25 or 12.5 mg in the USA. If this is ineffective, a second dose should not be taken for the same attack. If symptoms recur within 24 hours after an initial response, a second dose may be taken after an interval of at least 2 hours. No more than 2 doses should be taken in a 24-hour period. For doses in hepatic and renal impairment see below.

References.
1. Holm KJ, Spencer CM. Almotriptan. *CNS Drugs* 1999; 11: 159–64.
2. Keam SJ, *et al.* Almotriptan: a review of its use in migraine. *Drugs* 2002; 62: 387–414.

Administration in hepatic or renal impairment. In patients with hepatic or severe renal impairment, no more than 12.5 mg of oral almotriptan should be taken in 24 hours; a starting dose of 6.25 mg may be used. No dose adjustment is needed in patients with mild to moderate renal impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Mathew NT. Efficacy and tolerability of almotriptan in controlled clinical trials. *Eur Neurol* 2005; 53 (suppl 1): 29–33.
2. Pascual J. Efficacy and tolerability of almotriptan in postmarketing surveillance studies. *Eur Neurol* 2005; 53 (suppl 1): 34–40.
3. Dahlof CG, *et al.* Efficacy, speed of action and tolerability of almotriptan in the acute treatment of migraine: pooled individual patient data from four randomized, double-blind, placebo-controlled clinical trials. *Cephalalgia* 2006; 26: 400–8.
4. Chen LC, Ashcroft DM. Meta-analysis examining the efficacy and safety of almotriptan in the acute treatment of migraine. *Headache* 2007; 47: 1169–77.
5. Antonaci F, *et al.* Almotriptan for the treatment of acute migraine: a review of early intervention trials. *Expert Rev Neurother* 2010; 10: 351–64.
6. Pascual J, *et al.* Almotriptan: a review of 10 years' clinical experience. *Expert Rev Neurother* 2010; 10: 1505–17.
7. Lewis DW. Almotriptan for the acute treatment of adolescent migraine. *Expert Opin Pharmacother* 2010; 11: 2431–6.
8. Bussone G, *et al.* Almotriptan for menstrually related migraine. *Expert Opin Pharmacother* 2011; 12: 1933–43.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

Almotriptan should be given with caution to patients with hepatic impairment or severe renal impairment.

Patients with hypersensitivity to sulfonamides may theoretically show a similar reaction to almotriptan. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.)

Incidence of adverse effects. Results from studies involving more than 2500 patients with migraine suggested that adverse effects of almotriptan were infrequent.[1] The commonest adverse effects reported were dizziness, nausea and vomiting, headache, paraesthesia, fatigue, and drowsiness, all of which occurred in less than 3% of patients. The incidence of chest symptoms was 0.2% in 2 large phase III studies.

1. Dodick DW. Oral almotriptan in the treatment of migraine: safety and tolerability. *Headache* 2001; 41: 449–55.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies almotriptan 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 11/04/11)

Interactions

As for Sumatriptan, p. 681.3.

Pharmacokinetics

After oral doses, peak plasma-almotriptan concentrations occur in about 1 to 3 hours, with a bioavailability of about 70%. Protein binding is about 35%. Almotriptan is metabolised mainly by monoamine oxidase type A to the inactive indole acetic acid derivative, and to a lesser extent by cytochrome P450 isoenzymes CYP3A4 and CYP2D6 to the inactive gamma-aminobutyric acid derivative. More than 75% of an oral dose is excreted in the urine and the remainder in faeces. About 40% of the dose in the urine is excreted as unchanged drug. The plasma elimination half-life is about 3.5 hours in healthy subjects, increasing to about 7 hours in patients with severe renal impairment.

Distribution into milk has been found in studies in *rats.*

References.
1. Jansat JM, *et al.* Absolute bioavailability, pharmacokinetics, and urinary excretion of the novel antimigraine agent almotriptan in healthy male volunteers. *J Clin Pharmacol* 2002; 42: 1303–10.
2. McEnroe JD, Fleishaker JC. Clinical pharmacokinetics of almotriptan, a serotonin 5-$HT_{1B/1D}$ receptor agonist for the treatment of migraine. *Clin Pharmacokinet* 2005; 44: 237–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Almogran†; *Belg.*: Almogran; *Canad.*: Axert; *Denm.*: Almogran; *Fin.*: Almogran; *Fr.*: Almogran; *Ger.*: Almogran; *Gr.*: Almogran; Amignul†; *Irl.*: Almogran; *Ital.*: Almogran; Almotrex; *Neth.*: Almogran; *Norw.*: Almogran; *Port.*: Almogran; Amignul†; *Spain*: Almogran; Amignul; *Swed.*: Almogran; *Switz.*: Almogran; *UK*: Almogran; *USA*: Axert.

Dihydroergotamine *(BAN, rINN)*

Dihidroergotamina; Dihydroergotamiini; Dihydroergotamin; Dihydroergotamina; Dihydroergotaminum; Diidroergotamina; Дигидроэрготамин.

(5′*S*,8*R*)-5′-Benzyl-9,10-dihydro-12′-hydroxy-2′-methyl-3′,6′,18-trioxoergotaman.

$C_{33}H_{37}N_5O_5$=583.7

CAS — 511-12-6.

ATC — N02CA01.

ATC Vet — QN02CA01.

UNII — 436O5HM03C.

Dihydroergotamine Mesilate *(BANM, rINNM)*

Dihidroergotamina, mesilato de; Dihidroergotamin-mezilát; Dihidroergotamino mesilatas; Dihydroergotamiinimesilaatti; Dihydroergotamine, mésilate de; Dihydroergotamine Mesylate (USAN); Dihydroergotamine Methanesulphonate; Dihydroergotamini Mesilas; Dihydroergotaminmesilat; Dihydroergotamin-mesylát; Dihydroergotaminy mezylan; Mesilato de dihidroergotamina; Дигидроэрготамина Мезилат.

$C_{33}H_{37}N_5O_5,CH_4O_3S$=679.8

CAS — 6190-39-2.

ATC — N02CA01.

ATC Vet — QN02CA01.

UNII — 81AXN7R2QT.

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

Ph. Eur. 8: (Dihydroergotamine Mesilate). Colourless crystals or a white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 4.4 to 5.4. Protect from light.

USP 36: (Dihydroergotamine Mesylate). A white to slightly yellowish powder, or off-white to faintly red powder, having a faint odour. Soluble 1 in 125 of water, 1 in 90 of alcohol, 1 in 175 of chloroform, and 1 in 2600 of ether. pH of a 0.1% solution in water is between 4.4 and 5.4. Protect from light.

Dihydroergotamine Tartrate *(BANM, rINNM)*

Dihidroergotamina, tartrato de; Dihidroergotamino tartratas; Dihidroergotamin-tartarát; Dihydroergotamiinitartraatti; Dihydroergotamine, Tartrate de; Dihydroergotamini Tartras; Dihydroergotamin-tartarát; Dihydroergotamintartrat; Tartrato de dihidroergotamina; Дигидроэрготамина Тартрат.

$(C_{33}H_{37}N_5O_5)_2,C_4H_6O_6$=1317.5

CAS — 5989-77-5.

ATC — N02CA01.

ATC Vet — QN02CA01.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dihydroergotamine Tartrate). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. A 0.1% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Dihydroergotamine is a semisynthetic ergot alkaloid that has weaker oxytocic and vasoconstrictor effects than ergotamine (p. 674.1). Its activity as a 5-HT_1 agonist is believed to contribute to its antimigraine action. It is used in the treatment of migraine and cluster headache, and in the treatment of orthostatic hypotension. It has also been used for the prophylaxis of venous thromboembolism (see p. 673.1).

Dihydroergotamine is commonly used as the mesilate by subcutaneous, intramuscular, or intravenous injection, although it may also be given as a nasal spray or orally.

For the treatment of **migraine** and to terminate an acute attack of **cluster headache**, dihydroergotamine mesilate is usually given by subcutaneous or intramuscular injection in doses of 1 mg repeated, if necessary, after 30 to 60 minutes up to a maximum daily dose of 3 mg. If a more rapid effect is desired it may be given intravenously in doses of 0.5 or 1 mg up to a maximum daily dose of 2 mg. The total weekly dose given by any route of injection should not exceed 6 mg. The usual nasal dose of dihydroergotamine mesilate for an acute attack of migraine is 500 micrograms sprayed into each nostril as a 0.4% solution followed after 15 minutes by an additional 500 micrograms in each nostril. A total intranasal dose of 2 mg per attack should not be exceeded. In the USA, the maximum licensed intranasal dose in 24 hours is 3 mg and in a 7-day period is 4 mg, while maximum daily doses of up to 4 mg with a maximum dose of 12 mg in a 7-day period have been given in other countries. Dihydroergotamine may also be given orally; up to 10 mg daily has been given for the treatment of acute attacks of migraine while lower oral doses are recommended for migraine prophylaxis.

Dihydroergotamine mesilate has also been used alone or with etilefrine hydrochloride (p. 1379.1) in the treatment of **orthostatic hypotension**, in usual oral doses of up to 10 mg daily in divided doses. Doses of up to 40 to 60 mg have been used in some patients.

Dihydroergotamine tartrate has been used for indications similar to those of the mesilate.

Medication-overuse headache. Dihydroergotamine may be used in the treatment of medication-overuse headache (p. 670.2), including symptoms of ergotamine withdrawal.

Migraine and cluster headache. Although sumatriptan is often the treatment of choice to abort acute attacks of migraine that do not respond to simple analgesic preparations, parenteral dihydroergotamine, especially with an antiemetic, is an alternative for patients who develop severe or refractory migraine (p. 670.3).[1-3] Preparations for intranasal[4] and oral use are also available and one for inhalation[5] is under development. In a comparative study, relief of migraine was slower after subcutaneous dihydroergotamine than after subcutaneous sumatriptan, but headache recurred less often.[6] In other studies, intranasal dihydroergotamine was not as effective as subcutaneous[7] or intranasal[8] sumatriptan.

Dihydroergotamine is also used in the treatment of cluster headache (p. 670.1), usually in emergency settings, where it is given to abort individual headache attacks.

1. Scott AK. Dihydroergotamine: a review of its use in the treatment of migraine and other headaches. *Clin Neuropharmacol* 1992; 15: 289–316.
2. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; 45: 577–84.
3. Colman I, *et al.* Parenteral dihydroergotamine for acute migraine headache: a systematic review of the literature. *Ann Emerg Med* 2005; 45: 393–401.
4. Saper JR, Silberstein S. Pharmacology of dihydroergotamine and evidence for efficacy and safety in migraine. *Headache* 2006; 46 (suppl 4): S171–S181.
5. Aurora SK, *et al.* MAP0004, orally inhaled DHE: a randomized, controlled study in the acute treatment of migraine. *Headache* 2011; 51: 507–17.
6. Winner P, *et al.* A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol* 1996; 53: 180–4.
7. Touchon J, *et al.* A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology* 1996; 47: 361–5.
8. Boureau F, *et al.* A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. *Int J Clin Pract* 2000; 54: 281–6.

Orthostatic hypotension. Dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p. 1634.3). It is sometimes used in preparations with sympathomimetics such as etilefrine. After parenteral dihydroergotamine, standing blood pressure is increased, but total peripheral resistance and supine blood pressure are also increased.[1] It does not prevent postprandial hypotension, presumably because it does not constrict the splanchnic veins, although use with caffeine may overcome this problem. The main disadvantage of dihydroergotamine, however, is that it is ineffective, or at best weakly effective, when given orally, although there has been some evidence that oral ergotamine tartrate may be of value.

Dihydroergotamine has been suggested for use in the prevention of hypotension associated with epidural[2] or spinal anaesthesia,[3] the usual management of which is discussed in Treatment of Adverse Effects of Local Anaesthetics, p. 1983.1. It has also been tried in the management of hypotension associated with haemodialysis.[4]

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; i: 197–8.
2. Mattila M, *et al.* Dihydroergotamine in the prevention of hypotension associated with extradural anaesthesia. *Br J Anaesth* 1985; 57: 976–82.
3. Critchley LAH, Woodward DK. Haemodynamic effects of three doses of dihydroergotamine during spinal anaesthesia. *Br J Anaesth* 2001; 87: 499–501.
4. Milutinovic S. Dihydroergotamin in der Behandlung von Patienten mit symptomatischer Hypotonie während Dauerhämodialyse. *Arzneimittelforschung* 1987; 37: 554–6.

Venous thromboembolism. Standard prophylaxis for surgical patients at high risk of venous thromboembolism (p. 1274.1) is usually with anticoagulants, with unfractioned or low-molecular-weight heparin being the most widely used. Dihydroergotamine can reduce venous stasis by vasoconstriction of capacitance vessels and has enhanced postoperative prophylaxis when used with heparin.[1] The use of dihydroergotamine with low-molecular-weight heparin has been shown to be of similar efficacy to dihydroergotamine with heparin.[2,3] However, although dihydroergotamine might enhance the effect of heparin, a US National Institutes of Health consensus conference warned of the potential risk associated with its vasoconstrictive effects, and the contra-indications to its use[4] (see also Effects on the Cardiovascular System, under Adverse Effects, below).

1. Lindblad B. Prophylaxis of postoperative thromboembolism with low dose heparin alone or in combination with dihydroergotamine: a review. *Acta Chir Scand* 1988; (suppl 543): 31–42.
2. Sasahara AA, *et al.* Low molecular weight heparin plus dihydroergotamine for prophylaxis of postoperative deep vein thrombosis. *Br J Surg* 1986; 73: 697–700.
3. Haas S, *et al.* Prophylaxis of deep vein thrombosis in high risk patients undergoing total hip replacement with low molecular weight heparin plus dihydroergotamine. *Arzneimittelforschung* 1987; 37: 839–43.
4. NIH Consensus Development. Prevention of venous thrombosis and pulmonary embolism. *JAMA* 1986; 256: 744–9.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p. 674.2, although vasoconstriction may be less pronounced and the frequency of nausea and vomiting lower with dihydroergotamine mesilate than with ergotamine tartrate. Dihydroergotamine does not appear to produce physical dependence.

Effects on the cardiovascular system. There have been conflicting reports on the risk of vasospasm in patients given dihydroergotamine with heparin for thromboembolism prophylaxis. Vasospastic or necrotic reactions have been reported on several occasions during such therapy.[1-4] In an Austrian study of 147 290 patients given drug prophylaxis for thromboembolism, complications attributable to ergotism were seen in 142 of 61 092 (0.23%) who received dihydroergotamine and heparin.[5] Others,[6] however, saw only 1 case of vasospasm in 5100 trauma patients (0.02%) given the combination. In 1989 the Swedish Adverse Drug Reactions Advisory Committee reported[7] that up to the end of September 1987 the manufacturer had received 201 reports of vasospastic reactions associated with the use of *Orstanorm* (dihydroergotamine + lidocaine) with heparin. Permanent damage occurred in 59% of these patients. Vasospastic reactions had occurred more frequently in patients who had undergone surgery for trauma and the prognosis for such patients was generally poorer than for others. Since the risk of permanent damage appeared to be related to treatment length the Committee recommended that this preparation should not be given for more than 7 days.

1. van den Berg E, *et al.* Ergotism leading to threatened limb amputation or to death in two patients given heparin-dihydroergotamine prophylaxis. *Lancet* 1982; i: 955–6.
2. van den Berg E, *et al.* Vascular spasm during thromboembolism prophylaxis with heparin-dihydroergotamine. *Lancet* 1982; ii: 268–9.
3. Monreal M, *et al.* Skin and muscle necrosis during heparin-dihydroergotamine prophylaxis. *Lancet* 1984; ii: 820.
4. Kilroy BA, *et al.* Vascular spasm during heparin-dihydroergotamine prophylaxis. *Clin Pharm* 1987; 6: 575–7.
5. Gatterer R. Ergotism as complication of thromboembolic prophylaxis with heparin and dihydroergotamine. *Lancet* 1986; ii: 638–9.
6. Schlag G, *et al.* Risk/benefit of heparin-dihydroergotamine thromboembolic prophylaxis. *Lancet* 1986; ii: 1465.
7. Swedish Adverse Drug Reaction Advisory Committee. Dihydroergotamine + lidocaine – vasospasm. *Bull Swed Adverse Drug React Advisory Committee* 1989; (54): 1.

Fibrosis. For reference to fibrosis associated with the administration of dihydroergotamine, see Methysergide Maleate, p. 677.2.

Precautions

As for Ergotamine Tartrate, p. 675.1.

Cardiovascular disorders. For specific contra-indications and precautions in cardiovascular disorders, see under Ergotamine, p. 675.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dihydroergotamine 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 11/04/11)

Interactions

As for Ergotamine (p. 675.2).

Use with other vasoconstrictive drugs, including supplementary antimigraine treatment with ergotamine or sumatriptan, should be avoided.

Pharmacokinetics

Peak plasma-dihydroergotamine concentrations occur within about 1 to 2 hours after oral doses, about 30 minutes after intramuscular injection, about 15 to 45 minutes after subcutaneous injection, and about 45 to 55 minutes after intranasal doses. However, the bioavailability of dihydroergotamine after oral doses is very low; values ranging from less than 0.1 to 1.5% have been reported. Although dihydroergotamine is incompletely absorbed from the gastrointestinal tract, the low bioavailability is considered to be determined primarily by extensive first-pass hepatic metabolism. Bioavailability after intranasal doses is 43%. Dihydroergotamine is 90 to 95% bound to plasma proteins.

Dihydroergotamine undergoes extensive metabolism, the major metabolite, 8′-β-hydroxydihydroergotamine, being active. Plasma concentrations of this metabolite are greater than those of dihydroergotamine. A further oxidation step produces 8′,10′-dihydroxydihydroergotamine, which is also active. Other metabolites are also formed. Most of a dose is excreted as metabolites, mainly in the bile; 5 to 10% is excreted in the urine of which only trace amounts are of unchanged drug. The elimination of dihydroergotamine is biphasic; half-lives of about 1 to 2 hours and 22 to 32 hours have been reported for the 2 phases, respectively.

References.

1. Little PJ, *et al.* Bioavailability of dihydroergotamine in man. *Br J Clin Pharmacol* 1982; 13: 785–90.
2. Müller-Schweinitzer E. Pharmacological actions of the main metabolites of dihydroergotamine. *Eur J Clin Pharmacol* 1984; 26: 699–705.
3. de Marées H, *et al.* Relationship between the venoconstrictor activity of dihydroergotamine and its pharmacokinetics during acute and chronic oral dosing. *Eur J Clin Pharmacol* 1986; 30: 685–9.
4. Humbert H, *et al.* Human pharmacokinetics of dihydroergotamine administered by nasal spray. *Clin Pharmacol Ther* 1996; 60: 265–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dihydergot; ***Austria***: Detemes; DHE; Dihydergot; Ergont; Ergovasan; Migranal; ***Belg.***: Diergo; Dihydergot; Dystonal; ***Canad.***: Migranal; ***China***: Seglor (赛格乐); ***Cz.***: Dihydergot†; ***Fin.***: Orstanorm; ***Fr.***: Ikaran; Seglor; Tamik; ***Ger.***: Agit†; Angionorm†; DET MS; DHE†; Ergotam; Verladyn; ***Gr.***: Bobinum; Cozetamin; Dihydergot; Hemocinol; Pervone; Tusedon; Verteblan; Yugovasin; ***India***: DHE; Migranil; ***Indon.***: Dihydergot†; ***Ital.***: Diidergot; Seglor; ***Mex.***: Dihydergot; ***Neth.***: Migranal†; ***Port.***: Seglor; ***Spain***: Dihydergot†; ***Swed.***: Orstanorm; ***Switz.***: Dihydergot; Ergotonine†; ***Thai.***: Poligot; ***USA***: DHE; Migranal; ***Venez.***: Dihydergot.

Multi-ingredient Preparations. ***Arg.***: Polper Vascular; ***Austria***: Agilan; Effortil comp; Hypodyn†; Tonopan; Venotop†; ***Braz.***: Cefalium; Cefaliv; Enxak; Migraliv; Parcel; Tonopan; ***Chile***: Emagrim; Migratapsin†; Migrax; ***Fr.***: Diergospray; ***Ger.***: Dihydergot plus; Effortil plus†; ***Mex.***: Parsel; Tonopan; ***Spain***: Tonopan; ***Switz.***: Dihydergot plus†; Dihydergot; Effortil plus†; ***Venez.***: Brudol; Difen; Dol; Ivagan; Letydol; Parsel.

Pharmacopoeial Preparations

USP 36: Dihydroergotamine Mesylate Injection.

Eletriptan Hydrobromide

(BANM, USAN, rINNM)

Eletriptaanihydrobromidi; Élétriptan; Bromhydrate d'; Eletriptán, hidrobromuro de; Eletriptanhydrobromid; Eletriptani Hydrobromidum; Hidrobromuro de eletriptán; UK-116044-04; Элетриптана Гидробромид.

3-[[(*R*)-1-Methyl-2-pyrrolidinyl]methyl]-5-[2-(phenylsulfonyl)ethyl]indole hydrobromide.

$C_{22}H_{26}N_2O_2S,HBr$=463.4

CAS — 143322-58-1 (eletriptan); 177834-92-3 (eletriptan hydrobromide).

ATC — N02CC06.

ATC Vet — QN02CC06.

UNII — M4TW832TA3.

Uses and Administration

Eletriptan hydrobromide is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Eletriptan is given orally as the hydrobromide, but doses are expressed in terms of the base; eletriptan hydrobromide 24.2 mg is equivalent to about 20 mg of eletriptan.

UK licensed product information recommends a usual dose of 40 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur within 24 hours after an initial response, a second dose may be taken after an interval of at least 2 hours. Doses of 80 mg may be used in subsequent attacks, but should not be repeated within a 24-hour period. US licensed product information allows a lower dose of 20 mg with a maximum single dose of 40 mg and a maximum daily dose of 80 mg. For doses in renal impairment, see below.

Administration in renal impairment. UK licensed product information for eletriptan recommends an oral dose of 20 mg in patients with mild to moderate renal impairment; the maximum daily dose should not exceed 40 mg. Eletriptan should not be used in severe impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Mathew NT, *et al.* Tolerability and safety of eletriptan in the treatment of migraine: a comprehensive review. *Headache* 2003; 43: 962–74.
2. Takiya L, *et al.* Safety and efficacy of eletriptan in the treatment of acute migraine. *Pharmacotherapy* 2006; 26: 115–28.
3. McCormack PL, Keating GM. Eletriptan: a review of its use in the acute treatment of migraine. *Drugs* 2006; 66: 1129–49.
4. Sandrini G, *et al.* Eletriptan: a review and new perspectives. *Expert Rev Neurother* 2006; 6: 1413–21.
5. Sandrini G, *et al.* Eletriptan. *Expert Opin Drug Metab Toxicol* 2009; 5: 1587–98.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

Eletriptan should not be used in patients with severe hepatic impairment; however, this is due to a lack of data. No dosage adjustment is needed in mild or moderate hepatic impairment. Blood pressure effects of eletriptan are increased in renal impairment and therefore UK licensed product information recommends that it should be used with caution in patients with mild to moderate renal impairment; its use in those with severe renal impairment is contra-indicated.

Breast feeding. Eletriptan is distributed into breast milk. The licensed product information states that in a study of 8 women given a single, 80-mg dose of eletriptan, the mean total amount excreted into breast milk over 24 hours was 0.02% of the dose. Nonetheless, caution is advised when eletriptan is used in breast-feeding women; infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eletriptan 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 11/04/11)

Interactions

As for Sumatriptan, p. 681.3.

Eletriptan should not be given with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as erythromycin and ketoconazole; increased plasma levels of eletriptan have been noted after such combinations. It is recommended that eletriptan should not be taken within at least 72 hours of treatment with such drugs.

Pharmacokinetics

After oral doses eletriptan is rapidly and well absorbed (at least 81%) and has a bioavailability of about 50%. Peak plasma concentrations occur within 1.5 hours. Eletriptan is about 85% protein bound. It is mainly metabolised by the hepatic cytochrome P450 isoenzyme CYP3A4. Non-renal clearance accounts for about 90% of the elimination of eletriptan and the plasma elimination half-life is about 4 hours. A small amount is distributed into breast milk.

References.
1. Shah AK, *et al.* Pharmacokinetics and safety of oral eletriptan during different phases of the menstrual cycle in healthy volunteers. *J Clin Pharmacol* 2001; **41**: 1339–44.
2. Shah AK, *et al.* The pharmacokinetics and safety of single escalating oral doses of eletriptan. *J Clin Pharmacol* 2002; **42**: 520–7.
3. Milton KA, *et al.* Pharmacokinetics, pharmacodynamics, and safety of the 5-$HT_{1B/1D}$ agonist eletriptan following intravenous and oral administration. *J Clin Pharmacol* 2002; **42**: 528–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Relpax; *Austria*: Relpax; *Belg.*: Relert; *Canad.*: Relpax; *Chile*: Relpax; *Cz.*: Relpax; *Denm.*: Relert; Relpax; *Fin.*: Relert; *Fr.*: Relpax; *Ger.*: Relpax; *Gr.*: Relpax; *Hung.*: Relpax; *Irl.*: Relpax; *Israel*: Relert; *Ital.*: Relpax; *Mex.*: Relpax; *Neth.*: Relpax; *Norw.*: Relpax; *Pol.*: Relpax; *Port.*: Relert; *Rus.*: Relpax (Pennaxe); *S.Afr.*: Relpax; *Singapore*: Relpax; *Spain*: Relert; Relpax; *Swed.*: Relpax; *Switz.*: Relpax; *Thai.*: Relpax; *Turk.*: Relpax; *UK*: Relpax; *USA*: Relpax.

Ergotamine Tartrate *(BANM, rINNM)*

Ergotamiinitartraatti; Ergotamin Tartarat; Ergotamin Tartrat; Ergotamina, tartrato de; Ergotamine, tartrate d'; Ergotamini Tartras; Ergotamino tartratas; Ergotamin-tartarát; Ergotamin-tartrat; Ergotaminy winian; Tartrato de ergotamina; Эрготамина Тартрат.

(5'*S*)-12'-Hydroxy-2'-methyl-5'-benzylergotaman-3',6',18-trione tartrate; (5'*S*)-12'-Hydroxy-2'-methyl-3',6',18-trioxo-5-benzylergotaman (+)-tartrate.

$(C_{33}H_{35}N_5O_5)_2C_4H_6O_6$=1313.4

CAS — 113-15-5 (ergotamine); 379-79-3 (ergotamine tartrate).

ATC — N02CA02.

ATC Vet — QN02CA02.

UNII — MRU5XH3B48.

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

Ph. Eur. 8: (Ergotamine Tartrate). Slightly hygroscopic, colourless crystals or a white or almost white crystalline powder. It may contain 2 molecules of methanol of crystallisation. Slightly soluble in alcohol. Aqueous solutions slowly become cloudy owing to hydrolysis; this may be prevented by the addition of tartaric acid. A 0.25% suspension in water has a pH of 4.0 to 5.5. Store in airtight glass containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Ergotamine Tartrate). Colourless odourless crystals or a white or yellowish-white crystalline powder. Soluble 1 in about 3200 of water, but soluble 1 in about 500 of water in the presence of a slight excess of tartaric acid; soluble 1 in 500 of alcohol. Store at a temperature not exceeding 8 degrees. Protect from light.

Stability in solution. References.
1. Kreilgård B, Kisbye J. Stability of ergotamine tartrate in aqueous solution. *Arch Pharm Chemi (Sci)* 1974; **2**: 1–13 and 38–49.

Uses and Administration

Ergotamine is an alkaloid derived from ergot (p. 2137.1). It has marked vasoconstrictor effects, and a partial agonist action at serotonin (5-HT) receptors; it also has a powerful oxytocic action on the uterus, although less so than ergometrine (p. 2136.2). It is used in migraine and cluster headache, and has been tried in orthostatic hypotension.

Ergotamine is commonly used as the tartrate. It is usually given orally, but has also been given sublingually, rectally, and by oral inhalation. It was formerly given by subcutaneous or intramuscular injection. Caffeine is sometimes given with ergotamine tartrate with the intention of improving the latter's absorption, although whether it does so is not clear. Antiemetics such as cyclizine hydrochloride are sometimes included in combination preparations with ergotamine tartrate.

Ergotamine is used in **migraine** unresponsive to non-opioid analgesics. However, its adverse effects limit its use and prevent use for prophylaxis. It is most effective when given as early as possible in a migraine attack, preferably during the prodromal phase.

The usual oral dose is 2 mg of ergotamine tartrate; if necessary, doses of 1 to 2 mg may be given at half-hourly intervals thereafter. Usually not more than 6 mg should be given in 24 hours; some licensed product information recommends not more than 8 mg for each attack. The recommended minimum interval between successive 24-hour courses is 4 days, and the total weekly dose is limited to a maximum of 12 mg, although some recommend a lower weekly limit of 10 mg. It is also recommended that patients should receive no more than 2 courses in each month. Similar doses may be given sublingually.

Ergotamine tartrate may also be given rectally as suppositories, especially if the oral route is not effective or not practicable. The rectal dose of ergotamine tartrate is 2 mg repeated, if necessary, one hour later. Usually, not more than 4 mg should be given for each attack and not more than 10 mg in one week with an interval of at least 4 days between successive 24-hour courses.

Ergotamine is used in patients with **cluster headache** to treat individual attacks of headache. Doses used are similar to those given to treat migraine. It has also been used to prevent headache attacks during cluster periods, when it is usually given daily in low doses for up to 2 weeks, either orally or rectally (see below).

Migraine and cluster headache. Ergotamine was formerly one of the main drugs used to treat acute attacks of migraine (p. 670.3) unresponsive to non-opioid analgesics, but triptan serotonin (5-HT_1) agonists such as sumatriptan are now preferred. Since ergotamine may exacerbate the nausea and vomiting that commonly develops as a migraine attack progresses it is often necessary to give an antiemetic as well. Poor oral bioavailability may be reduced further during a migraine attack and ergotamine has sometimes been given sublingually, rectally, or by oral inhalation. Adverse effects limit the dose that can be used for an individual attack and prevent the long-term use that would be required for migraine prophylaxis.

Ergotamine may be used similarly in cluster headache (p. 670.1) to treat individual headaches during a cluster period. Ergotamine is also used in low doses given orally or rectally for limited periods of up to 2 weeks in the prophylaxis of headache attacks during a cluster period. Regimens that have been tried for such prophylaxis include 1 to 2 mg of ergotamine tartrate given 1 to 2 hours before an expected attack or 1 to 2 hours before bedtime for nocturnal attacks. The total maximum dose of ergotamine tartrate that may be given weekly for the prevention of cluster headache is less well established than for the treatment of migraine. Ergotamine is often given for only 5 to 6 days in each week, which allows the patient to assess whether the cluster period has ended.

References.
1. Silberstein SD, Young WB. Safety and efficacy of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus. *Neurology* 1995; **45**: 577–84.
2. Tfelt-Hansen P, *et al.* Ergotamine in the acute treatment of migraine: a review and European consensus. *Brain* 2000; **123**: 9–18.
3. Silberstein SD, McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. *Headache* 2003; **43**: 144–66.
4. Tfelt-Hansen PC, Koehler PJ. History of the use of ergotamine and dihydroergotamine in migraine from 1906 and onward. *Cephalalgia* 2008; **28**: 877–86.

Orthostatic hypotension. Ergotamine and dihydroergotamine may be of use in patients with refractory orthostatic hypotension (p. 1634.3). Ergotamine is believed[1] to be less selective than dihydroergotamine (p. 672.3) in its actions and affects both venous capacitance and peripheral resistance.[2,3] However, the oral bioavailability of ergotamine is greater[2] than that of dihydroergotamine and there have also been some reports of successful treatment with inhaled[3,4] or rectal[3] ergotamine.

1. Anonymous. Management of orthostatic hypotension. *Lancet* 1987; **i**: 197–8.
2. Ahmad RAS, Watson RDS. Treatment of postural hypotension: a review. *Drugs* 1990; **39**: 74–85.
3. Tonkin AL, Wing LMH. Hypotension: assessment and management. *Med J Aust* 1990; **153**: 474–85.
4. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. *Am J Hosp Pharm* 1994; **51**: 648–60.
5. Toh V, *et al.* Ergotamine use in severe diabetic autonomic neuropathy. *Diabet Med* 2006; **23**: 574–6.

Adverse Effects

The adverse effects of ergotamine may be attributed either to its effects on the CNS, or to vasoconstriction of blood vessels and possible thrombus formation.

After therapeutic doses nausea and vomiting commonly occur as a result of the direct emetogenic effect of ergotamine; some patients may also have abdominal pain. Weakness and muscle pains in the extremities and numbness and tingling of the fingers and toes may occur. There may occasionally be localised oedema and itching in hypersensitive patients. Treatment should be stopped if symptoms of vasoconstriction develop. Susceptible patients, especially those with sepsis, liver disease, kidney disease, or occlusive peripheral vascular disease, may show signs of acute or chronic poisoning with normal doses of ergotamine.

Symptoms of acute overdosage include nausea, vomiting, diarrhoea, extreme thirst, coldness, tingling, and itching of the skin, a rapid and weak pulse, hypertension or hypotension, shock, confusion, convulsions, and unconsciousness; fatalities have been reported. Further symptoms of peripheral vasoconstriction or of cardiovascular disturbances, as seen in chronic ergotamine poisoning, may also occur but may be delayed.

In chronic poisoning or ergotism, resulting from therapeutic overdosage or the use of ergotamine in susceptible patients, severe circulatory disturbances may develop. The extremities, especially the feet and legs, become numb, cold, tingling, and pale or cyanotic, with muscle pain; there may be no pulse in the affected limb. Eventually gangrene develops in the toes and sometimes the fingers. Anginal pain, tachycardia or bradycardia, and hypertension or hypotension have been reported. Myocardial infarction has occurred rarely. Pleural and pericardial fibrosis may occur with excessive use and there have been rare cases of fibrosis of the cardiac valves. Chronic, intractable headache (rebound headache) may occur and is also a major withdrawal symptom following the development of ergotamine dependence (see under Precautions, p. 675.1). Other adverse effects include confusion and convulsions. On rare occasions symptoms of vasoconstriction of blood vessels in the brain, eye, intestines, and kidneys occur. Anorectal ulceration, sometimes leading to rectal necrosis and stenosis or rectovaginal fistula, has been reported after excessive use of suppositories containing ergotamine.

Effects on the cardiovascular system. Reports[1-5] of adverse cardiovascular effects associated with ergotamine, including mention of fatalities.

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* 1982; **285**: 260–1.
2. Corrocher R, *et al.* Multiple arterial stenoses in chronic ergot toxicity. *N Engl J Med* 1984; **310**: 261.
3. Fisher PE, *et al.* Ergotamine abuse and extra-hepatic portal hypertension. *Postgrad Med J* 1985; **61**: 461–3.
4. Deviere J, *et al.* Ischemic pancreatitis and hepatitis secondary to ergotamine poisoning. *J Clin Gastroenterol* 1987; **9**: 350–2.
5. Galer BS, *et al.* Myocardial ischemia related to ergot alkaloids: a case report and literature review. *Headache* 1991; **31**: 446–50.
6. Redfield MM, *et al.* Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med* 1992; **117**: 50–2.
7. Lazarides MK, *et al.* Severe facial ischaemia caused by ergotism. *J Cardiovasc Surg* 1992; **33**: 383–5.
8. Hillis W, MacIntyre PD. Drug reactions: sumatriptan and chest pain. *Lancet* 1993; **341**: 1564–5. Correction. *ibid.*; **342**: 1310.
9. Zavaleta EG, *et al.* St. Anthony's fire (ergotamine induced leg ischemia)—a case report and review of the literature. *Angiology* 2001; **52**: 349–56.

Fibrosis. For reference to fibrosis associated with the use of ergotamine tartrate, see Methysergide Maleate, p. 677.2.

Treatment of Adverse Effects

Treatment of acute poisoning with ergotamine is symptomatic (see also p. 1537.1). Although the benefit of gastric decontamination is uncertain, activated charcoal may be given to patients who present within 1 hour of ingesting a toxic dose (more than 125 micrograms/kg in adults) or any amount in a child or in adults with peripheral vascular disease, ischaemic heart disease, severe infection, or hepatic or renal impairment. Alternatively, gastric lavage may be considered in adults within 1 hour of ingesting a potentially life-threatening overdose. In chronic poisoning, withdrawal of ergotamine may be all that is required in some patients.

In both acute and chronic poisoning, attempts must be made to maintain an adequate circulation to the affected parts of the body in order to prevent the onset of gangrene. In severe arterial vasospasm vasodilators such as sodium nitroprusside by intravenous infusion have been given; heparin and dextran 40 have also been advocated to minimise the risk of thrombosis. Analgesics may be required for severe ischaemic pain.

Cardiovascular effects. Sodium nitroprusside has been used in severe ergotamine poisoning for its vasodilating and hypotensive actions; it should, however, be used with care if hypotension is a symptom of poisoning. It is usually given by intravenous infusion[1-4] although there have also been reports of intra-arterial infusion for ergotamine-induced ischaemia;[5,6] for details of precautions, see p. 1498.1.

Many other drugs have been used in the treatment of circulatory disturbances induced by ergotamine. These include oral captopril,[7] alprostadil by intra-arterial infusion,[8,9] and glyceryl trinitrate by intravenous infusion.[10,11]

1. Carliner NH, *et al.* Sodium nitroprusside treatment of ergotamine-induced peripheral ischemia. *JAMA* 1974; **277**: 308–9.
2. Andersen PK, *et al.* Sodium nitroprusside and epidural blockade in the treatment of ergotism. *N Engl J Med* 1977; **296**: 1271–3.
3. Eurin B, *et al.* Ergot and sodium nitroprusside. *N Engl J Med* 1978; **298**: 632–3.
4. Carr P. Self-induced myocardial infarction. *Postgrad Med J* 1981; **57**: 64–5.
5. O'Dell CW, *et al.* Sodium nitroprusside in the treatment of ergotism. *Radiology* 1977; **124**: 73–4.
6. Whitsett TL, *et al.* Nitroprusside reversal of ergotamine-induced ischemia. *Am Heart J* 1978; **96**: 700.
7. Zimran A, *et al.* Treatment with captopril for peripheral ischaemia induced by ergotamine. *BMJ* 1984; **288**: 364.
8. Levy JM, *et al.* Prostaglandin E_1 for alleviating symptoms of ergot intoxication: a case report. *Cardiovasc Intervent Radiol* 1984; **7**: 28–30
9. Horstmann R, *et al.* Kritische Extremitätenischämie durch Ergotismus: Behandlung mit intraarterieller Prostaglandin-E_1-Infusion. *Dtsch Med Wochenschr* 1993; **118**: 1067–71.
10. Husum B, *et al.* Nitroglycerin infusion for ergotism. *Lancet* 1979; **ii**: 764–5.

11. Tfelt-Hansen P, *et al.* Nitroglycerin for ergotism: experimental studies in vitro and in migraine patients and treatment of an overt case. *Eur J Clin Pharmacol* 1982; **22:** 105–9.

Precautions

Ergotamine tartrate is contra-indicated in patients with severe or uncontrolled hypertension, shock, severe or persistent sepsis, peripheral vascular disease, ischaemic heart disease, temporal arteritis, hyperthyroidism, or hepatic or renal impairment. It is also contra-indicated in those with basilar or hemiplegic migraine. Ergotamine tartrate should be used with care in patients with anaemia. It is contra-indicated in pregnancy because of its oxytocic effect (see also below).

Patients should be warned to keep within the recommended dosage. Some symptoms of overdosage may mimic those of migraine. Numbness or tingling of the extremities generally indicates that ergotamine should be stopped. Although ergotamine is used for limited periods in the prevention of episodic cluster headache, it should not be given prophylactically in other circumstances, as prolonged use may give rise to gangrene. Dependence has occurred with regular use of ergotamine tartrate even if dosage recommendations are adhered to (see below).

Dizziness and feelings of anxiety have been reported; if affected, patients should avoid driving or operating machinery.

Breast feeding. Although the last available guidance from the American Academy of Pediatrics included ergotamine among those drugs that may be given with caution to breast-feeding mothers,[1] it notes that maternal use in doses equivalent to those given for the treatment of migraine has been associated with vomiting, diarrhoea, and convulsions in nursing infants. UK licensed product information recommends that ergotamine tartrate should be avoided during breast feeding; the distribution of unchanged drug and metabolites into breast milk presents a risk of ergotism in the infant and repeated doses of ergotamine may impair lactation.

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 27/01/09)

Cardiovascular disorders. US licensed product information contra-indicates the use of dihydroergotamine in patients with ischaemic heart disease and other cardiovascular disorders such as uncontrolled hypertension, peripheral arterial disease, or coronary artery vasospasm; it is also recommended that dihydroergotamine should not be given to those with a family history of ischaemic heart disease, to postmenopausal women, men aged over 40, or to those with other ischaemic risk factors such as hypertension, hypercholesterolaemia, smoking, diabetes, or obesity, unless cardiovascular evaluation to exclude such disease has been carried out. Similar precautions and contra-indications, which resemble those that apply to serotonin (5-HT_1) agonists such as sumatriptan (p. 681.2), may be applicable to other ergot derivatives used in migraine such as ergotamine.

In other countries, warnings concerning the use of ergot derivatives in patients with risk factors for myocardial ischaemia appear to be less stringent, although caution is clearly advisable.

Dependence. Dependence can develop insidiously when ergotamine tartrate is used for more than 2 days each week, even if total daily or weekly dosage recommendations are observed.[1] Individual reports indicate a state of addiction characterised by a predictable and irresistible pattern of drug usage, the development of tolerance to adverse effects, and a syndrome of withdrawal on stopping the drug. Ergotamine-dependent patients suffer from daily, or almost daily, migraine headaches, often referred to as medication-overuse headaches or 'rebound headaches', which are only alleviated by ergotamine. Intensifying headache with autonomic disturbances occurs within 24 to 48 hours of withdrawal of ergotamine and may continue for 72 hours or longer. As with other medication-overuse headaches (p. 670.2), supportive and symptomatic measures should be taken to treat the withdrawal syndrome.

1. Saper JR. Ergotamine dependency—a review. *Headache* 1987; **27:** 435–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, does not classify the porphyrinogenic risk for single-ingredient preparations containing ergotamine although combinations containing the drug are classified as porphyrinogenic; such products 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 11/04/11)

Pregnancy. Ergotamine is contra-indicated in pregnancy because of its oxytocic effect. Accidental dosage of ergotamine in the form of a *Cafergot* suppository (ergotamine tartrate 2 mg and caffeine 100 mg) to a patient at 39 weeks of pregnancy caused uterine contractions and fetal tachycardia.[1] An emergency caesarean section was undertaken because of suspected placental abruption but no clear signs of retroplacental haemorrhage were found. The neonate recovered quickly after delivery and had developed normally during the next 10 years.

Jejunal atresia has been reported[2] in an infant born prematurely to a woman who had taken ergotamine tartrate 6 to 8 mg daily, as *Cafergot* tablets, throughout her pregnancy. Two cases of Möbius syndrome (a condition characterised by facial paralysis as a result of hypoplasia of cranial nerve nuclei) have been associated with exposure to ergotamine during the first trimester of pregnancy.[3,4] In the first report[3] the mother had inadvertently been given three *Cafergot* suppositories within a period of 1 to 2 hours and at the time had uterine cramping and a bloody vaginal discharge. The second mother[4] had used 2-mg ergotamine suppositories on a regular basis during the first 8 weeks of pregnancy.

1. de Groot ANJA, *et al.* Ergotamine-induced fetal stress: review of side effects of ergot alkaloids during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1993; **51:** 73–7.
2. Graham JM, *et al.* Jejunal atresia associated with Cafergot ingestion during pregnancy. *Clin Pediatr (Phila)* 1983; **22:** 226–8.
3. Graf WD, Shepard TH. Uterine contraction in the development of Möbius syndrome. *J Child Neurol* 1997; **12:** 225–7.
4. Smets K, *et al.* Ergotamine as a possible cause of Möbius sequence: additional clinical observation. *J Child Neurol* 2004; **19:** 398.

Interactions

The vasoconstrictor effects of ergotamine are enhanced by sympathomimetics such as adrenaline. There is also an increased risk of peripheral vasoconstriction during use of ergotamine with beta blockers.

Ergotamine is metabolised by the cytochrome P450 isoenzyme CYP3A4 and consequently it should not be given with potent inhibitors of this isoenzyme; elevated ergotamine concentrations sufficient to cause ergotism may occur with azole antifungals, macrolide antibacterials such as erythromycin and clarithromycin, and HIV-protease inhibitors including indinavir and ritonavir. Use of tetracycline with ergotamine may also increase the risk of ergotism and should be avoided.

Ergotamine should not be used with or given until several hours *after stopping* a serotonin (5-HT_1) agonist, since there is an additional risk of prolonged vasospastic reactions; at least 6 hours is advised for almotriptan, rizatriptan, sumatriptan, and zolmitriptan, and at least 24 hours for eletriptan, frovatriptan, and naratriptan. Conversely, a delay is advised *before starting* a serotonin agonist in patients who have been receiving ergotamine: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, or zolmitriptan should not be given until at least 24 hours after stopping the use of preparations containing ergotamine.

Antibacterials. Acute reactions ranging from minor ergotism[1] to severe vasospasm[2] have been reported in patients given *erythromycin* in addition to ergotamine. There are also reports of acute ergotism in patients given ergotamine tartrate with *clarithromycin*[3,4] or *troleandomycin*.[5] The theoretical possibility exists that there may be a similar interaction with *azithromycin*. Ergotism has also been reported in patients given erythromycin[6] or troleandomycin[7] with dihydroergotamine.

1. Lagier G, *et al.* Un cas d'ergotisme mineur semblant en rapport avec une potentialisation de l'ergotamine par l'éthylsuccinate d'érythromycine. *Therapie* 1979; **34:** 515–21.
2. Ghali R, *et al.* Erythromycin-associated ergotamine intoxication: arteriographic and electrophysiologic analysis of a rare cause of severe ischemia of the lower extremities and associated ischemic neuropathy. *Ann Vasc Surg* 1993; **7:** 291–6.
3. Horowitz RS, *et al.* Clinical ergotism with lingual ischemia induced by clarithromycin-ergotamine interaction. *Arch Intern Med* 1996; **156:** 456–8.
4. Ausband SC, Goodman PE. An unusual case of clarithromycin associated ergotism. *J Emerg Med* 2001; **21:** 411–13.
5. Matthews NT, Havill JH. Ergotism with therapeutic doses of ergotamine tartrate. *N Z Med J* 1979; **89:** 476–7.
6. Leroy F, *et al.* Dihydroergotamine-erythromycin-induced ergotism. *Ann Intern Med* 1988; **109:** 249.
7. Franco A, *et al.* Ergotisme aigu par association dihydroergotamine-triacétyloléandomycine. *Nouv Presse Med* 1978; **7:** 205.

Antidepressants. There have been isolated case reports[1] of the serotonin syndrome (p. 443.2) in patients given dihydroergotamine with *amitriptyline, imipramine, paroxetine,* or *sertraline.*

1. Mathew NT, *et al.* Serotonin syndrome complicating migraine pharmacotherapy. *Cephalalgia* 1996; **16:** 323–7.

Antimigraine drugs. Arterial occlusion has been reported[1] in 2 patients given *methysergide* with a high parenteral dosage of ergotamine for cluster headache; the combination should be avoided. Use of ergotamine as supplementary antimigraine medication in patients receiving *dihydroergotamine* is not recommended.

For reports of arterial vasoconstriction in patients taking *beta blockers* and antimigraine drugs, see below. See also Interactions, above for a comment on the risk of vasospastic reactions with serotonin (5-HT_1) agonists such as *sumatriptan.*

1. Joyce DA, Gubbay SS. Arterial complications of migraine treatment with methysergide and parenteral ergotamine. *BMJ* 1982; **285:** 260–1.

Antivirals. There have been reports of ergotism in patients given ergotamine with combination antiviral treatment for HIV infection. It was suggested that the ergotism might have been caused by inhibition of ergotamine metabolism by *ritonavir* in 4 cases,[1-4] *indinavir* in one,[5] and *nelfinavir*[6] in another. One of the patients given ritonavir,[4] who had taken three 1-mg tablets of ergotamine tartrate over the 4 days before presentation, also developed signs of cerebrovascular involvement and eventually went into an irreversible coma.

The metabolism of ergot alkaloids may be inhibited by *delavirdine* or *efavirenz.*

1. Caballero-Granado FJ, *et al.* Ergotism related to concurrent administration of ergotamine tartrate and ritonavir in an AIDS patient. *Antimicrob Agents Chemother* 1997; **41:** 1207.
2. Montero A, *et al.* Leg ischemia in a patient receiving ritonavir and ergotamine. *Ann Intern Med* 1999; **130:** 329–30.
3. Liaudet L, *et al.* Severe ergotism associated with interaction between ritonavir and ergotamine. *BMJ* 1999; **318:** 771.
4. Pardo Rey C, *et al.* Irreversible coma, ergotamine, and ritonavir. *Clin Infect Dis* 2003; **37:** e72–e73.
5. Rosenthal E, *et al.* Ergotism related to concurrent administration of ergotamine tartrate and indinavir. *JAMA* 1999; **281:** 987.
6. Mortier E, *et al.* Ergotism related to interaction between nelfinavir and ergotamine. *Am J Med* 2001; **110:** 594.

Beta blockers. Peripheral vasoconstriction was reported in a patient with migraine after addition of *propranolol* to regular use of *Cafergot* (ergotamine and caffeine) suppositories twice daily.[1] This combination has been used without complication by others, who suggested that excessive dosage of ergotamine tartrate, rather than an interaction between ergotamine and propranolol, was responsible.[2] However, arterial vasoconstriction has been reported after use of methysergide with propranolol and *oxprenolol* with ergotamine.[3] Such combinations should therefore be used with caution.

1. Baumrucker JF. Drug interaction—propranolol and Cafergot. *N Engl J Med* 1973; **288:** 916–17.
2. Diamond S. Propranolol and ergotamine tartrate. *N Engl J Med* 1973; **289:** 159.
3. Venter CP, *et al.* Severe peripheral ischaemia during concomitant use of beta blockers and ergot alkaloids. *BMJ* 1984; **289:** 288–9.

Glyceryl trinitrate. Glyceryl trinitrate has been reported to increase the oral bioavailability and plasma concentrations of dihydroergotamine in patients with orthostatic hypotension.[1]

1. Bobik A, *et al.* Low oral bioavailability of dihydroergotamine and first-pass extraction in patients with orthostatic hypotension. *Clin Pharmacol Ther* 1981; **30:** 673–9.

Tacrolimus. Ergotamine may inhibit the metabolism of tacrolimus by cytochrome P450 isoenzymes (see p. 1977.3).

Pharmacokinetics

Absorption of ergotamine from the gastrointestinal tract is poor and may be further decreased by the occurrence of gastric stasis during migraine attacks. Bioavailability is also reduced by a high first-pass hepatic metabolism. Ergotamine has been given rectally or by inhalation in an attempt to overcome these effects, with some improvement in absorption, but bioavailability is still about 5% or less. Absorption of sublingual ergotamine is very poor. There is considerable interindividual variation in the bioavailability of ergotamine, regardless of the route. Caffeine is sometimes included in oral and rectal preparations of ergotamine to improve the latter's absorption, although whether it does so is not clear. Drugs such as metoclopramide are sometimes given with the aim of alleviating gastric stasis and thus improve the absorption of ergotamine.

Plasma protein binding is about 93 to 98%. Ergotamine is metabolised extensively in the liver via the cytochrome P450 isoenzyme CYP3A4; the majority of metabolites are excreted in the bile. About 4% of a dose is excreted in the urine. Some of the metabolites are pharmacologically active. The elimination of ergotamine is biphasic; half-lives of about 2 and 21 hours have been reported for the 2 phases, respectively. Ergotamine or its metabolites have been detected in breast milk.

References.

1. Schmidt R, Fanchamps A. Effect of caffeine on intestinal absorption of ergotamine in man. *Eur J Clin Pharmacol* 1974; **7:** 213–16.
2. Eadie MJ. Ergotamine pharmacokinetics in man: an editorial. *Cephalalgia* 1983; **3:** 135–8.
3. Perrin VL. Clinical pharmacokinetics of ergotamine in migraine and cluster headache. *Clin Pharmacokinet* 1985; **10:** 334–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ergokaptont; ***Chile***: Jaquedryl; ***Ger.***: Ergo-Kranit Migrane; ***Hung.***: Ergam; ***Ital.***: Ergotan; ***Philipp.***: Avamigran; ***Thai.***: Ergosia; Gynaemine; ***USA***: Ergomar.

Multi-ingredient Preparations. ***Arg.***: Cafergot; Cefalex Plus; Ibu-Tetralgin; Ibupirac Migra; Integrobe Plus; Migra Dioxadol; Migra Dorixina; Migral Compositum; Migral II; Migral; Mikesan; Solacil; Tetralgin Novo; Tetralgin; ***Austral.***: Cafergot; ***Austria***: Avamigran; Secokapton; Synkapton; ***Belg.***: Cafergot; ***Braz.***: Migrane; Neogrein; Ormigrein; ***Canad.***: Bellergal; Cafergot; Ergodryl; Gravergol†; ***Chile***: Cefadol; Cefalmin; Cinabel; Clonalgin Compuesto; Ergobelan; Ergonef; Esamigran; Fredol; Migra-Nefersil; Migragesic; Migranol; Migratam; Ultrimin; ***Denm.***: Ergokoffin; ***Fin.***: Anervan†; ***Fr.***: Gynergene Cafeine; ***Ger.***: Cafergot N†; ***Gr.***: Cafergot; Medalidon; ***Hong Kong***: Cafergot; ***Hung.***: Kefalgin; ***India***: Ergophen; Migranil; Migril; Mizeco; ***Indon.***: Bellapheen; Cafergot; Ericaf; ***Irl.***: Migranat†; ***Israel***: Cafergot†; Temigran†; ***Ital.***: Cafergot; Virdex; ***Malaysia***: Cafergot†; ***Mex.***: Cafergot; Caftar; Ergocaf; Optium; Sydolil; Trinergot; ***Neth.***: Cafergot; ***Norw.***: Anervan†; ***NZ***: Cafergot; ***Pol.***: Bellergot; Coffecorn; ***Port.***: Migretil; ***Rus.***: Bellataminal (Беллатаминал); Coffetamin (Кофетамин); Synkapton (Синкаптон); ***S.Afr.***: Cafergot; Migril; ***Singapore***: Cafergot; Caffox; ***Spain***: Cafergot; Hemicraneal; ***Swed.***: Anervan; ***Switz.***: Cafergot-PB†; Cafergot; ***Thai.***: Avamigran; Benera†; Cafergot; Degran; Hofergot; Migana; Neuramizone; Poligot-CF; Polygot; Tofago; ***Turk.***: Avmigran; Bellergal; Cafergot; Ergafein; ***UK***: Cafergot†; Migril; ***Ukr.***: Nomigren (Номигрен); ***USA***: Bel-Phen-Ergot S†; Bellamine†; Bellergal-S; Cafatine-PB; Cafatine; Cafergot; Ercaf; Folergot-DF; Migergot; Phenerbel-S; ***Venez.***: Ervostal; Migradorixina; Traveget.

Pharmacopoeial Preparations

BP 2014: Ergotamine Sublingual Tablets;
USP 36: Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Ergotamine Tartrate Inhalation Aerosol; Ergotamine Tartrate Injection; Ergotamine Tartrate Tablets.

Feverfew

Camomille, grande; Matrem; Matricaria; Mattram; Mutterkraut; Nat' kopretiny řimbaby; Partenio; Reunuspäivänkakkara; Rimbaba Obyčajná; Spilcuță; Tanaceti Parthenii Herba; Tanaceto; Vaistinių skaistenių žolė; Wermod Wen; Пиретрум Девичий; Őszi margitvirág; Девичья Трава.

ATC Herb — HN02CW5005 (Tanacetum parthenium: leaf).
UNII — 6GE7Z0761K (Tanacetum parthenium); Z64FK7P217 (Tanacetum parthenium leaf).

Pharmacopoeias. In *Eur.* (see p. vii) and in *US*. *US* also describes Powdered Feverfew.

Ph. Eur. 8: (Feverfew). The dried, whole or fragmented aerial parts of *Tanacetum parthenium*. It contains not less than 0.2% of parthenolide ($C_{15}H_{20}O_3$ = 248.3), calculated with reference to the dried drug. It has a camphoraceous odour. Protect from light.

USP 36: (Feverfew). It consists of the dried leaves of *Tanacetum parthenium* (Asteraceae), collected when the plant is in flower. Store in a dry place. Protect from light.

Uses and Administration

Feverfew consists of the dried leaves of the plant *Tanacetum parthenium* (Asteraceae). It is a traditional herbal remedy used in the prophylaxis of migraine. Its effects have been attributed to the plant's content of sesquiterpene lactones, notably parthenolide. A preparation of the dried leaf powder, which has been standardised to provide a minimum of 0.2% parthenolide, is available in some countries. A suggested oral dose is 250 mg daily; a lower dose of 100 mg daily has also been given.

Extracts of feverfew, particularly parthenolide-free extracts which have been promoted as less sensitising, have been used for their supposed anti-inflammatory benefits in cosmetics and topical products.

Parthenolide has also been investigated for its antineoplastic potential.

Migraine. Feverfew is a traditional herbal remedy used in the prophylaxis of migraine (p. 670.3). Studies of standardised preparations of the freeze-dried powdered leaf have produced variable results in preventing or ameliorating migraine attacks, and a systematic review[1] has concluded that its efficacy in preventing migraine is unproven.

1. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Rheumatoid arthritis. Feverfew has anti-inflammatory activity *in vitro* and has been tried in the treatment of rheumatic diseases. However, an evidence-based report by the Arthritis Research Campaign[1] in the UK considered that it was ineffective in rheumatoid arthritis (p. 13.2), although adverse effects were minor with short-term use.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_110120101543331.pdf (accessed 25/11/10)

Adverse Effects and Precautions

Most adverse effects noted with feverfew are mild and reversible. Mouth ulceration and soreness have been reported, and may be due to sensitisation; if they occur feverfew should be withdrawn. Contact dermatitis has also been reported. Gastrointestinal effects such as nausea, constipation or diarrhoea, and heartburn occur rarely and there have been spontaneous reports of eosinophilia, abnormal liver function tests, renal failure, Raynaud's phenomenon, and hypertension. Withdrawal symptoms such as rebound headache, anxiety, and insomnia have been seen in long-term users of feverfew who stop treatment suddenly.

Feverfew is reputed to have abortifacient properties and it is recommended that preparations should not be used in pregnancy.

Effects on the blood. There have been suggestions that feverfew may increase the risk of bleeding during surgery or in patients taking anticoagulants. However, although inhibition of platelet aggregation has been reported *in vitro* or in *animals* a review[1] of clinical studies noted that feverfew did not appear to affect haematological safety parameters.

1. Pittler MH, Ernst E. Feverfew for preventing migraine. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/05).

Interactions

It has been suggested that feverfew may enhance the effects of anticoagulants (but see Effects on the Blood, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Migraine Aid; ***Braz.***: Enxamed†; Tanaceto†; Tenliv; ***Canad.***: Tanacet†; ***Pol.***: Mariomigran†; ***UK***: DiaFeverfew; DiaMigraine; Migraherb; Tanacet.

Multi-ingredient Preparations. ***Austral.***: Albizia Complex; Extralife Arthri-Care†; Extralife Migrai-Care†; Rehmannia Complex; ***Ital.***: Neuralta Migren.

Homoeopathic Preparations. ***Fr.***: Poconeol no 43.

Frovatriptan *(BAN, rINN)*

Frovatriptaani; Frovatriptán; Frovatriptanum; SB-209509AX (frovatriptan or frovatriptan succinate); VML-251 (frovatriptan or frovatriptan succinate); Фроватриптан.

(6*R*)-5,6,7,8-Tetrahydro-6-methylaminocarbazole-3-carboxamide.

$C_{14}H_{17}N_3O$=243.3
CAS — 158747-02-5.
ATC — N02CC07.
ATC Vet — QN02CC07.
UNII — H82Q2D5WA7.

Frovatriptan Succinate *(BANM, USAN, rINNM)*

Frovatriptan, Succinate de; Frovatriptán, succinato de; Frovatriptani Succinas; SB-209509AX (frovatriptan or frovatriptan succinate); Succinato de frovatriptán; VML-251 (frovatriptan or frovatriptan succinate); Фроватриптана Суксинат.

$C_{14}H_{17}N_3O.C_4H_6O_4.H_2O$=379.4
CAS — 158930-17-7.
ATC — N02CC07.
ATC Vet — QN02CC07.
UNII — D28J6W18HY.

Uses and Administration

Frovatriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Frovatriptan is given orally as the succinate although doses are expressed in terms of the base; frovatriptan succinate 3.9 mg is equivalent to about 2.5 mg of frovatriptan.

The recommended dose is 2.5 mg; if this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of at least 2 hours. The maximum dose of frovatriptan in 24 hours is 5 mg in the UK although, in the USA, a maximum daily dose of 7.5 mg is allowed.

Reviews.

1. Markus P, Mikko K. Provatriptan review. *Expert Opin Pharmacother* 2007; 8: 3029–33.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1

Further references.

1. Poolsup N, *et al.* Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2005; 30: 521–32.
2. Markus P, Mikko K. Provatriptan review. *Expert Opin Pharmacother* 2007; 8: 3029–33.
3. Elkind AH, MacGregor EA. Provatriptan for the acute treatment of migraine and prevention of predictable menstrual migraine. *Expert Rev Neurother* 2008; 8: 723–36.
4. Guidotti M, Ravasio R. Clinical and economic comparison of frovatriptan versus other oral triptans in the treatment of acute migraine in the real-world setting. *Clin Drug Investig* 2009; 29: 693–702.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

UK licensed product information recommends that frovatriptan should not be used in patients with severe hepatic impairment (Child-Pugh class C); however, this is due to a lack of data and no dosage adjustment is needed in mild or moderate hepatic impairment.

Interactions

As for Sumatriptan, p. 681.3.

Frovatriptan is metabolised by the cytochrome P450 isoenzyme CYP1A2; fluvoxamine, a potent inhibitor of this isoenzyme, has been shown to increase the blood concentrations of frovatriptan by 27 to 49%.

Pharmacokinetics

After oral doses, peak plasma-frovatriptan concentrations occur in 2 to 4 hours, and bioavailability is about 20% in men and 30% in women. Food may delay the time to peak plasma concentrations by about 1 hour. Frovatriptan is 15% protein bound. It is mainly metabolised by the hepatic cytochrome P450 isoenzyme CYP1A2. About 32% of an oral dose is excreted in the urine and 62% in faeces. The plasma elimination half-life of frovatriptan is about 26 hours.

Distribution into milk has been found in studies in *rats*.

References.

1. Buchan P, *et al.* Clinical pharmacokinetics of frovatriptan. *Headache* 2002; 42 (suppl 2): S54–S62.
2. Elkind AH, *et al.* Pharmacokinetics of frovatriptan in adolescent migraineurs. *J Clin Pharmacol* 2004; 44: 1158–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Eumitan; Provamig; ***Belg.***: Provatex; Migard; ***Canad.***: Frova; ***Cz.***: Fromen; Recur; ***Denm.***: Migard; ***Fin.***: Migard; Tigreat†; ***Fr.***: Isimig; Tigreat; ***Ger.***: Allegro; ***Gr.***: Migard; Migralin; Pitunal; ***Irl.***: Frovex; ***Ital.***: Auradol; Rilamig; ***Neth.***: Fromirex; Migard; ***Port.***: Dorlise; Migard; ***Spain***: Forvey; Perlic; ***Swed.***: Migard; ***Switz.***: Menamig; ***Turk.***: Newart; ***UK***: Migard; ***USA***: Frova.

Iprazochrome *(rINN)*

Ipratsokromi; Iprazochromum; Iprazocromo; Iprazokrom; Ипразохром.

3-Hydroxy-1-isopropyl-5,6-indolinedione 5-semicarbazone.

$C_{12}H_{16}N_4O_3$=264.3
CAS — 7248-21-7.
ATC — N02CX03.
ATC Vet — QN02CX03.
UNII — 903A9K181P.

Profile

Iprazochrome is a serotonin antagonist used in the prophylaxis of migraine (p. 670.3) and in the management of diabetic retinopathy. It has been given in usual oral doses of 2.5 to 5 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Divascan; ***Pol.***: Divascan.

Lomerizine Hydrochloride *(rINNM)*

Flometizine Hydrochloride; Hidrocloruro de lomerizina; KB-2796; Lomérizine, Chlorhydrate de; Lomerizine Dihydrochloride; Lomerizini Hydrochloridum; Ломеризина Гидрохлорид.

1-[Bis(*p*-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl) piperazine dihydrochloride.

$C_{27}H_{30}F_2N_2O_3.2HCl$=541.5

CAS — 101477-55-8 (lomerizine); 101477-54-7 (lomerizine hydrochloride).
UNII — 3W473DSLIY.

Profile

Lomerizine is a calcium-channel blocker that is used orally as the hydrochloride in the treatment of migraine. It is also under investigation for its potential value in glaucoma.

References.

1. Hara H, *et al.* Clinical potential of lomerizine, a Ca_2, channel blocker as an anti-glaucoma drug: effects on ocular circulation and retinal neuronal damage. *Cardiovasc Drug Rev* 2004; **22**: 199–214.
2. Iwasaki S, *et al.* Migraine-associated vertigo: clinical characteristics of Japanese patients and effect of lomerizine, a calcium channel antagonist. *Acta Otolaryngol* 2007; (suppl 559): 45–9.
3. Imai N, *et al.* Do the effects of long-term lomerizine administration differ with age? *Intern Med* 2007; **46**: 683–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Hou Pu (后普); Luo Mei Er (罗美达); Qing Tian (清天); Shao Rong (绍容); Tesuxin (特苏欣); Xi Rui Li (西瑞利); XiJing (希静); Ya Yi Jia (亚伊加); *Jpn*: Migsis; Terranas.

Methysergide *(BAN, USAN, rINN)*

1-Methyl-D-lysergic Acid Butanolamide; Methysergid; Méthysergide; Methysergidum; Metisergida; Metysergid; Metysergidi; Метизергид.

N-[1-(Hydroxymethyl)propyl]-1-methyl-D-lysergamide; 9,10-Didehydro-*N*-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8β-carboxamide.

$C_{21}H_{27}N_3O_2$=353.5
CAS — 361-37-5.
ATC — N02CA04.
ATC Vet — QN02CA04.
UNII — XZA9HY6Z98.

Methysergide Maleate *(BANM, rINNM)*

Maleato de metisergida; Méthysergide, Maléate de; Methysergidi Maleas; Metisergida, maleato de; Метизергида Малеат.

$C_{21}H_{27}N_3O_2.C_4H_4O_4$=469.5
CAS — 129-49-7.
ATC — N02CA04.
ATC Vet — QN02CA04.
UNII — 2U7H1466GH.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Methysergide Maleate). A white or almost white crystalline powder which may have a yellow or pink tinge; odourless or almost odourless. Slightly soluble in water and in methyl alcohol; practically insoluble in chloroform and in ether. A 0.2% solution in water has a pH of 3.7 to 4.7. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Methysergide Maleate). A white to yellowish-white or reddish-white, crystalline powder. Is odourless or has not more than a slight odour. Soluble 1 in 200 of water and 1 in 165 of alcohol; soluble 1 in 3400 of chloroform; practically insoluble in ether. pH of a 1 in 500 solution is between 3.7 and 4.7. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Methysergide maleate is a semisynthetic ergot alkaloid. It is a potent serotonin antagonist and, compared with ergotamine, has only weak vasoconstrictor and oxytocic effects. It may be used to prevent severe recurrent migraine (p. 670.3) and headache attacks during cluster periods (p. 670.1), although its use has declined because of adverse effects. It is ineffective in the treatment of acute attacks.

Methysergide is given orally as the maleate but doses are often expressed in terms of the base; 1.33 mg of methysergide maleate is equivalent to about 1 mg of methysergide. A usual dosage is 2 to 6 mg daily given in divided doses with meals. It is suggested that treatment should be started with 1 mg at bedtime and doses increased gradually over about 2 weeks; the minimum effective dose should be used. Careful and regular observation of the patient is essential because of the high incidence of adverse effects and it is recommended that treatment should only be carried out under hospital supervision. If treatment still proves to be ineffective after 3 weeks, further use is unlikely to be of benefit. Treatment should not be continued for more than 6 months, after which it should be gradually withdrawn over 2 or 3 weeks and then stopped for at least a month for reassessment. Some have considered that treatment courses should not exceed 3 months without a break.

Methysergide maleate has also been used to control diarrhoea associated with carcinoid syndrome (see under Neuroendocrine Tumours, p. 716.3) in high doses equivalent to 12 to 20 mg of methysergide daily.

As a serotonin antagonist, methysergide might be expected to help reverse the serotonin syndrome (p. 443.2).

Reviews.

1. Koehler PJ, Tfelt-Hansen PC. History of methysergide in migraine. *Cephalalgia* 2008; **28**: 1126–35.

Adverse Effects

Gastrointestinal effects such as nausea, vomiting, heartburn, and abdominal pain are common on initial treatment with methysergide maleate, as are dizziness and drowsiness. Other CNS effects reported include ataxia, insomnia, weakness, restlessness, lightheadedness, euphoria, and hallucinations. Peripheral or localised oedema, leg cramps, and weight gain have occurred and there have been occasional reports of rashes, loss of hair, joint and muscle pain, neutropenia, and eosinophilia. Orthostatic hypotension and tachycardia have been noted. There have been isolated reports of myocardial infarction particularly in patients with ischaemic heart disease or when given with other vasoconstrictive drugs, both of which are contra-indications for methysergide therapy.

Arterial spasm has occurred in some patients, and may present as paraesthesia of the extremities or anginal pain, as with ergotamine (p. 674.2); if such symptoms occur methysergide should be withdrawn, although rebound headaches may occur if it is withdrawn suddenly. Vascular insufficiency of the lower limbs may represent arterial spasm or fibrotic changes. Treatment should be stopped at the first signs of impaired peripheral circulation. Retroperitoneal fibrosis, with obstruction of abdominal blood vessels and ureters, pleuropulmonary fibrosis, and fibrotic changes in heart valves have occurred in patients on long-term treatment. Methysergide must be withdrawn immediately if fibrosis occurs. Retroperitoneal fibrosis is usually reversible, but other fibrotic changes are less readily reversed.

Effects on the skin. Scleroderma-like changes to the legs, in addition to aortic fibrosis in the absence of retroperitoneal fibrosis, was associated with long-term methysergide therapy in a 63-year old woman.[1] The patient presented with a 2-month history of inflammatory oedema of the legs and feet.

1. Kluger N, *et al.* Methysergide-induced scleroderma-like changes of the legs. *Br J Dermatol* 2005; **153**: 224–5.

Fibrosis. Fibrosis has been associated with the long-term use of methysergide maleate. In one early report[1] in 27 patients retroperitoneal fibrosis was attributed to use of methysergide for periods of 9 to 54 months in doses ranging from 2 to 28 mg daily. There was partial or complete regression of fibrosis in 13 of the patients whose treatment was withdrawn. Improvement usually began within a few days, in some cases with the aid of prednisone. The other 14 patients were treated by surgery; those few who continued taking methysergide had difficult postoperative courses. Cardiac murmurs occurred in 7 patients, and regressed wholly or partially in 3 after therapy was stopped. Fibrotic changes affecting the aorta, heart valves, and pulmonary tissues occurred in a few of the patients. Others have reported the development of endocardial fibrosis indicated by cardiac murmurs in 48 patients receiving methysergide.[2] The murmurs gradually regressed in 27 when methysergide was stopped. Retroperitoneal fibrosis was present in 9 patients and pleuropulmonary fibrosis in 2. A patient with fibrosis of the iliac vein has been described.[3]

A few cases of retroperitoneal fibrosis associated with ergotamine tartrate or dihydroergotamine have also been noted.[1] These 2 drugs have also been implicated in a few other cases of retroperitoneal fibrosis or other fibrotic disorders in patients taking high doses for long periods.[4-7]

1. Graham JR, *et al.* Fibrotic disorders associated with methysergide therapy for headache. *N Engl J Med* 1966; **274**: 359–68.
2. Bana DS, *et al.* Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. *Am Heart J* 1974; **88**: 640–55.
3. Bucci JA, Manoharan A. Methysergide-induced retroperitoneal fibrosis: successful outcome and two new laboratory features. *Mayo Clin Proc* 1997; **72**: 1148–50.
4. Lepage-Savary D, Vallières A. Ergotamine as a possible cause of retroperitoneal fibrosis. *Clin Pharm* 1982; **1**: 179–80.
5. Robert M, *et al.* Fibrotic processes associated with long-term ergotamine therapy. *N Engl J Med* 1984; **311**: 601 and 602.
6. Damstrup L, Jensen TT. Retroperitoneal fibrosis after long-term daily use of ergotamine. *Int Urol Nephrol* 1986; **18**: 299–301.
7. Malaquin F, *et al.* Pleural and retroperitoneal fibrosis from dihydroergotamine. *N Engl J Med* 1989; **321**: 1760.

Treatment of Adverse Effects

As for Ergotamine Tartrate, p. 674.3.

Methysergide maleate should be withdrawn immediately if fibrosis develops. Corticosteroids have been used to treat fibrosis, although surgery may be required.

Precautions

As for Ergotamine Tartrate, p. 675.1.

In addition, methysergide maleate is contra-indicated in valvular heart disease, pulmonary and collagen diseases, diseases of the urinary tract, phlebitis and cellulitis of the lower extremities, and debilitated states. It should be used with caution in patients with peptic ulcer disease because it may increase gastric acidity. Patients should be closely supervised. Methysergide should not be given continuously for more than 6 months and should normally be withdrawn gradually (see Uses and Administration, above). However, it should be withdrawn immediately if symptoms of fibrosis or arterial spasm develop.

Interactions

Interactions involving those ergot alkaloids used mainly in the management of migraine are discussed under ergotamine (p. 675.2). References specific to methysergide may be found there under the headings Antimigraine Drugs (p. 675.2) and Beta Blockers (p. 675.3).

Pharmacokinetics

Methysergide maleate is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring within about one hour of ingestion. It is 66% bound to plasma proteins. Methysergide undergoes extensive first-pass hepatic metabolism to methylergometrine (p. 2137.3). About 50% of an oral dose is excreted in the urine as unchanged drug and metabolites. The elimination of methysergide is biphasic; half-lives of about 2.7 hours and 10 hours have been reported for the 2 phases respectively.

References.

1. Bredberg U, *et al.* Pharmacokinetics of methysergide and its metabolite methylergometrine in man. *Eur J Clin Pharmacol* 1986; **30**: 75–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Deseril; *Belg.*: Deseril; *Braz.*: Deserila; *Canad.*: Sansert†; *Fr.*: Desernil; *Neth.*: Deseril; *UK*: Deseril†.

Pharmacopoeial Preparations
BP 2014: Methysergide Tablets;
USP 36: Methysergide Maleate Tablets.

Naratriptan Hydrochloride

(BANM, USAN, rINNM)

GR-85548A; GR-85548X (naratriptan); Hidrocloruro de naratriptán; Naratriptan, Chlorhydrate de; Naratriptán, hidrocloruro de; Naratriptani Hydrochloridum; Нарατриптана Гидрохлорид.

N-Methyl-3-(1-methyl-4-piperidyl)indole-5-ethanesulfonamide hydrochloride.

$C_{17}H_{25}N_3O_2S.HCl$=371.9
CAS — 121679-13-8 (naratriptan); 121679-19-4 (naratriptan hydrochloride); 143388-64-1 (naratriptan hydrochloride).
ATC — N02CC02.
ATC Vet — QN02CC02.
UNII — 10X8X4P12Z.

Pharmacopoeias. In *US.*

USP 36: (Naratriptan Hydrochloride). A white to pale yellow solid. Soluble in water. Store in airtight containers at a temperature not exceeding 30 degrees.

Uses and Administration

Naratriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. It is given orally as the hydrochloride, and doses are expressed in terms of the base; naratriptan hydrochloride 1.11 mg is equivalent to about 1 mg of naratriptan.

The recommended dose of naratriptan in the UK is 2.5 mg; in the USA a dose of 1 or 2.5 mg is allowed. If no response is obtained with the initial dose, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of 4 hours, to a maximum of 5 mg in any 24-hour period. For doses in hepatic or renal impairment see below.

Administration in hepatic or renal impairment. Naratriptan is contra-indicated in patients with severe hepatic (Child-Pugh class C) or severe renal impairment (creatinine clearance less than 15 mL/minute). In patients with mild to moderate hepatic or renal impairment, the recommended maximum oral dose in 24 hours is 2.5 mg and a lower starting dose should be considered.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. *Pharmacoepidemiol Drug Safety* 2004; 13: 73–82.
2. Tfelt-Hansen PC. Published and not fully published double-blind, randomised, controlled trials with oral naratriptan in the treatment of migraine: a review based on the GSK Trial Register. *J Headache Pain* 2011; 12: 399–403.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

Naratriptan should not be used in patients with severe hepatic (Child-Pugh class C) or renal (creatinine clearance less than 15 mL/minute) impairment. Naratriptan should be used with caution in mild or moderate renal or hepatic impairment. Patients with hypersensitivity to sulfonamides may theoretically show a similar reaction to naratriptan. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.)

Medication-overuse headache. For a report of an association between naratriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p. 681.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naratriptan 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 11/04/11)

Interactions

As for Sumatriptan, p. 681.3.

Pharmacokinetics

After oral doses, peak plasma-naratriptan concentrations occur at 2 to 3 hours, and bioavailability is reported to be 63% in men and 74% in women. Plasma protein binding is about 29%. Naratriptan undergoes some hepatic metabolism via a wide range of cytochrome P450 isoenzymes. It is mainly excreted in the urine with 50% of a dose being recovered as unchanged drug and 30% as inactive metabolites. The elimination half-life is 6 hours, and is significantly prolonged in patients with renal or hepatic impairment.

Distribution into milk has been found in studies in *rats*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Naramig; *Austral.*: Naramig; *Austria*: Antimigrin†; Naramig; *Belg.*: Naramig; *Braz.*: Naramig; Naratrin; *Canad.*: Amerge; *Chile*: Bagomigral; Migtal; Miragran; Naramig; *Cz.*: Naramig; *Denm.*: Naragran; Naramig; *Fin.*: Naramig; *Fr.*: Naramig; *Ger.*: Formigran; Naramig; *Gr.*: Naramig; *India*: Naratrex; *Irl.*: Naramerg†; Naramig; Naraverg; *Israel*: Naramig; *Mex.*: Naramig†; *Neth.*: Migatane; Naramig; *Norw.*: Naramig; *NZ*: Naramig; *Port.*: Naramig; *Rus.*: Naramig (Нарамиг); *S.Afr.*: Naramig; *Singapore*: Naramig; *Spain*: Naramig; *Swed.*: Naramig; *Switz.*: Naramig; *Turk.*: Naramig; *UK*: Naramig; *USA*: Amerge.

Pharmacopoeial Preparations

USP 36: Naratriptan Hydrochloride Oral Suspension; Naratriptan Tablets.

Oxetorone Fumarate *(USAN, rINNM)*

Fumarato de oxetorona; L-6257; Oxetorona, fumarato de; Oxétorone, Fumarate d'; Oxetoróni Fumaras; Оксеторона Фумарат.

3-(6,12-Dihydrobenzofuro[3,2-c][1]benzoxepin-6-ylidene)-*NN*-dimethylpropylamine hydrogen fumarate.

$C_{21}H_{21}NO_2.C_4H_4O_4$=435.5

CAS — 26020-55-3 (oxetorone); 34522-46-8 (oxetorone fumarate).

ATC — N02CX06.

ATC Vet — QN02CX06.

UNII — 5SYZ8I05SH.

Profile

Oxetorone fumarate is an antihistamine and serotonin antagonist used orally in the treatment of migraine (p. 670.3) and cluster headache (p. 670.1) in doses of up to 180 mg daily. Oxetorone was reported to have induced hyperplastic changes in breast tissue and the uterine endometrium of *rodents*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Nocertone†; *Fr.*: Nocertone; *Gr.*: Nocertone.

Pizotifen *(BAN, rINN)*

BC-105; Pitsotifeeni; Pizotifène; Pizotifeno; Pizotifenum; Pizotyfen; Pizotyline (USAN); Пизотифен.

9,10-Dihydro-4-(1-methylpiperidin-4-yldene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene.

$C_{19}H_{21}NS$=295.4

CAS — 15574-96-6.

ATC — N02CX01.

ATC Vet — QN02CX01.

UNII — 0BYB440V3N.

Pharmacopoeias. In *Chin.*

Pizotifen Malate *(BANM, rINNM)*

Malato de pizotifeno; Pizotifen Hydrogen Malate; Pizotifène, Malate de; Pizotifeni Malas; Pizotifeno, malato de; Pizotyline Malate; Пизотифена Малат.

$C_{19}H_{21}NS.C_4H_6O_5$=429.5

CAS — 5189-11-7.

ATC — N02CX01.

ATC Vet — QN02CX01.

Pharmacopoeias. In *Br.*

BP 2014: (Pizotifen Malate). A white or slightly yellowish-white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in chloroform; sparingly soluble in methyl alcohol. Protect from light.

Uses and Administration

Pizotifen is a sedating antihistamine (p. 610.1) that has strong serotonin antagonist and weak antimuscarinic properties. It also antagonises the action of tryptamine. Pizotifen is used, usually as the malate, for the prophylaxis of migraine and for the prevention of headache attacks during cluster periods. It is not effective in treating an acute attack. Doses of pizotifen malate are expressed in terms of the base; pizotifen malate 1.45 mg is equivalent to about 1 mg of pizotifen. Pizotifen hydrochloride has also been used in the management of migraine.

The usual oral dose is the equivalent of 1.5 mg of pizotifen daily either in three divided doses or as a single dose at night. Gradual increase from an initial dose of 500 micrograms may help to avoid undue drowsiness. Doses may vary from 500 micrograms up to a maximum of 4.5 mg daily; not more than 3 mg should be given as a single dose.

For details of doses in children, see below.

Administration in children. For the prophylaxis of migraine and for the prevention of headache attacks during cluster periods, children aged over 2 years may be given up to 1.5 mg daily of pizotifen orally, although the maximum single dose (at night) should not exceed 1 mg. Gradual increase from an initial dose of 500 micrograms may help to avoid undue drowsiness.

Abdominal migraine. Abdominal migraine is a recurrent disorder seen mainly in children and characterised by episodic midline abdominal pain lasting for up to 72 hours. The pain is severe enough to disrupt normal activities and may be associated with pallor, anorexia, nausea, and vomiting.[1,2] Sleep, and sometimes vomiting, terminate the attack.

In one small study pizotifen was found to be effective for the prophylaxis of abdominal pain in children with abdominal migraine;[3] however, a systematic review concluded that there was only weak evidence in favour of such use in recurrent abdominal pain and suggested that pizotifen should only be used in the context of clinical trials or in children with severe problems refractory to conventional management.[4] Prophylactic treatment with propranolol or cyproheptadine may also be of benefit.[5]

1. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; 24 (suppl 1): 9–160. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/cha.2004.24.issue-s1/issuetoc (accessed 12/08/10)
2. Russell G, *et al.* The child with recurrent abdominal pain: is it abdominal migraine? *Br J Hosp Med* 2007; 68: M110–M113.
3. Symon DNK, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child* 1995; 72: 48–50.
4. Huertas-Ceballos A, *et al.* Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 14/12/10).
5. Worawattanakul M, *et al.* Abdominal migraine: prophylactic treatment and follow-up. *J Pediatr Gastroenterol Nutr* 1999; 28: 37–40.

Migraine and cluster headache. Pizotifen has been widely used for the prophylaxis of migraine (p. 670.3) but evidence for its efficacy is limited. It has also been tried in the management of cluster headache (p. 670.1) to prevent headache attacks during a cluster period.

References.

1. Cleland PG, *et al.* Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. *Eur Neurol* 1997; 38: 31–8.
2. Barnes N, Millman G. Do pizotifen or propranolol reduce the frequency of migraine headache? *Arch Dis Child* 2004; 89: 684–5.

Adverse Effects and Precautions

As for the sedating antihistamines in general, see p. 613. and p. 613.3.

Increased appetite and weight gain may occur with pizotifen. Drowsiness may be troublesome.

Incidence of adverse effects. Adverse effects were noted in 22 of 47 patients with severe migraine given pizotifen to 2 mg daily.[1] These reactions included weight increase (15 patients), muscle pain or cramps (3 patients), heavy or restless legs (3 patients), fluid retention (3 patients), drowsiness (2 patients), more frequent milder headaches (patients), facial flushing (1 patient), reduced libido (patient), exacerbation of epilepsy (1 patient), and dreaming (2 patients). Adverse effects necessitating withdrawa occurred in 11 patients.

1. Peet KMS. Use of pizotifen in severe migraine: a long-term study. *Curr Med Res Opin* 1977; 5: 192–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pizotifen 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 11/04/11)

Interactions

As for the sedating antihistamines in general, see p. 614.3.

Antihypertensives. After a report[1] of loss of blood pressure control when treatment with pizotifen was started in a patient receiving *debrisoquine* the manufacturer suggested that since pizotifen had a similar chemical structure to the tricyclic antidepressants it might antagonise the actions of adrenergic neurone blockers in a similar manner.

1. Bailey RR. Antagonism of debrisoquine sulphate by pizotifen (Sandomigran). *N Z Med J* 1976; 1: 449.

Pharmacokinetics

Pizotifen is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 5 hours after a single oral dose. Over 90% is bound to plasma proteins. Pizotifen undergoes extensive metabolism. Over half of a dose is excreted in the urine, mainly as metabolites; a significant proportion is excreted in the faeces. The primary metabolite of pizotifen (*N*-glucuronide conjugate) has a long elimination half-life of about 23 hours.

Distribution into milk has been found in *animal* studies.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sandomigran; *Austral.*: Sandomigran; *Belg.*: Sandomigran; *Braz.*: Sandomigran; *Canad.*: Sandomigran; *Cz.*: Sandomigran; *Denm.*: Sandomigrin; *Fr.*: Sanmigran; *Gr.*: Mosegor; *Hong Kong*: Sandomigran; *Indon.*: Lysagor; *Irl.*: Sanomigran; *Ital.*: Sandomigran; *Malaysia*: Sandomigran; *Neth.*: Sandomigran; *NZ*: Sandomigran; *Philipp.*: Litec; Mor-Vita; Mosegor; *Pol.*: Polomigran; *S.Afr.*: Sandomigran; *Spain*: Mosegor; Sandomigran; *Swed.*: Sandomigrin; *Switz.*: Mosegor†; *Thai.*: Anorsia; Bozo; Manzofen; Migrin; Mosegor; Moselar; Mozifen-EF; Pizomed; Zofen; *Turk.*: Sandomigran; *UK*: Sanomigran.

Multi-ingredient Preparations. *Philipp.*: Appetens; Mosegor Vita.

Pharmacopoeial Preparations

BP 2014: Pizotifen Tablets.

Rizatriptan Benzoate

(BANM, USAN, pINNM)

Benzoato de rizatriptán; MK-0462; MK-462; Ritsatriptaanibentsoaatti; Rizatriptan, Benzoate de; Rizatriptán, benzoato de; Rizatriptani Benzoas; Ризатриптана бензоат.

3-[2-(Dimethylamino)ethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl) indole monobenzoate; Dimethyl(2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)indol-3-yl]ethyl)amine monobenzoate.

$C_{15}H_{19}N_5.C_7H_6O_2$=391.5

CAS — 144034-80-0 (rizatriptan); 145202-66-0 (rizatriptan benzoate).
ATC — N02CC04.
ATC Vet — QN02CC04.
UNII — WR978S7QHH.

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

Ph. Eur. 8: (Rizatriptan Benzoate). A white or almost white powder or crystals. Soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. It shows polymorphism.

USP 36: (Rizatriptan Benzoate). A white to almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane.

Uses and Administration

Rizatriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (below). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Rizatriptan is given as the benzoate, and doses are expressed in terms of the base; rizatriptan benzoate 14.5 mg is equivalent to about 10 mg of rizatriptan.

The licensed dose in the UK of rizatriptan is the equivalent of 10 mg orally. If this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, a further dose of 10 mg may be taken after an interval of at least 2 hours. In the USA licensed doses of 5 or 10 mg are used. The recommended maximum dose in 24 hours is 20 mg in the UK and 30 mg in the USA. A reduced dose of 5 mg is recommended in patients also receiving propranolol (see Interactions, below), with the maximum dose in 24 hours reduced to 10 mg in the UK and 15 mg in the USA. It is also recommended that doses of the 2 drugs should be separated by at least 2 hours.

For doses in children and in hepatic or renal impairment, see below.

Administration in children. In the USA, rizatriptan is licensed for the treatment of acute migraine in children and adolescents aged 6 to 17 years. A single oral dose of 5 mg may be given to children weighing less than 40 kg and 10 mg to those weighing 40 kg or more. In children also receiving propranolol (see Interactions, below), a single dose of rizatriptan 5 mg is recommended in those who weigh 40 kg or more; however, it should not be given to those who weigh less than 40 kg. The safety and efficacy of a second dose have not been established.

Administration in hepatic or renal impairment. UK licensed product information recommends that in patients with mild to moderate hepatic or renal impairment, the oral dose of rizatriptan should be reduced to 5 mg. If the headache recurs after an initial response, a further dose of 5 mg may be taken after an interval of at least 2 hours. The recommended maximum dose in 24 hours in these patients is 10 mg. It is also recommended that rizatriptan should not be used in patients with severe hepatic or renal impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Wellington K, Plosker GL. Rizatriptan: an update of its use in the management of migraine. *Drugs* 2002; **62**: 1539–74.
2. Pascual J. A review of rizatriptan, a quick and consistent 5-HT1B/1D agonist for the acute treatment of migraine. *Expert Opin Pharmacother* 2004; **5**: 669–77.
3. Ahonen K, *et al.* A randomized trial of rizatriptan in migraine attacks in children. *Neurology* 2006; **67**: 1135–40.
4. Mannix LK. A review of the 5-HT1B/1D agonist rizatriptan: update on recent research and implications for the future. *Expert Opin Pharmacother* 2008; **9**: 1001–11.
5. Hargreaves RJ, *et al.* Ten years of rizatriptan: from development to clinical science and future directions. *Headache* 2009; **49** (suppl 1): S3–S20.
6. Göbel H. Efficacy and tolerability of rizatriptan 10 mg compared with sumatriptan 100 mg: an evidence-based analysis. *Expert Rev Neurother* 2010; **10**: 499–506.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2. Toxic epidermal necrolysis has also been reported with rizatriptan.

Rizatriptan should be given with caution to patients with mild or moderate hepatic or renal impairment; UK licensed product information contra-indicates its use in more severe impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rizatriptan 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 11/04/11)

Interactions

As for Sumatriptan, p. 681.3.

Propranolol increases plasma-rizatriptan concentrations and it is recommended that lower doses of rizatriptan should be used in patients receiving both drugs (see Uses and Administration, above).

Pharmacokinetics

After oral doses, peak plasma-rizatriptan concentrations occur in about 1 to 2.5 hours depending on the formulation. Bioavailability is about 40 to 45%. Food may delay the time to peak plasma concentrations of the tablet formulation by about 1 hour. Plasma protein binding is low (14%).

Rizatriptan is metabolised mainly by monoamine oxidase type A to the inactive indole acetic acid derivative. The active metabolite *N*-monodesmethyl-rizatriptan is formed to a minor degree; other minor metabolites are also produced. About 14% of an oral dose is excreted in the urine as unchanged rizatriptan, 51% as the indole acetic acid metabolite, and no more than 1% as *N*-monodesmethyl-rizatriptan. The plasma half-life is about 2 to 3 hours.

Distribution into milk has been found in studies in *rats.*

References.

1. Lee Y, *et al.* Pharmacokinetics and tolerability of oral rizatriptan in healthy male and female volunteers. *Br J Clin Pharmacol* 1999; **47**: 373–8.
2. Goldberg MR, *et al.* Rizatriptan, a novel $5\text{-}HT_{1B/1D}$ agonist for migraine: single- and multiple-dose tolerability and pharmacokinetics in healthy subjects. *J Clin Pharmacol* 2000; **40**: 74–83.
3. Vyas KP, *et al.* Disposition and pharmacokinetics of the antimigraine drug, rizatriptan, in humans. *Drug Metab Dispos* 2000; **28**: 89–95.
4. Swan SK, *et al.* Pharmacokinetic profile of rizatriptan 10-mg tablet and 10-mg orally disintegrating tablet administered with or without water in healthy subjects: an open-label, randomized, single-dose, 3-period crossover study. *J Clin Pharmacol* 2006; **46**: 172–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Maxalt; ***Austria***: Maxalt; ***Belg.***: Maxalt; ***Braz.***: Maxalt; ***Canad.***: Maxalt; ***Chile***: Maxalt; ***China***: Ouliting (欧立停); ShanQing (善清); Xin Qu (欣驱); ***Denm.***: Maxalt; ***Fin.***: Maxalt; ***Fr.***: Maxalt; Maxaltlyo; ***Ger.***: Maxalt; ***Gr.***: Maxalt; Modinol; ***India***: Rizact; ***Israel***: Rizalt; ***Ital.***: Maxalt; Rizaliv; Trizadol; ***Mex.***: Maxalt†; ***Neth.***: Latariz; Maxalt; Rizatan; Triptosig; ***Norw.***: Maxalt; ***NZ***: Maxalt; ***Pol.***: Maxalt; ***Port.***: Maxalt; Migroff†; ***S.Afr.***: Maxalt; ***Spain***: Maxalt; ***Swed.***: Maxalt; ***Switz.***: Maxalt; ***Turk.***: Maxalt; ***UK***: Maxalt; ***USA***: Maxalt; ***Venez.***: Maxalt.

Sumatriptan *(BAN, rINN)*

GR-43175X; Sumatriptaani; Sumatriptán; Sumatriptanum; Sumatryptan; Суматриптан.

3-(2-Dimethylaminoethyl)indol-5-yl-*N*-methylmethanesulfonamide.

$C_{14}H_{21}N_3O_2S$=295.4

CAS — 103628-46-2.
ATC — N02CC01.
ATC Vet — QN02CC01.
UNII — 8R78F6L9VO.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Sumatriptan). A white to pale yellow powder. Very slightly soluble in water. Protect from light.

USP 36: (Sumatriptan). A white to pale yellow powder. Very slightly soluble in water. Store in airtight containers at below 30 degrees. Do not allow to freeze. Protect from light.

Sumatriptan Succinate *(BANM, USAN, rINNM)*

GR-43175C; SN-308; Succinato de sumatriptán; Sumatriptaanisuksinaatti; Sumatriptan, succinate de; Sumatriptán, succinato de; Sumatriptani Succcinas; Sumatriptani succinas; Sumatriptano sukcinatas; Sumatriptansuccinat; Sumatriptansukcinát; Sumatriptanum Succinas; Sumatryptanu bursztynian; Szumatriptánszukcinát; Суматриптана Сукцинат.

$C_{14}H_{21}N_3O_2S,C_4H_6O_4$=413.5

CAS — 103628-47-3 (sumatriptan hemisuccinate); 103628-48-4 (sumatriptan succinate).
ATC — N02CC01.
ATC Vet — QN02CC01.
UNII — J88DZ68989.

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

Ph. Eur. 8: (Sumatriptan Succinate). A white or almost white powder. Freely soluble in water; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 5.3. Protect from light.

USP 36: (Sumatriptan Succinate). A white or almost white powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in dichloromethane. Store in airtight containers at a temperature not exceeding 30 degrees. Do not allow to freeze. Protect from light.

Stability. Oral liquid preparations of sumatriptan 5 mg/mL prepared from crushed sumatriptan succinate tablets in 3 different syrups were stable for at least 21 days when stored at 4 degrees and protected from light.[1]

1. Fish DN, *et al.* Stability of sumatriptan succinate in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997; **54**: 1619–22.

Uses and Administration

Sumatriptan is a selective serotonin agonist that acts at $5\text{-}HT_1$ receptors and produces vasoconstriction of cranial arteries. Drugs such as sumatriptan, which are commonly known as triptans, are believed to act mainly at $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ subtype receptors and are therefore sometimes referred to as $5HT_{1B/1D}$-receptor agonists.

Sumatriptan is used for the acute treatment of migraine attacks and of cluster headache. It should not be used for prophylaxis. It may be given orally, subcutaneously, or transdermally as the succinate and intranasally as the base. Doses are expressed in terms of the base; sumatriptan succinate 70 mg is equivalent to about 50 mg of sumatriptan.

For the acute treatment of **migraine** sumatriptan should be used as soon as possible after the onset of the headache phase, but efficacy is independent of the duration of the attack before starting treatment. If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

- It is given *orally* to adults aged 18 years and over; the recommended dose in the UK is 50 mg, although some patients may require 100 mg. A clinical response can be expected after about 30 minutes. If symptoms recur after an initial response, further doses may be given provided that there is a minimum interval of 2 hours between doses and that not more than 300 mg is taken in any 24-hour period. US licensed product information recommends that a lower dose of 25 mg may be used, although some patients require 50 or 100 mg. This may be followed by a second dose of up to 100 mg if the headache returns or the patient has a partial response provided that the total daily dose does not exceed the recommended maximum of 200 mg. A minimum interval of 2 hours is recommended between doses. A tablet supplying a dose equivalent to 85 mg of sumatriptan, as a fixed-dose combination with 500 mg of naproxen sodium, is also available in the USA; a single dose may be taken, repeated once within 24 hours if necessary, with a minimum interval of 2 hours.
- When used *intranasally* a clinical response can be expected in 15 minutes. UK licensed product information recommends that patients aged 18 years and over may be given a single dose of 20 mg into one nostril, although 10 mg may be effective in some patients. US licensed product information recommends that a dose of 5, 10, or 20 mg may be used. If symptoms recur, a second dose may be given at least 2 hours after the first dose. Not more than 40 mg should be used in a 24-hour period.
- In patients aged 18 years and over sumatriptan may be self-administered by *subcutaneous injection* in a single dose of 6 mg; a clinical response may be expected after 10 to 15 minutes. If symptoms recur, a second dose of 6 mg may be injected at least one hour after the first dose; not more than 12 mg should be given in a 24-hour period. US licensed product information recommends that it may also be used in single doses of 1 to 5 mg if adverse effects are dose-limiting. A *needle-free subcutaneous delivery system* is also available for the delivery of 6-mg doses.
- An *iontophoretic transdermal* delivery system, supplying 6.5 mg of sumatriptan over 4 hours, may also be used by patients aged 18 years and over. It should be applied to dry, intact, and non-irritated skin on the upper arm or thigh; it should not be applied to a previous application site until the skin remains erythema free for at least 3 days. If symptoms recur, a second system may be applied to a different site at least 2 hours after activation of the first system; not more than 2 systems should be used in a 24-hour period.

For the acute treatment of **cluster headache,** sumatriptan succinate is given by subcutaneous injection in similar doses to those used for migraine.

For doses in children and in hepatic impairment, see below and p. 680.1, respectively.

Administration in children. Sumatriptan may be given for the treatment of acute **migraine** in children and adolescents. Although not licensed for oral paediatric use in the UK, the *BNFC* suggests that a single *oral* dose of 25 mg may be given to children aged 6 to 10 years, 50 mg to those aged 10 to 12 years, and 50 to 100 mg to those aged

12 to 18 years. The dose may be repeated once after at least 2 hours if symptoms recur after an initial response. Children aged 10 to 18 years may also be given the usual adult *subcutaneous* dose (see p. 679.3).

In the UK, *intranasal* sumatriptan is licensed for use in adolescents aged 12 to 17 years in a dose of 10 mg into one nostril; the dose may be repeated after at least 2 hours if symptoms recur within 24 hours although not more than 20 mg should be used within a 24-hour period. Alternatively, the *BNFC* suggests that the usual adult dose of 10 to 20 mg (see p. 679.3) may be used in those aged 12 years and over.

If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

Sumatriptan has also been tried in the treatment of acute **cluster headache.** The *BNFC* suggests that children aged 10 to 18 years may be given *subcutaneous* doses similar to those suggested in adults (see p. 679.3); alternatively, sumatriptan may be given *intranasally* to children aged 12 to 18 years in doses similar to those suggested for use in adolescents with migraine.

Administration in hepatic impairment. Sumatriptan should be used with caution in patients with hepatic impairment. An oral dose of up to 50 mg is considered suitable. It should not be given to patients with severe impairment.

High-altitude disorders. Sumatriptan has been tried with some success in a small study[1] for the prevention of symptoms of acute mountain sickness (p. 1276.2).

1. Jafarian S, *et al.* Sumatriptan for prevention of acute mountain sickness: randomized clinical trial. *Ann Neurol* 2007; 62: 273–7.

Migraine and cluster headache. The use of sumatriptan and other triptans in the treatment of cluster headache (p. 670.1) and migraine (p. 670.3) has been reviewed.[1-7]

In **migraine** serotonin (5-HT_1) agonists are preferred to ergotamine for the treatment of acute attacks unresponsive to simple analgesics.

There are several *different triptans* clinically available. In a meta-analysis of 53 studies (involving 24 089 patients) and a separate analysis of all direct comparative studies of 5 other triptans with sumatriptan, all were found to be more effective than placebo.[2] At the marketed doses, all oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) were effective and well tolerated. Almotriptan, eletriptan, or rizatriptan were considered to provide the highest likelihood of consistent success. A review of the efficacy of the 5 triptans available in the USA also showed pain relief at 2 hours was comparable for all.[3] Almotriptan 12.5 mg offered high tolerability and good efficacy; eletriptan 80 mg provided high efficacy and low recurrence; and rizatriptan 10 mg was associated with consistent and rapid freedom from pain.[2] Frovatriptan was not included in the analyses, but publicly available data suggested lower efficacy. Only sumatriptan, though, has parenteral and transdermal formulations;[8] the 6-mg subcutaneous formulation is considered to be the fastest and most effective acute treatment[2] but there is a lack of comparative data with the newer iontophoretic transdermal delivery preparation.[8]

About 21 to 57% of patients who initially respond to sumatriptan have a *recurrence* of their headache within 24 to 48 hours; this may be related in part to its short half-life. Such recurrences usually respond to a second dose[9,10] but if a first dose is ineffective subsequent doses for the same attack are of no benefit and should not be given. Sumatriptan is considered[11] to be effective when given at any time once the headache phase of migraine has started but giving it during migraine aura appears to be of little benefit since it does not affect the aura or prevent or delay the development of headache.[12] Repeated or long-term use does not appear to be associated with reduced efficacy.[13,14] For reports of an association between sumatriptan and medication-overuse headache, see under Adverse Effects, p. 681.2. Oral sumatriptan may also be combined with naproxen sodium;[15-17] the combination is reported to be slightly more effective than either drug alone.[18]

Sumatriptan's efficacy appears to be maintained in *menstrual migraine*, a condition which is considered to be less responsive to treatment than nonmenstrual migraine;[19] it has also been given in a fixed-dose oral combination with naproxen sodium.[20,21] Frovatriptan,[22] rizatriptan,[23] and zolmitriptan[24] have also been found to be effective in menstrual migraine.

Experience of subcutaneous use in *children* has been reported.[25] Results of a randomised, placebo-controlled study[26] of intranasal sumatriptan in adolescents aged 12 to 17 years showed evidence of efficacy, tolerability, and safety in this age group; it was felt that the nasal spray might be particularly well suited for adolescent use. Intranasal sumatriptan has also been tried in younger children (aged 8 years and over) with some success.[27] For doses in children, see p. 679.3. The use of other triptans in children with migraine has also been reviewed.[28]

Subcutaneous sumatriptan has also been shown to be effective in relieving acute attacks of headache in patients with **cluster headache.** In studies about 75% of patients have obtained relief within 15 minutes of a 6-mg subcutaneous injection;[29,30] the use of higher doses was found to be of no advantage. Long term efficacy appears to be maintained[31] but the significance of the transient increase in the frequency of attacks seen in some patients remains to be determined.[32] It does not appear to be effective for the prevention of headache during cluster periods.[33] Another triptan found to be effective in the treatment of episodic cluster headache is zolmitriptan.[34]

1. Perry CM, Markham A. Sumatriptan: an updated review of its use in migraine. *Drugs* 1998; 55: 889–922.
2. Ferrari MD, *et al.* Oral triptans (serotonin $5\text{-HT}_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; 358: 1668–75.
3. Jamieson DG. The safety of triptans in the treatment of patients with migraine. *Am J Med* 2002; 112: 135–40.
4. Rapoport AM, Tepper SJ. Triptans are all different. *Arch Neurol* 2001; 58: 1479–80.
5. McCrory DC, Gray RN. Oral sumatriptan for acute migraine. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 27/04/05).
6. Law S, *et al.* Triptans for acute cluster headache. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 27/07/10).
7. Johnston MM, Rapoport AM. Triptans for the management of migraine. *Drugs* 2010; 70: 1505–18.
8. Garnock-Jones KP. Sumatriptan iontophoretic transdermal system: a review of its use in patients with acute migraine. *Drugs* 2013; 73: 1483–90.
9. Ferrari MD, *et al.* Oral sumatriptan: effect of a second dose, and incidence and treatment of headache recurrences. *Cephalalgia* 1994; 14: 330–8.
10. Dahlöf C. Headache recurrence after subcutaneous sumatriptan and early treatment. *Lancet* 1992; 340: 909.
11. Ferrari MD. Sumatriptan in the treatment of migraine. *Neurology* 1993; 43 (suppl 3): S43–S47.
12. Bates D, *et al.* Sumatriptan Aura Study Group. Subcutaneous sumatriptan during the migraine aura. *Neurology* 1994; 44: 1587–92.
13. Cady RK, *et al.* Efficacy of subcutaneous sumatriptan in repeated episodes of migraine. *Neurology* 1993; 43: 1363–8.
14. Tansey MJB, *et al.* Long-term experience with sumatriptan in treatment of migraine. *Eur Neurol* 1993; 33: 310–15.
15. Mathew NT, *et al.* Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. *Headache* 2009; 49: 971–82.
16. Cady R, *et al.* Multi-center comparison of response to a single tablet of sumatriptan 85 mg and naproxen 500 mg vs usual therapy treating multiple migraine attacks as measured by the completeness of response survey. *Headache* 2011; 51: 961–70.
17. Yang LPH. Sumatriptan/naproxen sodium: a review of its use in adult patients with migraine. *Drugs* 2013; 73: 1339–55.
18. Khoury CK, Couch JR. Sumatriptan-naproxen fixed combination for acute treatment of migraine: a critical appraisal. *Drug Des Devel Ther* 2010; 4: 9–17.
19. Solbach MP, Waymer RS. Treatment of menstruation-associated migraine headache with subcutaneous sumatriptan. *Obstet Gynecol* 1993; 82: 769–72.
20. Mannix LK, *et al.* Combination treatment for menstrual migraine and dysmenorrhea using sumatriptan-naproxen: two randomized controlled trials. *Obstet Gynecol* 2009; 114: 106–13.
21. Cady RK, *et al.* Sumatriptan-naproxen sodium for menstrual migraine and dysmenorrhea: satisfaction, productivity, and functional disability outcomes. *Headache* 2011; 51: 664–73.
22. Silberstein SD, *et al.* A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 2004; 27: 261–9.
23. Silberstein SD, et al. Rizatriptan in the treatment of menstrual migraine. *Obstet Gynecol* 2000; 96: 237–42.
24. Loder E, *et al.* Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache* 2004; 44: 120–30.
25. Linder SL. Subcutaneous sumatriptan in the clinical setting: the first 50 consecutive patients with acute migraine in a pediatric neurology office practice. *Headache* 1996; 36: 419–22.
26. Winner P, *et al.* A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. *Pediatrics* 2000; 106: 989–997.
27. Ahonen K, *et al.* Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. *Neurology* 2004; 62: 883–7.
28. Vollono C, *et al.* Triptans other than sumatriptan in child and adolescent migraine: literature review. *Expert Rev Neurother* 2011; 11: 395–401.
29. The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *N Engl J Med* 1991; 325: 322–6.
30. Ekbom K, *et al.* Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. *Acta Neurol Scand* 1993; 88: 63–9.
31. Ekbom K, *et al.* Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). *Cephalalgia* 1995; 15: 230–6.
32. Hardebo JE. Subcutaneous sumatriptan in cluster headache: a time study of the effect on pain and autonomic symptoms. *Headache* 1993; 33: 18–21.
33. Monstad I, *et al.* Preemptive oral treatment with sumatriptan during a cluster period. *Headache* 1995; 35: 607–13.
34. Bahra A, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; 54: 1832–39.

Adverse Effects

The most commonly reported adverse effects of serotonin (5-HT_1) agonists such as sumatriptan include dizziness, flushing, weakness, drowsiness, and fatigue. Nausea and vomiting may occur. Dyspnoea and sensory disturbance including paraesthesia and hypoaesthesia have been reported. Pain or sensations of heaviness, heat or cold, pressure, or tightness have also been commonly reported, can affect any part of the body including the throat and chest, and may be intense. These symptoms may be due to vasospasm, which on rare occasions has resulted in severe cardiovascular events including cardiac arrhythmias, myocardial ischaemia, or myocardial infarction. There have been isolated reports of associated cerebrovascular events in patients receiving sumatriptan. Transient increases in blood pressure may occur soon after treatment. Rarely, significant increases in blood pressure, including hypertensive crisis with acute impairment of organ systems, have occurred even in patients without a history of hypertension. Hypotension, bradycardia or tachycardia, palpitations, peripheral vascular disorders such as Raynaud's syndrome, and ischaemic colitis have been reported. Visual disturbances have also occurred.

Medication-overuse headache has been reported with sumatriptan and may necessitate withdrawal of the drug. Sumatriptan has occasionally been associated with minor disturbances in hepatic function. There have also been rare reports of seizures with sumatriptan. Hypersensitivity reactions ranging from rashes to, more rarely, anaphylaxis have occurred.

Transient pain at the injection site is common after subcutaneous sumatriptan injections; stinging, burning, erythema, bruising, and bleeding have also been reported. Irritation of the nasal mucosa and throat and epistaxis have been reported after intranasal use. Application site reactions such as pain, paraesthesia, pruritus, warmth, and discomfort have been commonly reported after use of the iontophoretic transdermal delivery preparation.

Incidence of adverse effects. In a Dutch postmarketing survey[1] completed by 1187 patients the most common adverse reactions attributed to sumatriptan were paraesthesia (reported by 11.7% of patients), dizziness (8.1%), feeling of heaviness (8.0%), chest pain (7.9%), nausea and/or vomiting (7.3%), drowsiness/sedation (7.0%), flushing (5.1%), fatigue (4.6%), pressure in throat (3.3%), headache (3.1%), injection site reaction (3.0%), palpitations (2.8%), abdominal pain (2.6%), muscle pain (2.4%), and dyspnoea (2.2%).

The safety and tolerability of the triptans have been reviewed.[2,3]

1. Ottervanger JP, *et al.* Adverse reactions attributed to sumatriptan: a postmarketing study in general practice. *Eur J Clin Pharmacol* 1994; 47: 305–9.
2. Nappi G, *et al.* Tolerability of the triptans: clinical implications. *Drug Safety* 2003; 26: 93–107.
3. Tfelt-Hansen P. Optimal balance of efficacy and tolerability of oral triptans and telcagepant: a review and a clinical comment. *J Headache Pain* 2011; 12: 275–80.

Effects on the cardiovascular system. About 10 months after sumatriptan injection had been made available commercially, the UK CSM noted that it had received 34 reports of pain or tightness in the chest and 2 reports of myocardial ischaemia.[1] The Netherlands Centre for Monitoring of Adverse Reactions to Drugs declared about the same time that it had received 12 reports of chest or anginal pain mostly associated with oral sumatriptan.[2] A later postmarketing survey based on data from Dutch general practitioners identified chest pain in 1.3% of 1727 patients,[3] a figure considered to be lower than that seen in earlier studies, but in a subsequent questionnaire completed by 1187 of these patients 7.9% reported chest pain.[4] The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[5] stated in December 1994 that it had received 114 reports of chest pain since sumatriptan had been marketed in mid 1992. Most patients had recovered quickly but 2 had died. The first developed a fatal myocardial infarction after coronary artery dissection but the causal relation with sumatriptan was unclear. The second patient, who had hypertrophic obstructive cardiomyopathy, developed ventricular fibrillation a few hours after the onset of chest pain and this led to fatal cardiac arrest

One group of workers[6] who studied the effect of sumatriptan 16 mg given subcutaneously suggested that the symptoms of chest pain might be due to an effect of sumatriptan on oesophageal function, but others have argued against this suggestion.[7] ADRAC[5] considered that the reaction in the 28 reports of throat tightness they had received by December 1994 was a different reaction to that of chest pain, and probably resulted from changes in oesophageal motility.

Several reports have provided details of individual cases of the adverse cardiovascular effects of sumatriptan including arrhythmias (ventricular tachycardia,[8] ventricular fibrillation,[8,9] or atrial fibrillation[10,11]), acute myocardial infarction,[12-19] and unstable angina.[20] Most of these reports concerned subcutaneous sumatriptan, but myocardial infarction[14,17-19] and cardiac arrhythmias[9,11] (sometimes fatal) may occur after oral use. These adverse effects have also been reported in patients with no predisposing factors.[9,12,17-19]

A review[21] of published reports on chest pain as well as relevant data held by the UK manufacturer considered that the risk of myocardial ischaemia after vasoconstriction induced by sumatriptan was small. However, the contra-indications and cautions given under Precautions,

p. 681.2, should be observed. A study[22] published in 2004 of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of cardiovascular death in those patients treated with serotonin agonists.

1. CSM. Sumatriptan (Imigran) and chest pain. *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 22/08/08)
2. Stricker BHC. Coronary vasospasm and sumatriptan. *BMJ* 1992; 305: 118.
3. Ottervanger JP, *et al.* Postmarketing study of cardiovascular adverse reactions associated with sumatriptan. *BMJ* 1993; 307: 1185.
4. Ottervanger JP, *et al.* Adverse reactions attributed to sumatriptan: a postmarketing study in general practice. *Eur J Clin Pharmacol* 1994; 47: 305–9.
5. Boyd IW, Rohan AP. Sumatriptan-induced chest pain. *Lancet* 1994; 344: 1704–5.
6. Houghton LA, *et al.* Is chest pain after sumatriptan oesophageal in origin? *Lancet* 1994; 344: 985–6.
7. Hood S, *et al.* Sumatriptan-induced chest pain. *Lancet* 1994; 344: 1500–1.
8. Curtin T, *et al.* Cardiorespiratory distress after sumatriptan given by injection. *BMJ* 1992; 305: 713–14.
9. Laine K, *et al.* Fatal cardiac arrhythmia after oral sumatriptan. *Headache* 1999; 39: 511–12.
10. Morgan DR, *et al.* Atrial fibrillation associated with sumatriptan. *BMJ* 2000; 321: 275.
11. Devadathan S, Gunning M. Atrial fibrillation following oral sumatriptan administration. *Int J Cardiol* 2006; 107: 112–3.
12. Ottervanger JP, *et al.* Transmural myocardial infarction with sumatriptan. *Lancet* 1993; 341: 861–2.
13. Kelly KM. Cardiac arrest following use of sumatriptan. *Neurology* 1995; 45: 1211–13.
14. O'Connor P, Gladstone P. Oral sumatriptan-associated transmural myocardial infarction. *Neurology* 1995; 45: 2274–6.
15. Mueller L, *et al.* Vasospasm-induced myocardial infarction with sumatriptan. *Headache* 1996; 36: 329–31.
16. Main ML, *et al.* Cardiac arrest and myocardial infarction immediately after sumatriptan injection. *Ann Intern Med* 1998; 128: 874.
17. Hack JB. Oral sumatriptan-induced myocardial infarction. *J Toxicol Clin Toxicol* 2004; 42: 309–11.
18. Anghileri E, *et al.* Acute myocardial infarction after sumatriptan administration for cluster headache. *Neurol Sci* 2006; 26: 456–9.
19. Weir RA, *et al.* Myocardial infarction after oral sumatriptan use in a woman with normal coronary arteries. *Am J Med* 2007; 120: A13. Available at: http://download.journals.elsevierhealth.com/pdfs/journals/0002-9343/PIIS0002934307004743.pdf (accessed 17/03/09)
20. Walton-Shirley M, *et al.* Unstable angina pectoris associated with Imirex therapy. *Cathet Cardiovasc Diagn* 1995; 34: 188.
21. Hillis WS, MacIntyre PD. Drug reactions: sumatriptan and chest pain. *Lancet* 1993; 341: 1564–5. Correction. *ibid.*; 342: 1310.
22. Hall GC, *et al.* Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; 62: 563–8.

Effects on the cerebrovascular system. Adverse cerebrovascular effects have been reported after the use of subcutaneous sumatriptan including hemiparesis,[1] stroke,[2,3] and intracerebral haemorrhage.[4] Cerebral vasospasm has also been reported[5] with the use of oral sumatriptan. However, a study[6] of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of stroke in those patients treated with serotonin agonists.

1. Luman W, Gray RS. Adverse reactions associated with sumatriptan. *Lancet* 1993; 341: 1091–2.
2. Cavazos J, *et al.* Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994; 343: 1105–6.
3. Meschia JF, *et al.* Reversible segmental cerebral arterial vasospasm and cerebral infarction: possible association with excessive use of sumatriptan and Midrin. *Arch Neurol* 1998; 55: 712–14.
4. Edwards KR, *et al.* Intracerebral hemorrhage associated with sumatriptan. *Headache* 1995; 35: 309.
5. Dash S, *et al.* Cerebral vasospasm from sumatriptan. *Neurology* 2004; 63: 2128.
6. Hall GC, *et al.* Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; 62: 563–8.

Effects on the gastrointestinal tract. Ischaemic colitis and mesenteric ischaemia have been reported in a few patients receiving sumatriptan,[1-3] including repeated episodes in 2 patients,[2] each within hours of a dose; some of these episodes were associated with doses above the recommended daily maximum.[2]

Oesophageal constriction or throat tightness has been reported in some patients using sumatriptan and may be due to a direct effect on the oesophagus (see Effects on the Cardiovascular System, p. 680.3).

1. Knudsen JF, *et al.* Ischemic colitis and sumatriptan use. *Arch Intern Med* 1998; 158: 1946–8.
2. Liu JJ, Ardolf JC. Sumatriptan-associated mesenteric ischemia. *Ann Intern Med* 2000; 132: 597.
3. Naik M, *et al.* Sumatriptan-associated ischemic colitis. *Dig Dis Sci* 2002; 47: 2015–16.

Effects on the respiratory system. See Asthma under Precautions, below.

Hypersensitivity. Reactions to sumatriptan such as rashes and, more rarely, anaphylaxis have been noted by the manufacturer. Published reports include angioedema occurring in a patient 5 minutes after subcutaneous sumatriptan,[1] and urticaria occurring 20 to 24 hours after oral or subcutaneous sumatriptan in another patient.[2]

1. Dachs R, Vitillo J. Angioedema associated with sumatriptan administration. *Am J Med* 1995; 99: 684–5.
2. Pradalier A, *et al.* Delayed urticaria with sumatriptan. *Cephalalgia* 1996; 16: 280–1.

Medication-overuse headache. Sumatriptan and other triptans may have a similar risk of misuse to that associated with analgesics and ergotamine compounds in patients with medication-overuse headache (p. 670.2). There have been reports[1-3] of patients using one or more daily doses of sumatriptan to control migraine.. Many of the patients had a history of abuse of other antimigraine drugs and were using sumatriptan to prevent recurrence of headache. Whether misuse of sumatriptan was due to addiction or rebound headache, as seen with ergotamine, is unknown. A postmarketing study in 952 patients receiving sumatriptan found that 36 of the patients (4%) used sumatriptan daily or more than 10 times each week. This overuse was related to poor efficacy and not to rebound headache.[4] One study[5] and an anecdotal report[6] suggest that, rather than producing euphoria or other effects associated with drugs of abuse such as morphine, sumatriptan is more likely to be associated with dysphoria and apathetic sedation.

The development of medication-overuse headache has also been reported with other serotonin (5-HT_1) agonists including naratriptan and zolmitriptan.[7] Indeed, US licensed product information for the triptans states that the safety of treating an average of more than 3 or 4 migraine attacks in a 30-day period has not been established.

1. Osborne MJ, *et al.* Is there a problem with long term use of sumatriptan in acute migraine? *BMJ* 1994; 308: 113.
2. Kaube H, *et al.* Sumatriptan. *BMJ* 1994; 308: 1573–4.
3. Gaist D, *et al.* Misuse of sumatriptan. *Lancet* 1994; 344: 1090.
4. Ottervanger JP, *et al.* Pattern of sumatriptan use and overuse in general practice. *Eur J Clin Pharmacol* 1996; 50: 353–5.
5. Sullivan JT, *et al.* Psychoactivity and abuse potential of sumatriptan. *Clin Pharmacol Ther* 1992; 52: 635–42.
6. Bakshi R, Yan-Go FL. Prolonged marijuana-like dysphoria after subcutaneous sumatriptan. *Ann Pharmacother* 1996; 30: 683.
7. Limmroth V, *et al.* Headache after frequent use of serotonin agonists zolmitriptan and naratriptan. *Lancet* 1999; 353: 378.

Precautions

Sumatriptan and other serotonin (5-HT_1) agonists should only be used where there is a clear diagnosis of migraine or cluster headache and care should be taken to exclude other potentially serious neurological conditions. They should not be used for prophylaxis and should not be given to patients with basilar, hemiplegic, or ophthalmoplegic migraine.

Serotonin (5-HT_1) agonists are contra-indicated in patients with uncontrolled hypertension, ischaemic heart disease (coronary artery disease), a history of myocardial infarction, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease, or a previous cerebrovascular accident or transient ischaemic attack. Unrecognised cardiovascular disease should be excluded before the use of serotonin (5-HT_1) agonists in postmenopausal women, men over 40 years of age, and those with risk factors for ischaemic heart disease. If chest pain and tightness occur during use, appropriate investigations should be performed. Sumatriptan should not be used intravenously because of the increased risk of producing coronary vasospasm.

Drowsiness may occur after treatment with serotonin (5-HT_1) agonists and patients thus affected should not drive or operate machinery.

Sumatriptan should be used with caution in patients with hepatic or renal impairment, and should generally be avoided if hepatic impairment is severe.

There have been rare reports of seizures after use of sumatriptan and it should therefore be used with caution in patients with a history of epilepsy or other conditions predisposing to seizures. Patients with hypersensitivity to sulfonamides may have a similar reaction to sumatriptan. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.)

Asthma. The manufacturers reviewed data from more than 75 clinical studies of sumatriptan involving 12 701 patients and reported[1] that the incidence of adverse events related to asthma did not differ between patients with or without the condition. Earlier there had been concern over the safety of sumatriptan in patients with asthma after 2 reports of bronchospasm and a report of a patient with asthma who died during a study of sumatriptan although the patient had not received sumatriptan in the month before her death.

1. Lloyd DK, Pilgrim AJ. The safety of sumatriptan in asthmatic migraineurs. *Cephalalgia* 1993; 13: 201–4.

Breast feeding. No adverse effects have been seen in breast-fed infants of mothers given sumatriptan, and the last available guidance from the American Academy of Pediatrics considered that it is therefore usually compatible with breast feeding.[1] However, licensed product information suggests that infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment. Product information for other triptans suggests avoiding breast feeding for 24 hours.

The distribution of sumatriptan into breast milk after a 6-mg subcutaneous dose has been studied in 5 mothers.[2] The mean total recovery of sumatriptan in breast milk was estimated to be 14.4 micrograms or 0.24% of the dose. It was calculated that on a weight-adjusted basis an infant could receive a maximum of 3.5% of the 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 01/06/04)
2. Wojnar-Horton RE, *et al.* Distribution and excretion of sumatriptan in human milk. *Br J Clin Pharmacol* 1996; 41: 217–21.

Cerebrovascular disorders. A patient with a superior sagittal sinus thrombosis who presented with headache and was misdiagnosed as having migraine variant developed a cortical stroke within minutes of a second 6-mg subcutaneous injection of sumatriptan.[1] The importance of establishing a diagnosis of typical migraine or cluster headache before using sumatriptan was emphasised and caution given against its use in any patient who may have unstable cerebrovascular disease or raised intracranial pressure. Additionally, there was no clinical evidence that a second injection would relieve a headache when the initial injection had been ineffective.

1. Cavazos J, *et al.* Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994; 343: 1105–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sumatriptan 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 11/04/11)

Pregnancy. Sumatriptan crosses the placenta; however, only a very small quantity reaches the fetus. A literature review concluded that exposure to sumatriptan in pregnancy posed no additional risk of birth defects compared with that in the general population,[1] but as for other drugs sumatriptan should only be used in pregnancy when the benefit justifies the potential risk to the fetus.

1. Hilaire ML, *et al.* Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother* 2004; 38: 1726–30.

Interactions

Sumatriptan and other serotonin (5-HT_1) agonists should not be given with ergotamine or related compounds (including methysergide) since there is an increased risk of vasospastic reactions. In addition, a delay is advised *before starting* a serotonin (5-HT_1) agonist in patients who have been receiving ergotamine or related compounds: sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, or zolmitriptan should not be given until at least 24 hours after stopping the use of ergotamine preparations. Conversely, ergotamine should not be given until 6 hours *after stopping* these drugs or at least 24 hours in the case of eletriptan, frovatriptan, and naratriptan. Serotonin (5-HT_1) agonists should not be given together.

Sumatriptan or rizatriptan should not be used with, and for 2 weeks after stopping, an MAOI. Use with the selective monoamine oxidase type B inhibitor selegiline is thought unlikely to provoke an interaction, but see p. 916.1. Opinion varies on the use of zolmitriptan with inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A whereas in the USA it contra-indicates such combinations. There have been rare reports of serotonin syndrome associated with the use of triptan serotonin (5-HT_1) agonists with SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs), but see also under Antidepressants, below.

Oral sumatriptan appeared to delay gastric emptying and might affect the absorption of other drugs, as judged by its delaying effect on paracetamol absorption in migraine patients.[1]

1. Rani PU, *et al.* Sumatriptan delays paracetamol absorption in migraine patients. *Clin Drug Invest* 1996; 11: 300–304.

Antidepressants. Sumatriptan and rizatriptan are metabolised mainly by monoamine oxidase type A and licensed product information advises that patients taking *MAOIs*, including reversible selective type A inhibitors such as moclobemide, should not be given these triptan serotonin (5-HT_1) agonists. Clearance of zolmitriptan was decreased after moclobemide and UK licensed product information recommends a reduced dose of zolmitriptan if the drug is used with an inhibitor of monoamine oxidase type A; in the USA, the use of these drugs together is contra-indicated.

SSRIs such as fluoxetine may also interact with serotonin (5-HT_1) agonists with an increased risk of serotonin

syndrome (p. 443.2), and it has been suggested that *lithium* and sumatriptan may interact similarly. However, a review of the use of sumatriptan with MAOIs, SSRIs, or lithium found little evidence of an increased risk of serotonin syndrome.[1] It was concluded that most patients tolerate the combination of sumatriptan and an SSRI or lithium without incident. However, it was suggested that the use of sumatriptan with an MAOI should continue to be avoided until further data supporting safety become available. As there have since been rare reports of serotonin syndrome associated with the use of triptans with SSRIs or *serotonin and noradrenaline reuptake inhibitors (SNRIs)*, licensed product information for the triptans states that when such use is clinically warranted, appropriate observation of the patient is advised, particularly when starting treatment, with dose increases, or with addition of another serotonergic drug. Product information for zolmitriptan also advises a reduction in dosage if it is given with fluvoxamine as the latter may inhibit zolmitriptan metabolism through its effects on the cytochrome P450 isoenzyme CYP1A2. The American Headache Society has stated[2] that caution is certainly warranted but that official FDA advice should be reviewed as it is not clear what role triptans might play in contributing to serotonin syndrome with or without SSRIs or SNRIs.

Increased serotonergic effects with increased incidence of adverse effects have been reported following the use of *St John's wort* with triptans.[3] Patients should be advised to stop taking St John's wort if treatment with a serotonin (5-HT_1) agonist is necessary.

1. Gardner DM, Lynd LD. Sumatriptan contraindications and the serotonin syndrome. *Ann Pharmacother* 1998; 32: 33–8.
2. Evans RW, *et al.* The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. *Headache* 2010; 50: 1089–99.
3. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; 26: 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)

Antimigraine drugs. Although the efficacy and tolerability of subcutaneous sumatriptan in the acute treatment of migraine did not appear to be affected in patients already taking *dihydroergotamine* orally for migraine prophylaxis,[1] the bioavailability of oral dihydroergotamine is low and it could not be assumed that it was safe to use parenteral dihydroergotamine with sumatriptan.[2] Licensed product information for sumatriptan contra-indicates its use with *ergotamine* or other related compounds and also recommend that it should not be given until at least 24 hours after stopping ergotamine or related compounds (see Interactions, p. 681.3).

Acute myocardial infarction has been reported[3] in a premenopausal woman with controlled hypertension and no known coronary artery disease after subcutaneous use of sumatriptan within a few hours of taking *methysergide* orally.

1. Henry P, *et al.* Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. *Headache* 1993; 33: 432–5.
2. Campbell JK. Editor's comment]. *Headache* 1993; 33: 435.
3. Liston H, *et al.* The association of the combination of sumatriptan and methysergide in myocardial infarction in a premenopausal woman. *Arch Intern Med* 1999; 159: 511–13.

Antipsychotics. For reference to a potential interaction between sumatriptan and *loxapine*, see Chlorpromazine, p. 1052.3.

Pharmacokinetics

Sumatriptan is rapidly but incompletely absorbed when given orally and undergoes first-pass metabolism, resulting in a low absolute bioavailability of about 14%. Peak plasma concentrations after oral doses occur in about 2 hours. Bioavailability is much higher (96%) after subcutaneous doses with peak concentrations occurring within 25 minutes. Bioavailability after intranasal doses is 16% of that achieved subcutaneously, with peak concentrations occurring in about 1.5 hours. Peak concentrations after iontophoretic transdermal delivery occur in about 1.1 hours; bioavailability is lower than that achieved after oral doses. Plasma protein binding is low at about 14 to 21%.

The elimination half-life of sumatriptan is about 2 hours. Sumatriptan is extensively metabolised in the liver mainly by monoamine oxidase type A and is excreted mainly in the urine as the inactive indole acetic acid derivative and its glucuronide. Sumatriptan and its metabolites also appear in the faeces. Small amounts of sumatriptan are distributed into breast milk (see Breast Feeding, p. 681.2).

Reviews.

1. Scott AK. Sumatriptan clinical pharmacokinetics. *Clin Pharmacokinet* 1994; 27: 337–44.
2. Lacey LF, *et al.* Single dose pharmacokinetics of sumatriptan in healthy volunteers. *Eur J Clin Pharmacol* 1995; 47: 543–8.
3. Fuseau E, *et al.* Clinical pharmacokinetics of intranasal sumatriptan. *Clin Pharmacokinet* 2002; 41: 801–11.
4. Moen MD, Keating GM. Sumatriptan fast-disintegrating/rapid-release tablets. *Drugs* 2006; 66: 883–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Imigran; Micranil; Migraneitor; *Austral.*: Imigran; Sumagran; Sumatab; Suvalan; *Austria*: Imigran; *Belg.*: Finigraine†; Imitrex; *Braz.*: Imigran; Sumax; Sutriptan; *Canad.*: Imitrex; *Chile*: Imigran; Somatran; *China*: Dan Tong Jing (丹同静); Na Chuan (纳川); Youshu (尤舒); *Cz.*: Cinie; Dolorstad†; Imigran; Rosemig; Sumamigren; Sumigra; Wispra; *Denm.*: Imigran; Imigrane; Oriptan; Sumavel; *Fin.*: Cinie†; Imigran; Oriptan; Sumaratio; *Fr.*: Imigrane; Imiject; *Ger.*: Imigran; Sumavel; *Gr.*: Altaxa; Forcet; Imigran; Precipitan; Sutriptan; *Hong Kong*: Imigran; *Hung.*: Cinie; Illument†; Imigran; Triptagram; *India*: Migratan; Suminat; *Indon.*: Cetatrex†; Imitrex†; Triptagic; *Irl.*: Imigran; Imitag†; Migrastat; Sumagran; Sumatran; Suvalan; *Israel*: Imitrex; Sumatridex; *Ital.*: Imigran; *Malaysia*: Imigran; Sumitran; *Mex.*: Fermig; Gesigran; Imigran; Sumitrex; Tebegran; *Neth.*: Imigran; Sumalin; Sumarix; *Norw.*: Imigran; *NZ*: Imigran; MyGran; Sumagran†; *Philipp.*: Imigran; Sumigran; *Pol.*: Amigrenex; Cinie; Frimig; Imigran; Sumamigren; Sumigra; Triptagram; *Port.*: Imigran; Imigranradis; *Rus.*: Amigrenin (Амигренин); Imigran (Имигран); Mygrepam (Мигрепам); Sumamigren (Сумамигрен); Sumig (Сумиг); Sumitran (Сумитран); Trimigren (Тримигрен); *S.Afr.*: Imigen; Imigran; Migrex; Triptam; *Singapore*: Imigran; Sumatran; Sumitran; *Spain*: Imigran; Sumamylan†; *Swed.*: Imigran; Oriptan; Zumo†; *Switz.*: Imigran; *Thai.*: Imigran; *Turk.*: Imigran; Sumatran; *UK*: Imigran; *Ukr.*: Algomax (Альгомакс); Antimigren (Антимигрен); Sumamigren (Сумамигрен); *USA*: Imitrex; Sumavel; Zecuity; *Venez.*: Imigran; Migraval.

Multi-ingredient Preparations. *USA*: Treximet.

Pharmacopoeial Preparations

BP 2014: Sumatriptan Injection; Sumatriptan Nasal Spray; Sumatriptan Tablets;
USP 36: Sumatriptan Injection; Sumatriptan Nasal Spray; Sumatriptan Succinate Oral Suspension; Sumatriptan Tablets.

Zolmitriptan *(BAN, USAN, rINN)*

311C90; Tsolmitriptaani; Zolmitriptán; Zolmitriptano; Zolmitriptanum; Zolmitryptan; Золмитриптан.

(*S*)-4-[3-[2-(Dimethylamino)ethyl]indol-5-ylmethyl]-1,3-oxazolidin-2-one.

$C_{16}H_{21}N_3O_2$=287.4

CAS — 139264-17-8.

ATC — N02CC03.

ATC Vet — QN02CC03.

UNII — 2FS66TH3YW.

Uses and Administration

Zolmitriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p. 679.3). It is used for the acute treatment of migraine attacks. Zolmitriptan should not be used for prophylaxis.

The licensed dose in the UK is 2.5 mg orally. A clinical response can be expected within 1 hour. If symptoms persist or return within 24 hours, a second dose may be taken not less than 2 hours after the first dose. If a patient does not achieve satisfactory relief with a dose of 2.5 mg, subsequent attacks may be treated with doses of 5 mg. The maximum dose of zolmitriptan in 24 hours is 10 mg. Licensed doses in the USA are somewhat lower; the dose is 1.25 or 2.5 mg with a maximum dose of 10 mg in 24 hours.

When used intranasally a clinical response can be expected in 15 minutes. The usual dose is 5 mg as a single dose into one nostril. If symptoms persist or return within 24 hours, a second dose may be given after at least 2 hours, up to a maximum of 10 mg daily.

Dose reductions are recommended in patients taking certain other drugs (see also Interactions, below). The maximum dose of zolmitriptan in 24 hours should be 5 mg in those receiving cimetidine or an inhibitor of monoamine oxidase type A (although use with inhibitors of monoamine oxidase type A is contra-indicated in US licensed product information). A similar reduction is also recommended in those taking drugs, such as fluvoxamine and ciprofloxacin, that inhibit the cytochrome P450 isoenzyme CYP1A2.

For dosage in children and in hepatic impairment, see below.

Administration in children. Although unlicensed for use in children in the UK, the *BNFC* suggests that zolmitriptan may be used in those aged 12 to 18 years for the treatment of acute cluster headache (intranasal route only) or migraine. Doses are similar to those used in adults (see above).

Administration in hepatic impairment. A study[1] has indicated that while there is no need to reduce the size of the initial dose of zolmitriptan in patients with moderate or severe hepatic impairment, accumulation may occur with repeated doses in patients with severe impairment and their total daily dosage should be reduced.

UK licensed product information recommends a maximum oral dose of 5 mg in 24 hours in patients with moderate to severe impairment. In the USA, a dose of 1.25 mg is recommended in those with moderate to severe impairment, with a maximum total daily dose of 5 mg in severe impairment.

1. Dixon R, *et al.* Effect of hepatic impairment on the pharmacokinetics of zolmitriptan. *J Clin Pharmacol* 1998; 38: 694–701.

Migraine and cluster headache. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p. 680.1.

Further references.

1. Spencer CM, *et al.* Zolmitriptan: a review of its use in migraine. *Drugs* 1999; 58: 347–74.
2. Bahra A, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; 54: 1832–9.
3. Dowson AJ, Charlesworth B. Review of zolmitriptan and its clinical applications in migraine. *Expert Opin Pharmacother* 2002; 3: 993–1005
4. Charlesworth BR, *et al.* Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs* 2003; 17: 653–67.
5. Dowson AJ, *et al.* Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. *CNS Drugs* 2003; 17: 839–51.
6. Lewis DW, *et al.* Adolescent Migraine Steering Committee. Efficacy of zolmitriptan nasal spray in adolescent migraine. *Pediatrics* 2007; 120: 390–6.
7. Rapoport AM, *et al.* Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology* 2007; 69: 821–. Correction. *ibid.*; 2029.
8. Hedlund C, *et al.* Zolmitriptan nasal spray in the acute treatment of cluster headache: a meta-analysis of two studies. *Headache* 2009; 49: 1315–23.

Adverse Effects and Precautions

As for Sumatriptan, p. 680.2 and p. 681.2.

Zolmitriptan should also be avoided in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways. It should be given with caution in patients with moderate to severe hepatic impairment.

Ischaemia. A spinal cord lesion related to the use of zolmitriptan has been reported in a 50-year-old woman;[1] clinical features suggested that the lesion was an ischaemic infarct.

1. Vijayan N, Peacock JH. Spinal cord infarction during use of zolmitriptan: a case report. *Headache* 2000; 40: 57–60.

Medication-overuse headache. For a report of an association between zolmitriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p. 681.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zolmitriptan 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 11/04/11)

Renal impairment. Although renal clearance of zolmitriptan and its metabolites was reduced in patients with moderate to severe impairment,[1] the resulting effect was unlikely to be of clinical importance and adjustment of zolmitriptan dosage in patients with renal impairment was considered unnecessary.

1. Gillotin C, *et al.* No need to adjust the dose of 311C90 (zolmitriptan), a novel anti-migraine treatment in patients with renal failure not requiring dialysis. *Int J Clin Pharmacol Ther* 1997; 35: 522–6.

Interactions

As for Sumatriptan, p. 681.3.

Zolmitriptan undergoes hepatic metabolism, mainly mediated by the cytochrome P450 isoenzyme CYP1A2 and also involving monoamine oxidase type A. It is recommended that the maximum dose of zolmitriptan in 24 hours should be reduced in patients receiving cimetidine, a general P450 inhibitor (see Uses and Administration, above). A similar reduction in zolmitriptan dosage is anticipated if it is given with drugs, such as fluvoxamine and ciprofloxacin, that inhibit the isoenzyme CYP1A2. Opinion varies on the use of zolmitriptan with inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A (see Uses and Administration, above), whereas US licensed product information states that such combinations are contra-indicated.

References.

1. Dixon R, *et al.* The metabolism of zolmitriptan: effects of an inducer and an inhibitor of cytochrome P450 on its pharmacokinetics in healthy volunteers. *Clin Drug Invest* 1998; 15: 515–22.

Beta blockers. *Propranolol* increased plasma-zolmitriptan concentrations in a study in 12 healthy subjects, but the changes were not thought to be clinically important enough to warrant dosage adjustment during concomitant use.[1]

1. Peck RW, *et al.* The interaction between propranolol and the novel antimigraine agent zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; 44: 595–9.

Pharmacokinetics

The absolute bioavailability of zolmitriptan after oral and intranasal doses is about 40%, and peak plasma concentrations occur about 1.5 to 3 hours after oral doses, depending on the formulation, and in about 3 hours with the intranasal spray. Plasma protein binding is about 25%. Zolmitriptan undergoes hepatic metabolism, mainly to the indole acetic acid, and also the *N*-oxide and *N*-desmethyl analogues. The *N*-desmethyl metabolite (183C91) was more active than the parent compound in *animal* studies, and would be expected to contribute to the therapeutic effect of zolmitriptan. The primary metabolism of zolmitriptan is mediated mainly by the cytochrome P450 isoenzyme CYP1A2 while monoamine oxidase type A is responsible for further metabolism of the *N*-desmethyl metabolite. Over 60% of a dose is excreted in the urine, mainly as the indole acetic acid, and about 30% appears in the faeces, mainly as unchanged drug. The elimination half-life is 2.5 to 3 hours, and is prolonged in patients with liver disease.

Distribution into milk has been found in studies in *rats*.

References.

1. Dixon R, *et al.* The pharmacokinetics and effects on blood pressure of multiple doses of the novel anti-migraine drug zolmitriptan (311C90) in healthy volunteers. *Br J Clin Pharmacol* 1997; 43: 273–81.
2. Seaber E, *et al.* The absolute bioavailability and metabolic disposition of the novel antimigraine compound zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; 43: 579–87.
3. Peck RW, *et al.* The pharmacodynamics and pharmacokinetics of the $5HT_{1B/1D}$-agonist zolmitriptan in healthy young and elderly men and women. *Clin Pharmacol Ther* 1998; 63: 342–53.
4. Dixon R, *et al.* A comparison of the pharmacokinetics and tolerability of the novel antimigraine compound zolmitriptan in adolescents and adults. *J Child Adolesc Psychopharmacol* 1999; 9: 35–42.
5. Yates R, *et al.* Pharmacokinetics, dose proportionality, and tolerability of single and repeat doses of a nasal spray formulation of zolmitriptan in healthy volunteers. *J Clin Pharmacol* 2002; 42: 1244–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zomigon; *Austral.*: Zomig; *Austria*: Zomig; *Belg.*: Zomig; *Braz.*: Zomig; *Canad.*: Zomig; *China*: Dining (帝宁); Heng Li An (恒力安); Ka Qu (卡曲); Lin Ke Shu (林可舒); Nao Rui An (瑙瑞安); Shu Fu Lai (枢复来); Tian Shu (天疏); Tuo Fu Ning (托肤宁); Zomig (佐米格); *Cz.*: Zolmiles; Zomig; *Denm.*: Zolmiles; Zomig; *Fin.*: Zolmistad; Zomig; *Fr.*: Zomig; Zomigoro; *Ger.*: AscoTop; *Gr.*: Zomigon; *Hong Kong*: Zomig; *Hung.*: Zomig; *Irl.*: Magrezol; Zolmiles†; Zomig; *Israel*: Zomig; *Ital.*: Headzol; Ponesta; Zomig; *Mex.*: Zomig; *Neth.*: Zalsterim; Zomig; *Norw.*: Zomig; *NZ*: Zomig; *Philipp.*: Zomig; *Pol.*: Zolmiles; Zomig; *Port.*: Zomig; *Rus.*: Zomig (Зомиг); *S.Afr.*: Zomig; *Singapore*: Zomig; *Spain*: Zomig; *Swed.*: Zomig; *Switz.*: Zomig; *Thai.*: Zomig; *Turk.*: Gravis; Zomig; *UK*: Zomig; *Ukr.*: Rapimig (Рапимиг); Zolmigren (Золмигрен); *USA*: Zomig; *Venez.*: Zomig.

The symbol † denotes a preparation no longer actively marketed

Antimyasthenics

This chapter includes those drugs used for their anticholinesterase action in the treatment of myasthenia gravis and related neuromuscular disorders. Other groups of drugs playing an important role in the management of myasthenia are the corticosteroids (p. 1597.1) and some drugs with immunosuppressant actions discussed in the chapters on Antineoplastics (p. 691.1) and Immunosuppressants (p. 1936.1).

Eaton-Lambert myasthenic syndrome

Eaton-Lambert myasthenic syndrome is a rare autoimmune disease of the neuromuscular junction. Unlike myasthenia gravis (below), in which autoantibodies affect acetylcholine receptors, antibodies in Eaton-Lambert syndrome act presynaptically to reduce release of acetylcholine. Weakness mostly affects the proximal muscles, particularly those of the limbs; respiratory and ocular muscles are usually spared. Autonomic symptoms including dry mouth, constipation, and impotence are common. Over half of patients also have underlying small cell carcinoma of the lung. Successful treatment of the tumour often leads to some improvement in symptoms.

The symptomatic treatment of Eaton-Lambert syndrome involves the use of drugs that increase the availability of acetylcholine at the neuromuscular junction.[1-8] Response to treatment with *anticholinesterases* alone is poor and treatment with *amifampridine*, which increases acetylcholine release, appears to be more effective, particularly when given with an anticholinesterase such as *pyridostigmine*. The use of drugs with a similar action such as *guanidine* and *fampridine* has been limited by severe adverse effects. Low-dose guanidine has been tried with pyridostigmine where amifampridine is not readily available;[9] although there has been some improvement with the combination, the incidence of adverse effects, especially gastrointestinal reactions, was still high. Immunosuppressants including *azathioprine* and *corticosteroids* are also used in patients who have an inadequate response to symptomatic treatment, and unlike in treatment for myasthenia gravis, corticosteroids do not appear to induce an initial exacerbation of symptoms. Plasma exchange or high-dose intravenous *normal immunoglobulin* have been tried in patients with severe weakness.

1. Seneviratne U, de Silva R. Lambert-Eaton myasthenic syndrome. *Postgrad Med J* 1999; 75: 516–20.
2. Pascuzzi RM. Myasthenia gravis and Lambert-Eaton syndrome. *Ther Apher* 2002; 6: 57–68.
3. Sanders DB. Lambert-Eaton myasthenic syndrome: diagnosis and treatment. *Ann N Y Acad Sci* 2003; 998: 500–8.
4. Newsom-Davis J, Lambert-Eaton myasthenic syndrome. *Rev Neurol (Paris)* 2004; 160: 177–80.
5. Verschuuren JJ, *et al.* Available treatment options for the management of Lambert-Eaton myasthenic syndrome. *Expert Opin Pharmacother* 2006; 7: 1323–36.
6. Pourmand R. Lambert-Eaton myasthenic syndrome. *Front Neurol Neurosci* 2009; 26: 120–5.
7. Skeie GO, *et al.* European Federation of Neurological Societies. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol* 2010; 17: 893–902.
8. Keogh M, *et al.* Treatment for Lambert-Eaton myasthenic syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 05/04/11).
9. Oh SJ, *et al.* Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1997; 20: 1146–52.

Myasthenia gravis

Myasthenia gravis is an auto-immune disorder characterised by defective neuromuscular transmission and consequent muscular weakness. It is caused by the formation of autoantibodies to elements of the neuromuscular junction. In most patients, antibodies to the postsynaptic nicotinic acetylcholine receptor are present (described as 'seropositive myasthenia'). However, about 10 to 15% of patients have so-called 'seronegative myasthenia', in whom antibodies to other elements such as muscle-specific tyrosine kinase (MuSK) may be present instead; the proportion of such patients is much higher among those with ocular myasthenia (where the disease is initially confined to the extra-ocular muscles but may progress to generalised myasthenia). The thymus appears to be involved in many patients and some have a thymoma. Classifications of the disease may be based on the distribution and severity of symptoms, on the age of onset, and on the presence or absence of thymoma. Other types of myasthenia include transient neonatal myasthenia due to transplacental passage of receptor antibodies, which may persist for 1 to 6 weeks in the infants of myasthenic mothers, penicillamine-induced myasthenia, and congenital myasthenia (see under Amifampridine, p. 685.1).

Diagnosis of myasthenia gravis.[1-7]

Antibody testing remains the gold standard for diagnosis of myasthenia gravis. Patients may often be tested first for their reaction to an anticholinesterase. Intravenous edrophonium preceded by atropine (Tensilon test) is the most commonly used anticholinesterase test because of its rapid onset and short duration of action. Severe adverse effects can occasionally occur so testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available. A positive result is considered to be a rapid but temporary increase in muscle strength. Repetitive nerve stimulation and/or single-fibre electromyography are also used as a diagnostic test but, like the anticholinesterase test, are not specific for myasthenia gravis. Computed tomography or magnetic resonance imaging may be used to detect thymoma.

Treatment of myasthenia gravis.[1-17]

- Symptomatic treatment is with an *anticholinesterase*; pyridostigmine and neostigmine are those most commonly used. Most patients prefer pyridostigmine as it produces less muscarinic adverse effects and has a longer duration of action, although the quicker onset of action of neostigmine may offer an advantage at the beginning of the day. The dose must be adjusted to give the optimum therapeutic response but muscle strength may not be restored to normal and some patients must live with a degree of disability. The effect may vary for different muscles and the dosage should be adjusted so that the bulbar and respiratory muscles receive optimum treatment. Generally, anticholinesterases only provide partial remission and their effects tend to diminish with continued treatment. Overdosage may lead to a 'cholinergic crisis' (see Adverse Effects of Neostigmine, p. 688.2). Edrophonium may be used to establish whether the patient is underdosed or overdosed.
- *Corticosteroids* are the main immunosuppressive drugs used for treatment. They are also useful in patients with ocular myasthenia, who as a group respond poorly to anticholinesterases and to thymectomy, provided that their disability is severe enough to warrant long-term corticosteroid treatment with its attendant adverse effects. Many start with low doses such as 5 to 20 mg of prednisolone daily or on alternate days, to reduce the risk of steroid-induced exacerbations of weakness, and increase the dose slowly thereafter according to response; an improvement is usually seen after a few weeks. Others use more aggressive regimens to obtain a more rapid response and start with large doses such as 60 to 80 mg of prednisolone daily. Whichever method is used, once clinical benefit has been obtained the regimen should be modified to alternate-day dosage, with the dose being slowly tapered when the patient is in remission. Patients taking corticosteroids require less anticholinesterase therapy and, if the dosage of the anticholinesterase is not reduced, an initial deterioration in the myasthenia may occur in the first few weeks of treatment (see also under Interactions of Neostigmine, p. 689.1). It is rarely possible to withdraw corticosteroids completely but some patients may be maintained satisfactorily on as little as 10 mg on alternate days. If remission cannot be maintained on low-dose prednisolone, addition of azathioprine at a dosage of 2 to 3 mg/kg daily may be considered.
- Addition of *azathioprine* to treatment may allow a reduction in the dose of both corticosteroids and anticholinesterases. Azathioprine may also be of use when corticosteroids are contra-indicated or when response to corticosteroids alone is insufficient, but it has a much slower onset of action than corticosteroids and is not usually used alone. *Ciclosporin* is effective in some patients unresponsive to standard combinations but serious adverse effects including nephrotoxicity may limit its use; the time to response is similar to that with corticosteroids. Other drugs such as *cyclophosphamide, mycophenolate mofetil,* and *methotrexate* have also been tried and benefit has been reported with *tacrolimus*. However, a systematic review[14] has found that only a small number of randomised controlled studies have been conducted on the use of immunosuppressive drugs for myasthenia gravis and most have been short-term. The review of this limited evidence concluded that, apart from cyclophosphamide used alone or ciclosporin used alone or with corticosteroids, there was no clear evidence of benefit from use of other immunosuppressants.
- Plasma exchange provides a dramatic but short-lived improvement and is useful as a short-term measure in myasthenic crisis to improve ill patients while other therapies take effect, but there is no evidence that repeated plasma exchange combined with immunosuppression is superior to immunosuppression alone. A similar short-term benefit has been seen from the use of high-dose intravenous *normal immunoglobulins*; however, a systematic review[15] considered further study to be warranted.
- Thymectomy may be offered to all patients sufficiently fit to undergo surgery unless they have minimal symptoms, purely ocular disease, or late onset or seronegative disease. Thymectomy is usually avoided in prepubertal children because of concern over the effect on growth and the developing immune system; it has been suggested that symptomatic treatment with anticholinesterases should be continued until adolescence, when the disease often improves spontaneously. After thymectomy, remission or improvement may be expected in about 80% of patients without thymomas, although this may take some years; the response is poorer in those with thymomas.

1. Vincent A, *et al.* Myasthenia gravis. *Lancet* 2001; 357: 2122–8.
2. Pascuzzi RM. Myasthenia gravis and Lambert-Eaton syndrome. *Ther Apher* 2002; 6: 57–68.
3. Vincent A, Drachman DB. Myasthenia gravis. *Adv Neurol* 2002; 88: 59–88.
4. Thanvi BR, Lo TCN. Update on myasthenia gravis. *Postgrad Med J* 2004; 80: 690–700.
5. Kothari MJ. Myasthenia gravis. *J Am Osteopath Assoc* 2004; 104: 377–84.
6. Romi F, *et al.* Myasthenia gravis: clinical, immunological, and therapeutic advances. *Acta Neurol Scand* 2005; 111: 134–41.
7. Juel VC, Massey JM. Myasthenia gravis. *Orphanet J Rare Dis* 2007; 2: 44. Available at: http://www.ojrd.com/content/pdf/1750-1172-2-44.pdf (accessed 21/12/10)
8. Newsom-Davis J. Myasthenia gravis. *Prescribers' J* 2000; 40: 93–8.
9. Richman DP, Agius MA. Treatment of autoimmune myasthenia gravis. *Neurology* 2003; 61: 1652–61.
10. Saperstein DS, Barohn RJ. Management of myasthenia gravis. *Semin Neurol* 2004; 24: 41–8.
11. Schwendimann RN, *et al.* Management of myasthenia gravis. *Am J Ther* 2005; 12: 262–8.
12. Schneider-Gold C, *et al.* Corticosteroids for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/02/06).
13. Benatar M, Kaminski H. Medical and surgical treatment for ocular myasthenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 26/05/06).
14. Hart IK, *et al.* Immunosuppressive agents for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/01/08).
15. Gajdos P, *et al.* Intravenous immunoglobulin for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 28/05/08).
16. Skeie GO, *et al.* European Federation of Neurological Societies. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol* 2010; 17: 893–902.
17. Mehndiratta MM, *et al.* Acetylcholinesterase inhibitor treatment for myasthenia gravis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 05/04/11).

Ambenonium Chloride *(BAN, rINN)*

Ambenonii Chloridum; Ambenonio, cloruro de; Ambenonium Chlorid; Ambénonium, Chlorure d'; Ambenonlumklorid; Ambenoniumkloridi; Ambestigmini Chloridum; Cloruro d'Ambénonio; Cloruro de ambenonio; Win-8077; Амбенония Хлорид.

N,N'-Oxalylbis(*N*-2-aminoethyl-*N*-2-chlorobenzyldiethylammonium) dichloride.

$C_{28}H_{42}Cl_4N_4O_2$=608.5

CAS — 7648-98-8 (ambenonium); 115-79-7 (anhydrous ambenonium chloride); 52022-31-8 (ambenonium chloride tetrahydrate).

ATC — N07AA30.

ATC Vet — QN07AA30.

UNII — 51FOB87G3I (ambenonium chloride); 9T1OT01KW1 (ambenonium chloride tetrahydrate).

Pharmacopoeias. In *Jpn*.

Uses and Administration

Ambenonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p. 687.2), but of longer duration. Ambenonium chloride is given orally in the treatment of myasthenia gravis (above) in usual doses of 5 to 25 mg three or four times daily, adjusted according to response. It may be of value in patients who cannot tolerate neostigmine or pyridostigmine.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2.

Ambenonium produces fewer muscarinic adverse effects than neostigmine. As there is only slight warning of overdosage, routine use of atropine with ambenonium is contra-indicated because the muscarinic symptoms of overdosage may be suppressed leaving only the more

serious nicotinic effects (fasciculation and paralysis of voluntary muscle).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ambenonium 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 27/07/11)

Pharmacokinetics

Ambenonium chloride is poorly absorbed from the gastrointestinal tract. It does not appear to be hydrolysed by cholinesterases.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Mytelase; *Fr.*: Mytelase; *Gr.*: Mytelase; *Hung.*: Mytelase; *Pol.*: Mytelase; *Swed.*: Mytelase; *USA*: Mytelase.

Amifampridine *(BAN, rINN)*

Amifampridin; Amifampridina; Amifampridinum; 3,4-Diaminopiridina; 3,4-Diaminopyridine; Амифампридин.

Pyridine-3,4-diamine.

$C_5H_7N_3$=109.1

CAS — 54-96-6.

ATC — N07XX05.

ATC Vet — QN07XX05.

UNII — RU4S6E2G0J.

Amifampridine Phosphate *(rINNM)*

Amifampridine, Phosphate de; Amifampridini Phosphas; Fosfato de amifampridina; Амифампридина Фосфат.

$C_5H_7N_3H_3PO_4$=207.1

ATC — N07XX05.

ATC Vet — QN07XX05.

Uses and Administration

Amifampridine enhances the release of acetylcholine from nerve terminals; its actions and uses are similar to those of fampridine (p. 686.2) but it is reported to be more potent. It is used in the Eaton-Lambert myasthenic syndrome (below) and other myasthenic conditions. It has been tried in multiple sclerosis and in botulism. Amifampridine is given as the phosphate but doses are expressed as the base; 18.98 mg of amifampridine phosphate is equivalent to about 10 mg of amifampridine. The recommended oral starting dose in adults with Eaton-Lambert myasthenic syndrome is the equivalent of 15 mg daily given in 3 or 4 divided doses; the dose may be increased in steps of 5 mg every 4 or 5 days to a maximum of 60 mg daily. For doses in patients with hepatic or renal impairment see below.

Administration in hepatic or renal impairment. An oral starting dose the equivalent of amifampridine 5 mg daily is recommended in patients with moderate to severe hepatic or renal impairment; those with mild impairment may be given a starting dose of 10 mg daily. The dose may be increased in steps of 5 mg every 7 days.

Congenital myasthenia. Congenital or hereditary myasthenia[1-3] is a heterogeneous group of rare disorders associated with various defects in neuromuscular transmission including presynaptic impairment of acetylcholinesterase release, postsynaptic abnormality of acetylcholine receptors, or a deficiency of acetylcholinesterase. Consequently, for any given congenital myasthenic syndrome, the synaptic response to acetylcholine is either increased or decreased. Symptoms may be similar to those of myasthenia gravis (p. 684.1) but there are no immunological abnormalities. Treatment[2,3] is symptomatic and depends on both the structural defect of the neuromuscular junction and the underlying genetic defect. Drugs that are beneficial for one type of congenital myasthenia can be harmful for another; hence, a precise diagnosis including genetic testing is recommended for rational therapy. Anticholinesterases and amifampridine may be used when there is a decreased synaptic response to acetylcholine; up to 1 mg/kg daily of amifampridine has been given in divided doses. Quinidine sulfate and fluoxetine, both open-channel blockers of acetylcholine receptors, have been used when the synaptic response is increased, such as in the slow-channel syndromes. Initially, quinidine sulfate 200 mg may be given 3 times daily for a week, adjusted according to serum levels thereafter; when quinidine is not tolerated, fluoxetine may be given in gradual increments until a total daily dose of 80 to 100 mg is reached. Ephedrine, given in doses of 25 to 50 mg 2 or 3 times daily, has also been shown to be of benefit in certain types of congenital myasthenia although its mode of action is unclear.

1. Engel AG. Congenital myasthenic syndromes. *Neurol Clin North Am* 1994; 12: 401–37.
2. Engel AG. The therapy of congenital myasthenic syndromes. *Neurotherapeutics* 2007; 4: 252–7.
3. Schara U, Lochmüller H. Therapeutic strategies in congenital myasthenic syndromes. *Neurotherapeutics* 2008; 5: 542–7.

Eaton-Lambert myasthenic syndrome. Oral daily doses of up to 100 mg of amifampridine have been found[1,2] to be effective in the treatment of both the motor and autonomic deficits of patients with Eaton-Lambert syndrome (p. 684.1). However, some workers have recommended limiting the dose to 80 mg daily because of the increased risk of seizures with higher doses.[3,4] (UK licensed product information recommends a maximum daily dose of 60 mg.) Amifampridine can produce mild excitatory effects and some patients may have difficulty in sleeping.

1. McEvoy KM, *et al.* 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med* 1989; 321: 1567–71.
2. Newsom-Davis J. Myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Prescribers' J* 1993; 33: 205–212.
3. Sanders DB, *et al.* A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* 2000; 54: 603–7.
4. Oh SJ, *et al.* 3,4-Diaminopyridine is more effective than placebo in a randomized, double-blind, cross-over drug study in LEMS. *Muscle Nerve* 2009; 40: 795–800.

Multiple sclerosis. Amifampridine has been tried in the management of multiple sclerosis (p. 996.3). In a crossover study[1] involving 36 patients with multiple sclerosis, amifampridine given in a dosage of up to 100 mg daily improved symptoms of leg weakness to a greater extent than placebo but paraesthesia and abdominal pain, which occurred in most patients, were dose-limiting in some. A systematic review[2] of the use of aminopyridines for symptomatic management of multiple sclerosis was unable to come to any conclusion, and commented on the problem of publication bias in this area.

1. Bever CT, *et al.* Treatment with oral 3,4-diaminopyridine improves leg strength in multiple sclerosis patients: results of a randomized, double-blind, placebo-controlled, crossover trial. *Neurology* 1996; 47: 1457–62.
2. Solari A, *et al.* Aminopyridines for symptomatic treatment in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 15/02/06).

Adverse Effects and Precautions

The most common adverse effects with amifampridine are paraesthesias and gastrointestinal disturbances such as epigastralgia, diarrhoea, nausea, and abdominal pain. Sleep disorders, anxiety, weakness, fatigue, headache, chorea, myoclonus, Raynaud's syndrome, cough, bronchial hypersecretion, and elevated liver enzyme values have also been reported. The severity and incidence of most adverse effects are dose-dependent.

Arrhythmias have been reported with amifampridine and ECG monitoring should be performed at the start of treatment and yearly thereafter; amifampridine should not be used in patients with congenital QT interval prolongation. There have also been isolated reports of seizures and amifampridine is therefore contra-indicated in patients with epilepsy. Asthma attacks have occurred in patients with asthma or a history of the disease; amifampridine should not be used in those with uncontrolled asthma.

Blurred vision, drowsiness, and dizziness have been reported with amifampridine and may affect the ability of a patient to drive or operate machinery.

References.

1. Flet L, *et al.* 3,4-Diaminopyridine safety in clinical practice: an observational, retrospective cohort study. *J Neurol* 2010; 257: 937–46.

Overdosage. A 65-year-old woman with Eaton-Lambert myasthenic syndrome suffered a cardiac arrest 11 days after her dose of amifampridine had been mistakenly altered to 60 mg 6 times daily instead of her usual dose of 10 mg 6 times daily;[1] she had also complained of paraesthesia, nausea, vomiting, and palpitations and had suffered generalised convulsions in the days preceding the cardiac arrest. She recovered completely after amifampridine was stopped.

1. Boerma CE, *et al.* Cardiac arrest following an iatrogenic 3,4-diaminopyridine intoxication in a patient with Lambert-Eaton myasthenic syndrome. *J Toxicol Clin Toxicol* 1995; 33: 249–51.

Pregnancy. Licensed product information states that there are no adequate clinical data on the use of amifampridine during pregnancy; it is recommended that men and women of child-bearing potential use effective contraception during amifampridine treatment.

A healthy infant was born to a woman with congenital myasthenia who took pyridostigmine and amifampridine throughout her pregnancy.[1] Her dose of pyridostigmine was maintained at her pre-conception dose of 180 mg daily while her amifampridine dose was progressively reduced to about 20 mg daily which allowed an acceptable level of fatigue. The infant's weight and height were within normal limits when seen aged 5 months.

1. Pelufo-Pellicer A, *et al.* Fetal exposure to 3,4-diaminopyridine in a pregnant woman with congenital myasthenia syndrome. *Ann Pharmacother* 2006; 40: 762–6.

Interactions

Use of amifampridine with sultopride is contra-indicated due to the increased risk of ventricular tachycardia, particularly torsade de pointes. The risk of seizures is increased if amifampridine is used with other drugs that are known to lower the seizure threshold.

Pharmacokinetics

Amifampridine is rapidly absorbed after oral use and peak plasma concentrations occur after 20 to 60 minutes. Its elimination half-life is about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Firdapse; *Denm.*: Firdapse; *Fr.*: Firdapse; *Ger.*: Firdapse; *Irl.*: Firdapse; *Israel*: Firdapse; *Neth.*: Firdapse; *Pol.*: Firdapse; *Port.*: Firdapse; *Swed.*: Firdapse; *Switz.*: Firdapse; *UK*: Firdapse.

Distigmine Bromide *(BAN, rINN)*

BC-51; Bispyridostigmine Bromide; Bromure de Distigmine; Bromuro de distigmina; Distigmiinibromidi; Distigmin Bromid; Distigmina, bromuro de; Distigminbromid; Distigmine, Bromure de; Distigmini Bromidum; Hexamarium Bromide; Дистигмина Бромид.

3,3'-[*N*,*N*'-Hexamethylenebis(methylcarbamoyloxy)]bis(1-methylpyridinium bromide).

$C_{22}H_{32}Br_2N_4O_4$=576.3

CAS — 15876-67-2.

ATC — N07AA03.

ATC Vet — QN07AA03.

UNII — 750F36OP6J.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Distigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p. 687.2) but more prolonged. Maximum inhibition of plasma cholinesterase occurs 9 hours after a single intramuscular dose, and persists for about 24 hours.

Although it is rarely used, distigmine bromide may be given orally with other short-acting parasympathomimetics for the treatment of **myasthenia gravis** (p. 684.1); patients being treated with parasympathomimetics tend to prefer pyridostigmine. The initial dose is 5 mg daily 30 minutes before breakfast, increased at intervals of 3 to 4 days if necessary to a maximum of 20 mg daily. For details of doses in children, see below.

Distigmine is one of several drugs that have been used in the prevention and treatment of **postoperative gastrointestinal atony** (see Decreased Gastrointestinal Motility, p. 1808.2). It has also been used in **postoperative urinary retention** (p. 2349.2), although it has been superseded by catheterisation. An oral dose of 5 mg daily 30 minutes before breakfast may be given. A similar oral dose, given daily or on alternate days, has been used in the management of **neurogenic bladder.**

Distigmine has been given by intramuscular injection.

Administration in children. Although it is rarely used, distigmine bromide may be given to children for the treatment of myasthenia gravis in oral doses of up to 10 mg daily according to age.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2. The anticholinesterase action of distigmine, and hence its adverse effects, may be prolonged, and if treatment with atropine is required it should be maintained for at least 24 hours. Distigmine may stimulate uterine contractions and licensed product information advises that it should be avoided in pregnancy.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Distigmine is poorly absorbed from the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Ubretid; *Ger.*: Ubretid; *Gr.*: Ubretid; *Hong Kong*: Ubretid; *Neth.*: Ubretid; *Pol.*: Ubretid; *Rus.*: Ubretid (Убретид); *Singapore*: Ubretid; *Switz.*: Ubretid; *UK*: Ubretid†.

Edrophonium Chloride *(BAN, rINN)*

Cloruro de edrofonio; Edrofonio cloridas; Edrofonio, cloruro de; Edrofonium-chlorid; Edrofoniumklorid; Edrofoniumklorid; Edrofonyum Klorür; Edrophonii Chloridum; Edrophonium Chlorid; Edrophonium, chlorure d'; Edrophoniumchlorid; Эдрофония Хлорид.

Ethyl(3-hydroxyphenyl)dimethylammonium chloride.

$C_{10}H_{16}ClNO$=201.7

CAS — 312-48-1 (edrophonium); 116-38-1 (edrophonium chloride).

UNII — QO611KSM5P.

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

Ph. Eur. 8: (Edrophonium Chloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Edrophonium Chloride). A white odourless crystalline powder. Soluble 1 in 0.5 of water and 1 in 5 of alcohol; insoluble in chloroform and in ether. A 10% solution in water is practically colourless and the pH is between 4.0 and 5.0.

Uses and Administration

Edrophonium is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity. It has actions similar to those of neostigmine (p. 687.2) but its effect on skeletal muscle is claimed to be particularly prominent. It has a rapid onset but short duration of action. In patients with myasthenia gravis, there is immediate subjective improvement and muscle strength increases. This effect usually lasts only for about 5 to 15 minutes, after which time the typical signs and symptoms return; because of its brief action the drug is not suitable for the routine treatment of myasthenia gravis.

Edrophonium chloride is used in **myasthenia gravis** (p. 684.1) both diagnostically and to distinguish between under- and over-treatment with other anticholinesterases.

- The usual *diagnostic procedure* is to inject 2 mg intravenously and, if no adverse reaction occurs within 30 to 45 seconds, to continue with the injection of a further 8 mg; the test may be repeated after 30 minutes if necessary.
  When intravenous injection is difficult edrophonium chloride may be given by intramuscular injection in a usual dose of 10 mg. Atropine should always be available when the test is carried out in order to treat any severe muscarinic reactions that may occur.
- To *detect under- or over-treatment*, test doses of 1 to 2 mg of edrophonium chloride are given intravenously to distinguish severe symptoms of myasthenia gravis due to inadequate therapy from the effects of overdosage with anticholinesterase drugs. If treatment has been inadequate, edrophonium chloride will produce an immediate amelioration of symptoms, whereas in cholinergic crises due to over-treatment the symptoms will be temporarily aggravated. Licensed product information suggests testing one hour after the last dose of treatment but the *BNF* recommends testing just before the next dose is due. Testing should only be undertaken when facilities for endotracheal intubation and controlled ventilation are immediately available.

Edrophonium chloride was originally introduced for the **reversal of neuromuscular blockade** in anaesthesia. In the UK, the recommended dose for the reversal of the effects of competitive neuromuscular blockers is 500 to 700 micrograms/kg given by intravenous injection over several minutes either with or after atropine sulfate 7 micrograms/kg. It has been suggested that in the presence of bradycardia atropine sulfate should be given several minutes before edrophonium. In the USA, a dose of 10 mg of edrophonium chloride is given over 30 to 45 seconds and repeated as required up to a maximum of 40 mg. The brevity of its action limits its value. Prolonged apnoea may occur in patients treated with a depolarising neuromuscular blocker, such as suxamethonium; to determine if this is caused by a phase II block (see p. 2037.2), edrophonium chloride 10 mg may be given intravenously with atropine.

For details of doses in children, see below.

Edrophonium bromide has been used similarly to edrophonium chloride.

Administration in children. The use of edrophonium chloride in children with **myasthenia gravis** is similar to that in adults (see Uses and Administration, above).

- The usual *diagnostic procedure* in the UK is to inject 20 micrograms/kg intravenously and, if no adverse reaction occurs within 30 seconds, to continue with the injection of a further 80 micrograms/kg. The *BNFC* suggests that this dose may be given to those aged from 1 month to 12 years. Older children may be given the usual adult dose. In the USA a total intravenous dose of 5 mg for children weighing less than 34 kg and 10 mg for heavier children is recommended, with one-fifth of the dose being given initially followed by increments of 1 mg every 30 to 45 seconds. Alternatively, a total of 200 micrograms/kg may be given, with one-fifth of the dose being given initially over 1 minute followed by the remainder if no adverse reactions occur within 45 seconds. The recommended total dose for infants is 500 micrograms. When intravenous injection is difficult edrophonium chloride may be given by intramuscular injection; children weighing under 34 kg may be given 2 mg and heavier children 5 mg. The recommended dose for infants is 0.5 to 1 mg given intramuscularly or subcutaneously.
- To *detect under- or over-treatment*, the *BNFC* recommends that children aged from 1 month to 12 years be given a dose of 20 micrograms/kg by intravenous injection just before the next dose of anticholinesterase. Older children may be given the usual adult dose.

For the **reversal of neuromuscular blockade** in anaesthesia, usual doses in the UK for children are as for adults; the *BNFC* suggests that these doses may be given to children as young as 1 month of age.

Reversal of neuromuscular blockade. For a discussion of whether edrophonium might be more suitable than neostigmine for reversal of residual block after the use of the shorter-acting competitive neuromuscular blockers, see under Uses and Administration of Neostigmine, p. 688.1.

Snake bite. For the use of anticholinesterases in the treatment of snake bite, see under Uses and Administration of Neostigmine, p. 688.1.

Tetrodotoxin poisoning. Management of poisoning due to tetrodotoxin, a heat stable neuromuscular blocking toxin found in various marine animals, such as puffer fish, is mainly symptomatic and supportive. Reports[1-4] on the efficacy of intravenous anticholinesterases such as edrophonium or neostigmine in reversing muscle weakness in tetrodotoxin poisoning have been conflicting. Although it appears that anticholinesterases may only be effective during partial block produced by tetrodotoxin, some consider[5] that, as there is no specific antidote, any measure that brings about improvement may be tried.

For a discussion of the general principles of the management of acute poisoning, see p. 1537.1.

1. Chew SK, *et al.* Anticholinesterase drugs in the treatment of tetrodotoxin poisoning. *Lancet* 1984; ii: 108.
2. Tibballs J. Severe tetrodotoxic fish poisoning. *Anaesth Intensive Care* 1988; 16: 215–17.
3. Isbister GK, Kiernan MC. Neurotoxic marine poisoning. *Lancet Neurol* 2005; 4: 219–28.
4. Hwang D-F, Noguchi T. Tetrodotoxin poisoning. *Adv Food Nutr Res* 2007; 52: 141–236.
5. Karalliedde L. Management of puffer fish poisoning. *Br J Anaesth* 1995; 75: 500.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2.

Interactions

As for Neostigmine, p. 688.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Tensilon; *Gr.*: Anticude; *Singapore*: Tensilon; *Spain*: Anticude; *USA*: Enlon-Plus; Enlon; Reversol†; Tensilon.

Pharmacopoeial Preparations
BP 2014: Edrophonium Injection;
USP 36: Edrophonium Chloride Injection.

Fampridine *(rINN)*

Dalfampridine (USAN); EL-970; Fampridin; Fampridina; Fampridinum; Фампридин.

4-Aminopyridine; 4-Pyridinamine.

$C_5H_6N_2$=94.12

CAS — 504-24-5.

ATC — N07XX07.

ATC Vet — QN07XX07.

UNII — BH3B64OKL9.

Uses and Administration

Fampridine is an aminopyridine that, like its derivative amifampridine (p. 685.1), enhances the release of acetylcholine from nerve terminals. It is used to improve walking in patients with multiple sclerosis (below); the licensed dose is 10 mg twice daily as an oral modified-release preparation. Fampridine has also been tried in the management of Guillain-Barré syndrome (p. 2406.1) and spinal cord injury; oral doses used in patients with spinal cord injuries have ranged from 30 to 50 mg daily. Other uses of fampridine that have been investigated include the neurological disorders Eaton-Lambert myasthenic syndrome (p. 684.1) and Alzheimer's disease (see Dementia, p. 388.1), and the reversal of neuromuscular blockade in patients with botulism (p. 2380.2) or after the use of competitive neuromuscular blockers.

Fampridine has also been considered as a specific antidote in poisoning with calcium-channel blockers (see Overdosage under Treatment of Adverse Effects of Nifedipine, p. 1452.3).

References.
1. Soni N, Kam P. 4-Aminopyridine: a review. *Anaesth Intensive Care* 1992; 20: 120–6.
2. Ter Wee PM, *et al.* 4-Aminopyridine and haemodialysis in the treatment of verapamil intoxication. *Hum Toxicol* 1985; 4: 327–9.
3. Davidson M, *et al.* 4-Aminopyridine in the treatment of Alzheimer's disease. *Biol Psychiatry* 1988; 23: 485–90.
4. Hansebout RR, *et al.* 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients. *J Neurotrauma* 1993; 10: 1–18.
5. Halter JA, *et al.* Intrathecal administration of 4-aminopyridine in chronic spinal injured patients. *Spinal Cord* 2000; 38: 728–32.
6. DeForge D, *et al.* Effect of 4-aminopyridine on gait in ambulatory spinal cord injuries: a double-blind, placebo-controlled, crossover trial. *Spinal Cord* 2004; 42: 674–85.
7. Cardenas DD, *et al.* Phase 2 trial of sustained-release fampridine in chronic spinal cord injury. *Spinal Cord* 2007; 45: 158–68.

Multiple sclerosis. Fampridine has potassium-channel blocking activity and has been tried in the treatment of multiple sclerosis (p. 996.3) to improve conduction in demyelinated fibres. Improvements have been reported in walking, dexterity, and vision, but only small numbers of patients have been studied. An early systematic review[1] was unable to come to a conclusion about its safety and efficacy, noting that publication bias posed a problem in this area. However, further multicentre randomised controlled studies,[2-4] and reviews[5-7] of these studies, suggested that fampridine improved walking ability in some patients. Any benefit is generally noted within 2 weeks of starting treatment.

1. Solari A, *et al.* Aminopyridines for symptomatic treatment in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 15/02/06).
2. Goodman AD, *et al.* Fampridine MS-F202 Study Group. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology* 2008; 71: 1134–41.
3. Goodman AD, *et al.* Fampridine MS-F203 Investigators. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet* 2009; 373: 732–8.
4. Goodman AD, *et al.* MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010; 68: 494–502.
5. Korenke AR, *et al.* Sustained-release fampridine for symptomatic treatment of multiple sclerosis. *Ann Pharmacother* 2008; 42: 1458–65.
6. Blight AR. Treatment of walking impairment in multiple sclerosis with dalfampridine. *Ther Adv Neurol Dis* 2011; 4: 99–109.
7. McDonald S, Clements JN. Dalfampridine: a new agent for symptomatic management of multiple sclerosis. *Am J Health-Syst Pharm* 2011; 68: 2335–40.

Adverse Effects and Precautions

The most common adverse effect with fampridine is urinary-tract infection. Other adverse effects include insomnia, dizziness, headache, gastrointestinal disturbances such as constipation, dyspepsia, and nausea, asthenia, back pain, paraesthesia, and nasopharyngitis.

A dose-dependent increase in the incidence of seizures has been noted with fampridine treatment and therefore its use is contra-indicated in patients with a history of seizures.

Fampridine is mainly eliminated unchanged by the kidneys and patients with renal impairment therefore have an increased risk of adverse effects, particularly neurological reactions. Consequently, its use is contra-indicated in patients with moderate to severe renal impairment (creatinine clearance of 50 mL/min or less). In patients with mild renal impairment (creatinine clearance of 80 mL/min or less), the risk of seizures is unknown although plasma levels of fampridine may approach those associated with an increased risk; UK licensed product information also contra-indicates fampridine use in this patient group.

Overdosage. An 8-month-old boy had dramatic opisthotonic posturing and vermiform tongue fasciculations after ingestion of up to 20 mg of fampridine;[1] the child was also noted to be tachycardic and tachypnoeic. His symptoms resolved after treatment with benzodiazepines. Choreoathetoid movements in all limbs were also reported in a 45-year-old woman with multiple sclerosis who accidentally overdosed with fampridine;[2] when rechallenged,

symptoms including confusion, opisthotonus, risus sardonicus, motor distress, and head tremor were noted instantly.

Three adult patients[3] with multiple sclerosis developed status epilepticus within minutes to hours of taking incorrectly-compounded tablets that contained between 90.1 and 125.6 mg of fampridine per tablet instead of the prescribed 10 mg. Although acute recovery was seen in all 3 patients after treatment with benzodiazepines and phenytoin, chronic neurological disabilities remained.

In another case, a 56-year-old man developed altered mental status, hypothermia, and atrial fibrillation after taking an unknown quantity of fampridine for toothache.[4] He had rubbed a large 'rock' of fampridine against his tooth in an attempt to relieve the pain, inadvertently swallowing some flakes of drug, which resulted in the overdose.

1. Velez L, *et al.* Opisthotonic posturing with neuromuscular irritability attributable to 4-aminopyridine ingestion by a healthy pediatric patient. Abstract: *Pediatrics* 2003; **111**: 192–3. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/1/e82 (accessed 15/02/06)
2. De Cauwer H, *et al.* An unusual case of 4-aminopyridine toxicity in a multiple sclerosis patient: epileptic disorder or toxic encephalopathy? *Acta Neurol Belg* 2009; **109**: 40–1.
3. Burton JM, *et al.* 4-Aminopyridine toxicity with unintentional overdose in four patients with multiple sclerosis. *Neurology* 2008; **71**: 1833–4.
4. Johnson NC, Morgan MW. An unusual case of 4-aminopyridine toxicity. *J Emerg Med* 2006; **30**: 175–7.

Pharmacokinetics

Fampridine is rapidly and extensively absorbed from the gastrointestinal tract after oral use. Plasma protein binding is minimal (1 to 3%). Fampridine is eliminated mostly unchanged in the urine; less than 10% of the drug is metabolised, some via the cytochrome P450 isoenzyme CYP2E1. Two major metabolites have been identified: 3-hydroxy-4-aminopyridine and 3-hydroxy-4-aminopyridine sulfate.

References.
1. Hayes KC, *et al.* Pharmacokinetics of an immediate-release oral formulation of fampridine (4-aminopyridine) in normal subjects and patients with spinal cord injury. *J Clin Pharmacol* 2003; **43**: 379–85.
2. Smith W, *et al.* Single-dose pharmacokinetics of sustained-release fampridine (fampridine-SR) in healthy volunteers and adults with renal impairment. *J Clin Pharmacol* 2010; **50**: 151–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Fampyra; *Denm.*: Fampyra; *Fr.*: Fampyra; *Ger.*: Fampyra; *Israel*: Fampyra; *Neth.*: Fampyra; *Norw.*: Fampyra; *Swed.*: Fampyra; *UK*: Fampyra; *USA*: Ampyra.

Ipidacrine *(rINN)*

Amiridin (base or hydrochloride); Ipidacrina; Ipidacrinum; NIK-247 (hydrochloride); Ипидакрин.

9-Amino-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta[*b*]quinoline.

$C_{12}H_{16}N_2$=188.3

CAS — 62732-44-9 (ipidacrine); 90043-86-0 (ipidacrine hydrochloride); 118499-70-0 (ipidacrine hydrochloride monohydrate).

UNII — CV71VTP0VN.

Profile

Ipidacrine, an analogue of tacrine (p. 396.1), is a cholinesterase inhibitor. It is used in the management of various neurological disorders including CNS and peripheral nervous system disorders, demyelinating disease, myasthenia gravis (p. 684.1) and other myasthenic syndromes, Alzheimer's disease (see Dementia, p. 388.1), and gastrointestinal atony. For myasthenic syndromes an oral dose of 20 to 40 mg has been given up to 5 times daily. A usual dosage in Alzheimer's disease is 10 to 20 mg given 2 or 3 times daily but this may be increased gradually up to 200 mg daily given in divided doses.

Ipidacrine has also been given by injection as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Amiridine (Амиридин); Axamon (Аксамон); Neiromidin (Нейромидин); *Ukr.*: Neiromidinum (Нейромидин).

Neostigmine *(BAN)*

Neostigmiini; Neostigmin; Neostigmina; Neostigminum; Neostygmina; Neosztigmin.

3-(Dimethylcarbamoyloxy)trimethylanilinium ion.

$C_{12}H_{19}N_2O_2$=223.3

CAS — 59-99-4.

ATC — N07AA01; S01EB06.

ATC Vet — QA03AB93; QN07AA01; QS01EB06.

UNII — 3982TWQ96G.

Neostigmine Bromide *(BANM, pINN)*

Bromuro de neostigmina; Bromuro de Sinstigmina; Neostig. Brom.; Neostigmiinibromidi; Neostigmina, bromuro de; Neostigminbromid; Néostigmine, Bromure de; Néostigmini Bromidum; Neostigminii Bromidum; Neostigminium-bromid; Neostigmino bromidas; Neostiginum Bromatum; Neosztigmin-bromid; Synstigminium Bromatum; Неостигмина Бромид.

$C_{12}H_{19}BrN_2O_2$=303.3

CAS — 114-80-7.

ATC — N07AA01; S01EB06.

ATC Vet — QN07AA01; QS01EB06.

UNII — 005SYP50G5.

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

Ph. Eur. 8: (Neostigmine Bromide). Hygroscopic, colourless crystals or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Neostigmine Bromide). Store in airtight containers.

Stability. References.
1. Porst H, Kny L. Kinetics of the degradation of neostigmine bromide in aqueous solution. *Pharmazie* 1985; **40**: 713–17.

Neostigmine Metilsulfate *(BANM)*

Neostig. Methylsulph.; Neostigmiinimetilsulfaatti; Neostigmina, metilsulfato de; Neostigmine Methylsulfate; Neostigmine Methylsulphate; Néostigmine, métilsulfate de; Neostigmini metilsulfas; Neostigminii Metilsulfas; Neostigminium-methylsulfát; Neostigminmetilsulfat; Neostigminmetylsulfat; Neostigmino metilsulfatas; Neostygminy metylosiarczan; Neosztigmin-metilszulfát; Proserinum.

$C_{13}H_{22}N_2O_6S$=334.4

CAS — 51-60-5.

ATC — N07AA01; S01EB06.

ATC Vet — QN07AA01; QS01EB06.

UNII — 98IMH7M386.

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

Ph. Eur. 8: (Neostigmine Metilsulfate). Hygroscopic, colourless crystals or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Neostigmine Methylsulfate). Store in airtight containers.

Uses and Administration

Neostigmine is a quaternary ammonium compound that inhibits cholinesterase activity and thus prolongs and intensifies the physiological actions of acetylcholine (p. 2003.2). It probably also has direct effects on skeletal muscle fibres. The anticholinesterase actions of neostigmine are reversible.

Neostigmine is used in the treatment of myasthenia gravis, and has been used as an alternative to edrophonium in the diagnosis of myasthenia gravis (p. 684.1). It is used in anaesthesia to reverse the neuromuscular blockade produced by competitive neuromuscular blockers (see p. 688.1). It is also used in the management of paralytic ileus. Neostigmine has been used in the management of postoperative urinary retention (p. 2349.2) but has generally been superseded by catheterisation. It has also been used to lower intra-ocular pressure in the management of glaucoma and to reduce rises in intra-ocular pressure associated with ophthalmic surgery, although other parasympathomimetics are usually used when such miotics are required.

Neostigmine is given as the bromide and as the metilsulfate. Neostigmine bromide is given orally and has been used topically as eye drops; the metilsulfate is given by intramuscular, intravenous, or subcutaneous injection.

Licensed product information states that 500 micrograms of neostigmine metilsulfate by intravenous injection is equivalent in effect to about 1 to 1.5 mg of neostigmine metilsulfate by intramuscular or subcutaneous injection, or 15 mg of neostigmine bromide orally.

In the treatment of **myasthenia gravis**, neostigmine bromide is given orally in a total daily dose that ranges from 75 to 300 mg, divided throughout the day, and if necessary the night, according to response; larger portions of the total dose may be given at times of greater fatigue. The *BNF* states that the maximum daily dose that most patients can tolerate is 180 mg. In patients in whom oral therapy is impractical neostigmine metilsulfate may be given in doses of 0.5 to 2.5 mg by intramuscular or subcutaneous injection at intervals, giving a total daily dose usually in the range 5 to 20 mg.

To **reverse neuromuscular blockade** produced by competitive neuromuscular blockers, the usual licensed dose in the UK is 50 to 70 micrograms/kg given by intravenous injection over a period of 60 seconds; the *BNF* suggests giving a dose of 2.5 mg. In the USA licensed doses of 0.5 to 2 mg are recommended. Additional neostigmine may be given until the muscle power is normal but a total of 5 mg should not be exceeded. The patient should be ventilated until complete recovery of normal respiration is assured. To counteract any muscarinic effects 0.6 to 1.2 mg (20 to 30 micrograms/kg) of atropine sulfate is given by intravenous injection with or before the dose of neostigmine. It has been suggested that in the presence of bradycardia atropine sulfate should be given several minutes before neostigmine. Glycopyrronium bromide has been used as an alternative to atropine sulfate.

In the treatment of paralytic **ileus** and postoperative **urinary retention**, oral doses of 15 to 30 mg of the bromide, or more usually 0.5 to 2.5 mg of the metilsulfate by subcutaneous or intramuscular injection, have been used.

For details of doses in children, see below.

Administration in children. The use of neostigmine in children is similar to that in adults (see Uses and Administration above).

For the treatment of **myasthenia gravis** UK licensed product information states that neostigmine bromide may be given orally in an initial dose of 7.5 mg to children aged under 6 years, or 15 mg to those aged 6 to 12 years. This is adjusted according to response to a usual total daily dose of 15 to 90 mg, divided throughout the day.

When oral therapy is impractical, children aged under 12 years may be given intramuscular or subcutaneous injections of neostigmine metilsulfate in doses of 200 to 500 micrograms, repeated at suitable intervals throughout the day.

For all routes of administration, children aged over 12 years may be given the usual adult dose.

In the treatment of neonatal myasthenia gravis, UK licensed product information states that neostigmine metilsulfate may be given in an initial intramuscular dose of 100 micrograms followed by a usual dose of 50 to 250 micrograms, or 30 micrograms/kg, every 2 to 4 hours. The *BNFC* recommends higher doses: an initial intramuscular or subcutaneous dose of 150 micrograms/kg every 6 to 8 hours, increased to a maximum of 300 micrograms/kg every 4 hours if necessary. Alternatively, the *BNFC* suggests that neostigmine bromide may be given in an initial oral dose of 1 to 2 mg followed by 1 to 5 mg every 4 hours. For all routes of administration, doses should be given 30 minutes before feeding. Treatment is rarely needed beyond 8 weeks of age.

To **reverse neuromuscular blockade** produced by competitive neuromuscular blockers, children may be given doses similar to those used in adults; the *BNFC* recommends an intravenous dose of 50 micrograms/kg (to a maximum of 2.5 mg) in neonates and those aged up to 18 years; a further dose of 25 micrograms/kg may be given if required. To counteract any muscarinic effects, neonates and children may be given atropine sulfate 20 micrograms/kg (to a maximum of 1.2 mg) by intravenous injection with or before the dose of neostigmine. Glycopyrronium may be used as an alternative to atropine.

For the treatment of paralytic **ileus** or postoperative **urinary retention** in children, oral doses of 2.5 to 15 mg of the bromide, or more usually 0.125 to 1 mg of the metilsulfate by subcutaneous or intramuscular injection, have been used.

Decreased gastrointestinal motility. Parasympathomimetics enhance gastric contractions and increase intestinal motility and have been used in conditions associated with decreased gastrointestinal motility (p. 1808.2). Good results have been reported with intravenous neostigmine in the treatment of acute colonic pseudo-obstruction,[1,2] a condition that appears to be due to parasympathomimetic dysfunction. These results have been confirmed in a randomised double-blind study.[3] It has therefore been suggested that parasympathomimetics should be tried before colonic decompression or surgery when conservative management has failed or a rapid resolution is required.[3] Neostigmine has also been used in the treatment of severe constipation due to disrupted intestinal motility.[4-6]

1. Hutchinson R, Griffiths C. Acute colonic pseudo-obstruction: a pharmacological approach. *Ann R Coll Surg Engl* 1992; **74**: 364–7.
2. Stephenson BM, *et al.* Parasympathomimetic decompression of acute colonic pseudo-obstruction. *Lancet* 1993; **342**: 1181–2.
3. Ponec RJ, *et al.* Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999; **341**: 137–41.
4. Miller LS. Neostigmine for severe constipation with spinal cord lesions. *Ann Intern Med* 1984; **101**: 279.
5. Thurtle OA, *et al.* Intractable constipation in malignant phaeochromocytoma: combined treatment with adrenergic blockade and cholinergic drugs. *J R Soc Med* 1984; **77**: 327–8.
6. Rosman AS, *et al.* Intramuscular neostigmine and glycopyrrolate safely accelerated bowel evacuation in patients with spinal cord injury and defecatory disorders. *Dig Dis Sci* 2008; **53**: 2710–13.

Local anaesthesia. Intrathecal neostigmine has been added to spinal local anaesthetics or opioids as an adjunct to prolong regional analgesia and improve haemodynamic stability. A systematic review[1] of studies of such use found that although neostigmine in doses up to 500 micrograms produced a very modest increase in analgesia in the perioperative and peripartum setting, it did not appear to improve haemodynamic stability and the incidence of adverse effects was greatly increased, even at low doses. The disadvantages were felt to outweigh whatever benefits such therapy might have.

Neostigmine has also been given by the epidural route as an adjunct to analgesia;[2] some adverse effects such as nausea may be less with this route.

1. Ho KM, *et al.* Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta-analysis. *Anaesth Intensive Care* 2005; 33: 41–53.
2. Ross VH, *et al.* Neostigmine decreases bupivacaine use by patient-controlled epidural analgesia during labor: a randomized controlled study. *Anesth Analg* 2009; 109: 524–31.

Reversal of neuromuscular blockade. Anticholinesterases have often been used after surgery to antagonise residual neuromuscular block induced by long-acting competitive neuromuscular blockers. However, there has been continuing debate[1-3] on whether anticholinesterases can be used in reduced doses or even omitted for intermediate-acting blockers such as atracurium and vecuronium and shorter-acting blockers such as mivacurium.

Decreasing the anticholinesterase dose may reduce adverse effects. Although it is not clear whether omitting neostigmine reversal reduces nausea and vomiting,[3,4] it avoids any adverse effects neostigmine may have on gut anastomoses. One commentator[1] considered that the wide variation in recovery time with aminosteroid blockers such as rocuronium was an indication for always using at least a small dose of anticholinesterase when these drugs were used. However, it was suggested that, if the block was being carefully monitored and recovery was established, a reduced dose of 1.25 mg of neostigmine might be preferable after a benzylisoquinolinium blocker such as atracurium or mivacurium. In children, smaller doses of an anticholinesterase could be used, even after an aminosteroid blocker, and after a blocker such as mivacurium, they might not be needed at all.

Others have preferred to reserve neostigmine reversal for cases where it was deemed clinically necessary: in a study[4] using such a protocol, 68% of those receiving rocuronium were given neostigmine, against 10% of those receiving mivacurium.

It has been suggested that because of its shorter duration of action edrophonium might be more suitable than neostigmine to antagonise residual block for neuromuscular blockers with shorter actions and in particular, that edrophonium might be more appropriate than neostigmine for use with mivacurium. Neostigmine inhibits the plasma cholinesterase responsible for the metabolism of mivacurium and its use can in theory delay rather than speed recovery, although in practice there is considered to be little evidence for such an effect.[1] Edrophonium also has lesser effects on the vagus, a more rapid onset of action, and may be associated with a lower incidence of nausea and vomiting than neostigmine.[5] Neostigmine can cause clinically significant neuromuscular blockade if it is given to a patient who has already recovered a large degree of neuromuscular function[6,7] but edrophonium appears not to have this effect.[8] However, the antagonism produced by edrophonium is not adequately and reliably sustained especially after profound block.[9,10]

1. Hunter JM. Is it always necessary to antagonize residual neuromuscular block? Do children differ from adults? *Br J Anaesth* 1996; 77: 707–9.
2. Fawcett WJ. Neuromuscular block in children. *Br J Anaesth* 1997; 78: 627.
3. Fuchs-Buder T, Mencke T. Use of reversal agents in day care procedures (with special reference to postoperative nausea and vomiting). *Eur J Anaesthesiol* 2001; 18 (suppl 23): 53–9.
4. Joshi GP, *et al.* The effects of antagonizing residual neuromuscular blockade by neostigmine and glycopyrrolate on nausea and vomiting after ambulatory surgery. *Anesth Analg* 1999; 89: 628–31.
5. Watcha MF, *et al.* Effect of antagonism of mivacurium-induced neuromuscular block on postoperative emesis in children. *Anesth Analg* 1995; 80: 713–17.
6. Hughes R, *et al.* Neuromuscular blockade by neostigmine. *Br J Anaesth* 1979; 51: 568P.
7. Payne JP, *et al.* Neuromuscular blockade by neostigmine in anaesthetized man. *Br J Anaesth* 1980; 52: 69–75.
8. Astley BA, *et al.* Electrical and mechanical responses after neuromuscular blockade with vecuronium, and subsequent antagonism with neostigmine or edrophonium. *Br J Anaesth* 1987; 59: 983–8.
9. Caldwell JE, *et al.* Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium: comparison of neostigmine with edrophonium. *Br J Anaesth* 1986; 58: 1285–9.
10. Mirakhur RK, *et al.* Antagonism of vecuronium-induced neuromuscular blockade with edrophonium or neostigmine. *Br J Anaesth* 1987; 59: 473–7.

Snake bite. The general management of snake bites is discussed on p. 2419.2. Many reports from India have claimed benefit for anticholinesterases in the treatment of neurotoxic snake bites but failure to distinguish between cobra and krait bites, lack of controls, and inadequate information about other therapy weaken the claims.[1] However, edrophonium has been shown in 2 double-blind studies to be more effective than placebo[2] and antivenom[3] in the treatment of snake bite due to the Philippine cobra (*Naja naja philippinensis*). Neostigmine has also been reported[4] to have been effective in reversing paralysis in 2 patients bitten by *Micrurus frontalis* (a coral snake). Similarly, another patient made a remarkable recovery when treated with neostigmine after being bitten by an Asiatic cobra (*Naja naja kaouthia*).[5] Anticholinesterases would be expected to be of little value for bites from snakes whose venom contains neurotoxins which act presynaptically, including the Asian krait, the Australian tiger snake, and the taipan[6] and, although beneficial results have been reported in individual patients,[7] overall results are considered to be inconsistent.[2,8] However, it is recommended that a test dose of edrophonium preceded by atropine should be given to patients with neurological signs after a snake bite by any species and if improvement occurs, a longer acting anticholinesterase such as neostigmine can be given.[2,3]

1. Reid HA. Venoms and antivenoms. *Trop Dis Bull* 1983; 80: 23.
2. Watt G, *et al.* Positive response to edrophonium in patients with neurotoxic envenoming by cobras (Naja naja philippinensis). *N Engl J Med* 1986; 315: 1444–8.
3. Watt G, *et al.* Comparison of Tensilon and antivenom for the treatment of cobra-bite paralysis. *Trans R Soc Trop Med Hyg* 1989; 83: 570–3.
4. Vital Brazil O, Vieira RJ. Neostigmine in the treatment of snake accidents caused by Micrurus frontalis: report of two cases. *Rev Inst Med Trop Sao Paulo* 1996; 38: 61–7.
5. Gold BS. Neostigmine for the treatment of neurotoxicity following envenomation by the Asiatic cobra. *Ann Emerg Med* 1996; 28: 87–9.
6. Brophy T, Sutherland SK. Use of neostigmine after snake bite. *Br J Anaesth* 1979; 51: 264–5.
7. Warrell DA, *et al.* Severe neurotoxic envenoming by the Malayan krait Bungarus candidus (Linnaeus): response to antivenom and anticholinesterase. *BMJ* 1983; 286: 678–80.
8. Trevett AJ, *et al.* Failure of 3,4-diaminopyridine and edrophonium to produce significant clinical benefit in neurotoxicity following the bite of Papuan taipan (Oxyuranus scutellatus canini). *Trans R Soc Trop Med Hyg* 1995; 89: 444–6.

Tetrodotoxin poisoning. For reference to the use of neostigmine in the treatment of tetrodotoxin poisoning caused by eating puffer fish, see under Uses and Administration of Edrophonium Chloride, p. 686.2.

Adverse Effects

The adverse effects of neostigmine are chiefly due to excessive cholinergic stimulation and most commonly include increased salivation, nausea and vomiting, abdominal cramps, and diarrhoea. Allergic reactions have been reported; rashes have been associated with the use of the bromide salt. Neostigmine penetrates the blood-brain barrier poorly and CNS effects are usually only seen with high doses.

Overdosage may lead to a 'cholinergic crisis', characterised by both muscarinic and nicotinic effects. These effects may include excessive sweating, lachrymation, increased peristalsis, involuntary defaecation and urination or desire to urinate, miosis, ciliary spasm, nystagmus, bradycardia and other arrhythmias, hypotension, muscle cramps, fasciculations, weakness and paralysis, tight chest, wheezing, and increased bronchial secretion combined with bronchoconstriction. CNS effects include ataxia, convulsions, coma, slurred speech, restlessness, agitation, and fear. Death may result from respiratory failure, due to a combination of the muscarinic, nicotinic, and central effects, or cardiac arrest.

It has been reported that a paradoxical increase in blood pressure and heart rate may result from nicotinic stimulation of sympathetic ganglia, especially where atropine has been given to reverse the muscarinic effects (see Treatment of Adverse Effects, below).

In patients with myasthenia gravis, in whom other symptoms of overdosage may be mild or absent, the major symptom of cholinergic crisis is increased muscular weakness, which must be differentiated from the muscular weakness caused by an exacerbation of the disease itself (myasthenic crisis).

The adverse effects of parasympathomimetics applied topically for their miotic action are discussed under Pilocarpine on p. 2011.2.

Treatment of Adverse Effects

If a life-threatening amount of neostigmine has been taken orally and the patient presents within 1 hour, the stomach may be emptied by lavage; giving activated charcoal to decrease absorption should also be considered. When necessary maintenance of respiration should take priority. Atropine sulfate should be given in usual doses of 1 to 2 mg, preferably intravenously, or else intramuscularly and repeated as necessary to control the muscarinic effects; single doses of up to 4 mg have also been suggested. Nicotinic effects, including muscle weakness and paralysis, are not antagonised by atropine; small doses of a competitive neuromuscular blocker have been suggested for the control of muscle twitching. Use of the cholinesterase reactivator pralidoxime as an adjunct to atropine has also been suggested (see p. 1571.2). Further supportive treatment should be given as required.

For a discussion of the general principles of the management of acute poisoning, see p. 1537.1.

Precautions

The precautions and contra-indications to be observed with neostigmine use relate mainly to its cholinergic effects.

Neostigmine is contra-indicated in patients with mechanical gastrointestinal or urinary-tract obstruction, or peritonitis. It should be used with extreme caution in patients who have undergone recent intestinal or bladder surgery and in patients with bronchial asthma. It should be used with caution in patients with cardiovascular disorders including arrhythmias, bradycardia, recent myocardial infarction, and hypotension, as well as in patients with vagotonia, epilepsy, hyperthyroidism, parkinsonism, renal impairment, or peptic ulcer disease. When neostigmine is given by injection, atropine should always be available to counteract any excessive muscarinic reactions; atropine may also be given before, or with, neostigmine to prevent or minimise muscarinic adverse effects but this may mask the initial symptoms of overdosage and lead to cholinergic crisis.

UK licensed product information states that as the severity of myasthenia gravis often fluctuates considerably during pregnancy, particular care is needed to avoid cholinergic crisis caused by overdosage; it has also been reported that neonatal myasthenia may follow large doses during pregnancy. The amount of neostigmine distributed into breast milk is very small but breast-fed infants need to be monitored.

Large oral doses of neostigmine should be avoided in conditions where there may be increased absorption from the gastrointestinal tract. It should be avoided in patients known to be hypersensitive to neostigmine; the bromide ion from neostigmine bromide may contribute to any allergic reaction.

The precautions of parasympathomimetics applied topically for their miotic action are discussed under Pilocarpine on p. 2011.2.

Neuromuscular disorders. Residual non-depolarising neuromuscular block in a patient with dystrophia myotonica was only partly reversed by neostigmine and atropine, and following a second dose of both drugs complete neuromuscular block developed.[1] In a second patient with a history of progressive muscle dystrophy, the use of neostigmine to reverse residual non-depolarising blockade gave rise to a tonic response in the indirectly stimulated muscle. The type and degree of the response to neostigmine, and probably other anticholinesterases, cannot be predicted in patients with neuromuscular disease.

A patient with sero-negative ocular myasthenia gravis had exaggerated responses to both vecuronium and neostigmine.[2] The dose of neuromuscular blockers and their antagonists used in patients with myasthenia gravis should be titrated carefully regardless of the severity of the condition.

1. Buzello W, *et al.* Hazards of neostigmine in patients with neuromuscular disorders: report of two cases. *Br J Anaesth* 1982; 54: 529–34.
2. Kim J-M, Mangold J. Sensitivity to both vecuronium and neostigmine in a sero-negative myasthenic patient. *Br J Anaesth* 1989; 63: 497–500.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies neostigmine 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 27/07/11)

Renal impairment. The dosage of neostigmine may need to be adjusted in patients with renal impairment. The mean serum elimination half-life of 79.8 minutes obtained in patients with normal renal function was found to be prolonged to 181.1 minutes in anephric patients.[1]

1. Cronnelly R, *et al.* Renal function and the pharmacokinetics of neostigmine in anesthetized man. *Anesthesiology* 1979; 51: 222–6.

Interactions

Drugs with neuromuscular blocking activity, such as the aminoglycosides, clindamycin, colistin, cyclopropane, and the halogenated inhalational anaesthetics, may antagonise the effects of neostigmine. Those such as quinine, chloroquine, hydroxychloroquine, quinidine, procainamide, propafenone, lithium, and the beta blockers, that have the potential to aggravate myasthenia gravis, can reduce the efficacy of treatment with parasympathomimetics. Prolonged bradycardia has also occurred in patients receiving beta blockers when given neostigmine. Anticholinesterases, such as neostigmine, can inhibit the metabolism of suxamethonium, a depolarising neuro-

muscular blocker, and enhance and prolong its action; combined use is not recommended.

Ophthalmic use of anticholinesterases, such as ecothiopate, should be undertaken with care in patients receiving neostigmine systemically for myasthenia gravis, because of possible additive toxicity.

Antimuscarinics such as atropine antagonise the muscarinic effects of neostigmine.

Beta blockers. There have been several reports of bradycardia and hypotension when neostigmine or physostigmine were given to patients receiving beta blockers[1-4] but no significant changes in heart rate were noted in a study of pyridostigmine given to 8 patients taking beta blockers.[5] Beta blockers have the potential to aggravate the symptoms of myasthenia gravis and may therefore reduce the efficacy of parasympathomimetic treatment.

1. Sprague DH. Severe bradycardia after neostigmine in a patient taking propranolol to control paroxysmal atrial tachycardia. *Anesthesiology* 1975; 42: 208–10.
2. Seidl DC, Martin DE. Prolonged bradycardia after neostigmine administration in a patient taking nadolol. *Anesth Analg* 1984; 63: 365–7.
3. Baraka A, Dajani A. Severe bradycardia following physostigmine in the presence of beta-adrenergic blockade: a case report. *Middle East J Anesthesiol* 1984; 7: 291–3.
4. Eldor J, *et al.* Prolonged bradycardia and hypotension after neostigmine administration in a patient receiving atenolol. *Anaesthesia* 1987; 42: 1294–7.
5. Arad M, *et al.* Safety of pyridostigmine in hypertensive patients receiving beta blockers. *Am J Cardiol* 1992; 69: 518–22.

Calcium-channel blockers. Use of calcium-channel blockers such as *verapamil* with neuromuscular blockers may produce an enhanced muscle block which is resistant to reversal with neostigmine[1] but which can be reversed by edrophonium.[2]

1. van Poorten JF, *et al.* Verapamil and reversal of vecuronium neuromuscular blockade. *Anesth Analg* 1984; 63: 155–7.
2. Jones RM, *et al.* Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium. *Anesth Analg* 1985; 64: 1021–5.

Corticosteroids. Although use of glucocorticoids alone may improve strength in myasthenic patients, use of *methylprednisolone* in patients receiving neostigmine or pyridostigmine has exacerbated symptoms and produced profound weakness needing assisted ventilation.[1] Since the adverse effects of combined therapy usually occur before any expected benefits it has been suggested that the glucocorticoid should be given on alternate days in small doses which are increased gradually until the optimal effect is achieved.[2]

1. Brunner NG, *et al.* Corticosteroids in management of severe, generalized myasthenia gravis: effectiveness and comparison with corticotrophin therapy. *Neurology* 1972; 22: 603–10.
2. Jubiz W, Meikle AW. Alterations of glucocorticoid actions by other drugs and disease states. *Drugs* 1979; 18: 113–21.

Pharmacokinetics

Neostigmine is a quaternary ammonium compound and, as the bromide, is poorly absorbed from the gastrointestinal tract. After parenteral doses as the metilsulfate, neostigmine is rapidly eliminated and is excreted in the urine both as unchanged drug and metabolites. Neostigmine undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Protein binding to human serum albumin is reported to range from 15 to 25%. Penetration into the CNS is poor. Neostigmine crosses the placenta and very small amounts are distributed into breast milk.

Neostigmine appears to be poorly and variably absorbed when given orally. In 3 myasthenic patients peak plasma concentrations were obtained 1 to 2 hours after a single 30-mg oral dose and the mean plasma half-life was 0.87 hours; bioavailability was estimated to be 1 to 2%.[1] Mean plasma half-lives of 0.89 and 1.20 hours have been obtained after intravenous[1] and intramuscular[2] injections of neostigmine metilsulfate, respectively, although again only a few patients were studied. Metabolism and biliary excretion may play significant roles in the elimination of neostigmine.[2] About 80% of a dose may be excreted in the urine within 24 hours: about 50% of a dose as unchanged drug and 15% as 3-hydroxyphenyltrimethylammonium.[2] Mean plasma elimination half-lives for neostigmine have been found to be shorter in infants (0.65 hours) and children (0.80 hours) compared with adults (1.12 hours) but this does not appear to be related to its duration of effect in antagonising neuromuscular blockade.[3] For the half-life in anephric patients, see Renal Impairment, p. 688.3.

1. Aquilonius S-M, *et al.* A pharmacokinetic study of neostigmine in man using gas chromatography–mass spectrometry. *Eur J Clin Pharmacol* 1979; 15: 367–71.
2. Somani SM, *et al.* Kinetics and metabolism of intramuscular neostigmine in myasthenia gravis. *Clin Pharmacol Ther* 1980; 28: 64–8.
3. Fisher DM, *et al.* The neuromuscular pharmacology of neostigmine in infants and children. *Anesthesiology* 1983; 59: 220–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fadastigmina; Prostigmin; *Austral.*: Prostigmin†; *Austria*: Normastigmin; Prostigmin†; *Belg.*: Prostigmine; Robinul-Neostigmine; *Braz.*: Normastig; Prostigmine; *Canad.*: Prostigmin; *China*: Yi Ding (依定); *Cz.*: Syntostigmin; *Denm.*: Robinul-Neostigmin; *Fin.*: Glycostigmin; Robinul-Neostigmin; *Fr.*: Prostigmine; *Ger.*: Neostig; *Gr.*: Normastigmin; Prostigmine; *Hung.*: Stigmosan; *India*: Beemine; Myostigmin; Tilstigmin; *Indon.*: Prostigmin; *Ital.*: Intrastigmina; Prostigmina; *Malaysia*: Setisin; *Mex.*: Prostigmine; *Neth.*: Prostigmin; *Norw.*: Robinul-Neostigmin; *Philipp.*: Prostig; Prostigmin; *Pol.*: Polstigminum; *Port.*: Intrastigmina; *Singapore*: Prostigmin; Setisin; *Spain*: Prostigmine†; *Swed.*: Robinul-Neostigmin; *Switz.*: Prostigmin; Robinul-Neostigmine; *Thai.*: Prostigmin; *Turk.*: Plantigmin; *UK*: Robinul-Neostigmine†; *USA*: Bloxiverz; Neostigmine Min-I-Mix; Prostigmin.

Multi-ingredient Preparations. *Austria*: Normastigmin mit Pilocarpin; *China*: Xin Le Dun (新乐敦); *India*: Myo-Pyrolate.

Pharmacopoeial Preparations

BP 2014: Neostigmine Injection; Neostigmine Tablets;
USP 36: Neostigmine Bromide Tablets; Neostigmine Methylsulfate Injection.

Pyridostigmine Bromide *(BAN, rINN)*

Bromure de Pyridostigmine; Bromuro de piridostigmina; Piridostigmin Bromür; Piridostigmina, bromuro de; Piridostigmino bromidas; Piridosztigmin-bromid; Pyridostig. Brom.; Pyridostigmilnibromidi; Pyridostigmin Bromid; Pyridostigminbromid; Pyridostigmine, Bromure de; Pyridostigmini bromidum; Pyridostigminii Bromidum; Pyridostigminium-bromid; Пиридостигмина Бромид.

3-Dimethylcarbamoyloxy-1-methylpyridinium bromide.

$C_9H_{13}BrN_2O_2$=261.1

CAS — 155-97-5 (pyridostigmine); 101-26-8 (pyridostigmine bromide).

ATC — N07AA02.

ATC Vet — QN07AA02.

UNII — KVI301NA53.

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

Ph. Eur. 8: (Pyridostigmine Bromide). A white or almost white deliquescent crystalline powder. Very soluble in water and in alcohol. Store in airtight containers. Protect from light.

USP 36: (Pyridostigmine Bromide). A white or practically white, hygroscopic, crystalline powder, having an agreeable characteristic odour. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether; slightly soluble in petroleum spirit. Store in airtight containers.

Uses and Administration

Pyridostigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p. 687.2), but is slower in onset and of longer duration. It is given as the bromide.

Pyridostigmine is mainly used in the treatment of myasthenia gravis (p. 684.1) although its use in neonatal myasthenia has declined in favour of neostigmine. It has also been used in the treatment of paralytic ileus. Pyridostigmine is sometimes used to reverse the neuromuscular blockade produced by competitive neuromuscular blockers but is generally considered less satisfactory than neostigmine. It has also been used as prophylaxis against the neuromuscular effects of nerve gas poisoning (below). Pyridostigmine has been used in the management of postoperative urinary retention (p. 2349.2) but has generally been superseded by catheterisation.

For **myasthenia gravis**, UK licensed product information states that total daily oral doses may range from 300 mg to 1.2 g; however, the *BNF* states that daily doses of 450 mg should not be exceeded in order to avoid receptor downregulation. It also noted that patients receiving pyridostigmine in doses over 360 mg daily may need more aggressive therapy. In the USA, licensed doses are somewhat higher, ranging up to 1.5 g daily.

The dose should be divided throughout the day and, if necessary, the night, according to response; larger portions of the total daily dose may be given at times of greater fatigue.

Pyridostigmine has also been given as modified-release tablets, usually once or twice daily but these offer less flexibility of dosage. If necessary it has also been given by intramuscular injection or in severe cases by very slow intravenous injection. However, the intravenous route is hazardous and, if used, atropine must be available to counteract any severe muscarinic reactions. Parenteral doses are about one-thirtieth of the usual oral dose.

To **reverse neuromuscular blockade** produced by *competitive neuromuscular blockers*, doses of 100 to 250 micrograms/kg (about 10 to 20 mg) have been given intravenously, with or preceded by intravenous atropine sulfate 0.6 to 1.2 mg to counteract any muscarinic effects. Glycopyrronium bromide has been used as an alternative to atropine.

Pyridostigmine is also used for prophylaxis against the neuromuscular effects of nerve gas poisoning, including *soman*, in military combat use only; the recommended oral dose is 30 mg every 8 hours started at least several hours before exposure. If nerve gas poisoning occurs, pyridostigmine should be stopped and the patient should be treated with atropine and pralidoxime immediately.

In the treatment of paralytic **ileus** and postoperative **urinary retention** pyridostigmine bromide has been given in oral doses of 60 to 240 mg.

For details of doses in children, see below.

Administration in children. The use of pyridostigmine in children is similar to that in adults (see Uses and Administration, above).

UK licensed product information states that children may be given pyridostigmine, as the bromide, for the treatment of **myasthenia gravis** in an initial oral dose of 30 mg for those aged under 6 years or 60 mg for those aged 6 to 12 years, repeated throughout the day. This is increased gradually by increments of 15 to 30 mg daily until a satisfactory response is obtained, which is usually within the dosage range of 30 to 360 mg daily. Alternatively, the *BNFC* suggests that children aged 1 month to 12 years may be given an initial oral dose of 1 to 1.5 mg/kg daily, increased gradually to 7 mg/kg daily in 6 divided doses, to a usual total dose of 30 to 360 mg daily. Older children may be given the usual adult dose. In the USA, an oral dose of 7 mg/kg daily in 5 or 6 divided doses has also been suggested. Those patients who require parenteral therapy have been given an intramuscular or intravenous dose of 50 to 150 micrograms/kg (up to a maximum of 10 mg) every 4 to 6 hours.

In the treatment of neonatal myasthenia doses in the range of 50 to 150 micrograms/kg by intramuscular injection or 5 mg orally have been given every 4 to 6 hours. Alternatively, the *BNFC* recommends an oral dose based on neonatal weight: initially 1 to 1.5 mg/kg, increased gradually to a maximum of 10 mg, repeated throughout the day, and given 30 to 60 minutes before feeds. Treatment is rarely needed beyond 8 weeks of age.

For the treatment of paralytic **ileus** and postoperative **urinary retention**, children have been given oral doses of 15 to 60 mg.

Decreased gastrointestinal motility. Parasympathomimetics such as pyridostigmine enhance gastric contractions and increase intestinal motility; they have been used in conditions associated with decreased gastrointestinal motility (p. 1808.2).

Pyridostigmine, generally in doses of 60 mg up to 3 times daily, has been used to relieve severe constipation in patients with impaired intestinal motility due to Parkinson's disease.[1] It has also been tried in patients with constipation due to autonomic neuropathy;[2] however, results have been equivocal.

1. Sadjadpour K. Pyridostigmine bromide and constipation in Parkinson's disease. *JAMA* 1983; 249: 1148.
2. Bharucha AE, *et al.* Pilot study of pyridostigmine in constipated patients with autonomic neuropathy. *Clin Auton Res* 2008; 18: 194–202.

Growth hormone deficiency. Although the value of stimulated growth hormone secretion tests in children has been questioned (see Growth Retardation, p. 1921.3), pyridostigmine with somatorelin has been found to be a potent and reproducible test for distinguishing adults with severe growth hormone deficiency from normal subjects.[1] However, the combination is not effective in patients over 55 years of age,[2] and somatorelin with arginine is generally preferred where an alternative to the gold standard of the insulin-tolerance test is required.[1]

1. Ghigo E, *et al.* Diagnostic and therapeutic uses of growth hormone-releasing substances in adult and elderly subjects. *Baillieres Clin Endocrinol Metab* 1998; 12: 341–58.
2. Vierhapper H, *et al.* The use of the pyridostigmine growth hormone-releasing hormone stimulation test to detect growth hormone deficiency in patients with pituitary adenomas. *Metabolism* 2002; 51: 34–7.

Nerve gas poisoning. Pyridostigmine has been used prophylactically to protect soldiers in the event of an attack with nerve gas agents (p. 2568.3) that inhibit acetylcholinesterase.[1] Pyridostigmine binds reversibly to acetylcholinesterase and provides a protected store from which acetylcholinesterase is later released.[1-3] Prophylaxis with pyridostigmine greatly enhances the efficacy of treatment with atropine and pralidoxime against exposure to *soman* but it is not effective alone and may not be uniformly effective against other nerve agents.[1] Giving 30 mg of pyridostigmine every 8 hours provides the optimum level of protection[2] and, although adverse effects are common at this dosage, the performance of military duties is not impaired.[4] However, neurological symptoms in veterans suffering the so-called Gulf War Syndrome appear to be

more common in those who reported exposure to a range of potentially toxic substances which include pyridostigmine.[5] It has been suggested that these symptoms may be evidence of organophosphate-induced polyneuropathy resulting from exposure to a combination of organophosphorus compounds and other cholinesterase inhibitors such as pyridostigmine.[6] A study in *hens*[7] (a species susceptible to anticholinesterases) has also found symptoms of enhanced neurotoxicity when pyridostigmine, the insect repellent diethyltoluamide, and the pyrethroid insecticide permethrin were used together.

1. United States Army. *Medical management of chemical casualties handbook*. 3rd ed. Aberdeen, Maryland: Medical Research Institute of Chemical Defense;1999. Also available at: http://www.brooksidepress.org/Products/OperationalMedicine/DATA/operationalmed/Manuals/Red-Handbook/001TitlePage.htm (accessed 15/02/06)
2. Ministry of Defence. *Medical manual of defence against chemical agents*. London: HMSO, 1987. (JSP312).
3. Anonymous. Prevention and treatment of injury from chemical warfare agents. *Med Lett Drugs Ther* 2002; 44: 1–4.
4. Keeler JR, *et al*. Pyridostigmine used as a nerve agent pretreatment under wartime conditions. *JAMA* 1991; 266: 693–5.
5. The Iowa Persian Gulf Study Group. Self-reported illness and health status among gulf war veterans: a population-based study. *JAMA* 1997; 277: 238–45.
6. Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the gulf war: a cross-sectional epidemiologic study. *JAMA* 1997; 277: 231–7.
7. Abou-Donia MB, *et al*. Neurotoxicity resulting from coexposure to pyridosigmine bromide, DEET, and permethrin: implications of gulf war chemical exposure. *J Toxicol Environ Health* 1996; 48: 35–56.

Orthostatic hypotension. Pyridostigmine has been investigated in the treatment of orthostatic hypotension (p. 1634.3). A review[1] of 4 single-dose studies and a follow-up survey (involving a total of 106 patients and generally reporting an improvement in haemodynamic measurements) concluded that there was insufficient long-term data to support the routine use of pyridostigmine in the treatment of orthostatic hypotension.

1. Gales BJ, Gales MA. Pyridostigmine in the treatment of orthostatic intolerance. *Ann Pharmacother* 2007; 41: 314–18.

Post-poliomyelitis syndrome. Although pyridostigmine has been reported[1] in some patients to reduce fatigue associated with post-poliomyelitis syndrome, a systematic review failed to find any benefit.[2] Doses used[3] have included 30 mg daily increased gradually to about 60 mg three times daily but adverse effects are common.

1. Trojan DA, Cashman NR. Anticholinesterases in post-poliomyelitis syndrome. *Ann N Y Acad Sci* 1995; 753: 285–95.
2. Koopman FS, *et al*. Treatment for postpolio syndrome. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2011 (accessed 12/04/11).
3. Thorsteinsson G. Management of postpolio syndrome. *Mayo Clin Proc* 1997; 72: 627–38.

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2. It has been stated that muscarinic adverse effects occur less frequently with pyridostigmine treatment than with neostigmine.

Breast feeding. Pyridostigmine was present in the breast milk of 2 nursing mothers, receiving maintenance therapy for myasthenia gravis, in a concentration between 36 and 113% of that in maternal plasma,[1] but in both cases the dose ingested per kg body-weight by the nursing infant was 0.1% or less of that ingested by the mother. Maternal medication with pyridostigmine should be no obstacle to breast feeding, at least with doses in the range of 180 to 300 mg daily.

On the basis of this study, the last available guidance from the American Academy of Pediatrics considered[2] that pyridostigmine is usually compatible with breast feeding.

1. Hardell L-I, *et al*. Pyridostigmine in human breast milk. *Br J Clin Pharmacol* 1982; 14: 565–7.
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 15/02/06)

Effects on the joints. Several years after starting oral pyridostigmine bromide 60 mg five times daily, a middle-aged woman had episodes of bilateral arthralgia and hyperalgesia of her hips, knees, toes, and shoulders.[1] Symptoms resolved when pyridostigmine was stopped and rechallenge was positive on several occasions.

1. Rostedt A, Stålberg E. Joint pain and hyperalgesia due to pyridostigmine bromide in a patient with myasthenia gravis. *Neurology* 2004; 62: 835–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pyridostigmine 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 27/07/11)

Psychosis. Postoperative psychosis in a patient with myasthenia gravis who received large doses of pyridostigmine bromide was attributed to bromide intoxication,[1] but this diagnosis has been challenged.[2]

1. Rothenberg DM, *et al*. Bromide intoxication secondary to pyridostigmine bromide therapy. *JAMA* 1990; 263: 1121–2.
2. Senecal P-E, Osterloh J. Confusion from pyridostigmine bromide: was there bromide intoxication? *JAMA* 1990; 264: 454–5.

Renal impairment. During use of pyridostigmine for the reversal of neuromuscular blockade produced by competitive neuromuscular blockers, pyridostigmine kinetics were not significantly different after renal transplantation in 5 patients compared with those in 5 patients with normal renal function. However, in 4 anephric patients the elimination half-life was significantly increased and the plasma clearance significantly decreased.[1] It appeared that about 75% of the plasma clearance of pyridostigmine depended on renal function.

1. Cronnelly R, *et al*. Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther* 1980; 28: 78–81.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Pyridostigmine bromide is poorly absorbed from the gastrointestinal tract. It undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Pyridostigmine is excreted mainly in the urine as unchanged drug and metabolites. Pyridostigmine crosses the placenta and is distributed into breast milk (see Breast Feeding, above). Penetration into the CNS is poor.

It has been suggested[1] that data from pharmacokinetic studies of pyridostigmine might have varied because of the analytical methods used or inappropriate storage conditions of plasma samples; it was recommended that samples should be acidified and stored at -75 degrees. Mean terminal elimination half-life was 200 minutes in 11 healthy subjects given 60 mg of pyridostigmine orally; peak plasma concentrations were obtained 1 to 5 hours after dosing. The mean terminal elimination half-life after a 4-mg intravenous infusion in 10 of these subjects was 97 minutes.[1] Oral bioavailability was calculated to vary from 11.5 to 18.9%. In an earlier study food did not appear to affect bioavailability but did delay the time taken to achieve peak plasma concentrations.[2] It appears that 75% of the plasma clearance of pyridostigmine depends on renal function.[3] 3-Hydroxy-*N*-methylpyridinium has been identified as one of the 3 metabolites isolated from the urine of patients taking pyridostigmine.[4]

1. Breyer-Pfaff U, *et al*. Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis. *Clin Pharmacol Ther* 1985; 37: 495–501.
2. Aquilonius S-M, *et al*. Pharmacokinetics and oral bioavailability of pyridostigmine in man. *Eur J Clin Pharmacol* 1980; 18: 423–8.
3. Cronnelly R, *et al*. Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther* 1980; 28: 78–81.
4. Somani SM, *et al*. Pyridostigmine in man. *Clin Pharmacol Ther* 1972; 3: 393–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mestinon; Piridos†; *Austral.*: Mestinon; *Austria*: Mestinon; *Belg.*: Mestinon; *Bra.*: Mestinon; *Canad.*: Mestinon; *Chile*: Mestinon; *Cz.*: Mestinon; *Denm.*: Mestinon; *Fin.*: Mestinon; *Fr.*: Mestinon; *Ger.*: Kalimin; Mestinon; *Gr.*: Mestinon; *Hong Kong*: Mestinon; *Hung.*: Mestinon; *India*: Distinon; Gravitor; Mesilon; Mustone; Myestin; *Indon.*: Mestinon; *Irl.*: Mestinon; *Israel*: Mestinon; *Ital.*: Mestinon; *Malaysia*: Mestinon; *Mex.*: Mestinon; *Neth.*: Mestinon; *Norw.*: Mestinon; *NZ*: Mestinon; *Philipp.*: Astinon; Mestinon; Pyrinon; *Pol.*: Mestinon; *Port.*: Mestinon; *Rus.*: Kalimin (Калимин); *S.Afr.*: Mestinon†; *Singapore*: Mestinon; *Spain*: Mestinon; *Swed.*: Mestinon; *Switz.*: Mestinon; *Thai.*: Mestinon; Pyrimine; *Turk.*: Mestinon; *UK*: Mestinon; Nerve Agent Pre-Treatment Tablet Set L1A1; *USA*: Mestinon; *Venez.*: Mestinon.

Pharmacopoeial Preparations
BP 2014: Pyridostigmine Tablets;
USP 36: Pyridostigmine Bromide Injection; Pyridostigmine Bromide Syrup; Pyridostigmine Bromide Tablets.

Antineoplastics

Choice of Antineoplastic, p. 691
- Management of malignant disease, p. 691
  - Gestational trophoblastic tumours, p. 691
  - Histiocytic syndromes, p. 692
  - Leukaemias, acute, p. 692
    - Acute lymphoblastic leukaemia, p. 692
    - Acute myeloid leukaemias, p. 693
  - Leukaemias, chronic, p. 693
    - Chronic lymphocytic leukaemia, p. 693
    - Chronic myeloid leukaemia, p. 694
    - Hairy-cell leukaemia, p. 694
    - Myelodysplastic syndromes, p. 694
    - Myelofibrosis, p. 695
    - Polycythaemia vera, p. 695
    - Primary thrombocythaemia, p. 695
  - Lymphomas, p. 695
    - Hodgkin's disease, p. 696
    - Non-Hodgkin's lymphomas, p. 696
    - AIDS-related lymphomas, p. 697
    - Burkitt's lymphoma, p. 697
    - Primary CNS lymphoma, p. 698
    - MALT lymphoma, p. 698
    - Mantle cell lymphoma, p. 698
    - Mycosis fungoides, p. 698
    - Waldenström's macroglobulinaemia, p. 699
    - Plasma cell neoplasms, p. 699
    - Multiple myeloma, p. 699
  - Malignant effusions, p. 700
  - Malignant neoplasms of the bladder, p. 700
  - Malignant neoplasms of the bone, p. 700
  - Malignant neoplasms of the brain, p. 701
  - Malignant neoplasms of the breast, p. 702
    - Prophylaxis of breast cancer, p. 703
    - Malignant neoplasms of the male breast, p. 704
  - Malignant neoplasms of the cervix, p. 704
  - Malignant neoplasms of the endometrium, p. 704
  - Malignant neoplasms of the eye, p. 705
  - Malignant neoplasms of the gastrointestinal tract, p. 705
    - Malignant neoplasms of the oesophagus, p. 705
    - Malignant neoplasms of the stomach, p. 706
    - Malignant neoplasms of the colon and rectum, p. 706
    - Prophylaxis of cancer of the colon and rectum, p. 707
    - Malignant neoplasms of the anus, p. 708
  - Malignant neoplasms of the head and neck, p. 708
  - Malignant neoplasms of the kidney, p. 708
    - Wilms' tumour, p. 709
  - Malignant neoplasms of the liver, p. 709
  - Malignant neoplasms of the lung, p. 710
    - Small cell lung cancer, p. 710
    - Non-small cell lung cancer, p. 711
    - Malignant pleural mesothelioma, p. 711
  - Malignant neoplasms of the ovary, p. 711
  - Malignant neoplasms of the pancreas, p. 712
  - Malignant neoplasms of the prostate, p. 712
  - Malignant neoplasms of the skin, p. 714
    - Basal cell and squamous cell carcinoma, p. 714
    - Melanoma, p. 714
  - Malignant neoplasms of the testis, p. 715
  - Malignant neoplasms of the thymus, p. 715
  - Malignant neoplasms of the thyroid, p. 716
  - Neuroblastoma, p. 716
  - Neuroendocrine tumours, p. 716
  - Retinoblastoma, p. 717
  - Sarcomas, p. 717
    - Bone sarcoma, p. 717
    - Kaposi's sarcoma, p. 718
    - Soft-tissue sarcoma, p. 718

Adverse Effects, p. 726
Treatment of Adverse Effects, p. 730
Precautions, p. 732
Interactions, p. 733
Pharmacokinetics, p. 734
Action, p. 734
Resistance, p. 734
- Antiresistance agents, p. 734

Antineoplastic drugs are used in the treatment of malignant neoplasms
- as the primary treatment in responsive neoplasms
- when surgery or radiotherapy is not possible or has proved ineffective
- combined in different ways with surgery or radiotherapy such as concurrently, sequentially, neoadjuvant (preoperative), or adjuvant (postoperative)

Therapy with antineoplastics is notably successful in a few malignant conditions and may be used to palliate symptoms and prolong life in others.

Factors that are taken into account when prescribing chemotherapy include the type of cancer and its primary location, the general health of the patient (patient status), and the extent, or stage, of the disease. There are different staging systems; one commonly used system, the TNM staging system, describes the extent of solid cancers by numbers:
- T (tumour) refers to the size of the cancer: from 1 (small) to 4 (large)
- N (node) refers to whether the cancer has spread to the lymph nodes: from 0 (no positive nodes) to 3 (many positive nodes)
- M (metastases) refers to whether the cancer has metastasised: 0 (no metastases) or 1 (metastases)

Haematological cancers are classified differently and depend on the particular malignancy, but the extent of the disease is often described by the number and spread of affected lymph nodes and the symptoms of the patient.

The two main groups of classical cytotoxic drugs used in the treatment of malignant disease are the alkylating agents and the antimetabolites. Nitrogen mustards, ethyleneimine compounds, and alkyl sulfonates are the main **alkylating agents**. Other compounds with an alkylating action are the various nitrosoureas. Dacarbazine and the **platinum-containing complex** cisplatin appear to act similarly.

The **antimetabolites** may be subdivided into folic acid, purine, or pyrimidine antagonists.

Several natural products, or their derivatives, are used for their actions as **mitotic inhibitors**; they include the vinca alkaloids and the taxanes. Other drugs act as **topoisomerase inhibitors**, interfering with the coiling and uncoiling of DNA during replication. Drugs thought to act in this way include the podophyllotoxin derivatives such as etoposide, and camptothecin derivatives such as irinotecan and topotecan.

Some **antibiotics** such as the anthracyclines, bleomycin, and mitomycin C, also interfere with nucleic acids and are effective as antineoplastics.

Further described in this section are **other drugs** that act by various routes to affect the growth and proliferation of malignant cells. Better understanding of the biology of tumour cells has led to the development of new classes of these, including **tyrosine kinase inhibitors** such as imatinib and related drugs. Some neoplasms express receptors to endogenous sex hormones, and various **hormone antagonists**, including, notably, the **aromatase inhibitors** are used in their management. **Photosensitisers** such as porfimer sodium are used in photodynamic therapy.

In recent years considerable interest has focused on immunological approaches to the treatment of malignant disease and many **monoclonal antibodies** have been, or are being, developed. The use of **biological response modifiers** such as interleukins continues to be the subject of investigation and attempts to develop vaccines against individual neoplasms also continue.

Glucocorticoids (see Corticosteroids, p. 1597.3) are used with antineoplastics in the treatment of malignant disease, especially in acute leukaemias and lymphomas. Other agents used in antineoplastic therapy include sex hormones (p. 2231.1) and radiopharmaceuticals (p. 2222.1). Haematopoietic stem cell transplantation (p. 1937.1) is used for haematological malignancies.

Choice of Antineoplastic

The following section describes the treatment of some of the major malignant neoplasms, and in particular the role of combination chemotherapy with antineoplastics.

Table 1 (p. 719) lists published initial doses for some well-known combination chemotherapy regimens. Doses may be modified (particularly in subsequent cycles) to allow for patient status and toxic effects, although in some cases this may be at the expense of efficacy. Regimens can also vary slightly between institutions, or may be modified as part of the ongoing evolution of cancer chemotherapy; such therapy should preferably take place only in expert centres. The same acronym has sometimes been used for regimens containing different drugs, or using the same drugs in different doses or in different ways, and the reader should consult the literature for further details.

Management of malignant disease

Gestational trophoblastic tumours. The gestational trophoblastic diseases arise from the trophoblast, the first tissue to differentiate in the early embryo: they are associated with conception and pregnancy and affect women of reproductive age. They may be divided into premalignant forms such as molar pregnancy (complete or partial hydatidiform mole) and malignant forms (gestational trophoblastic tumours) which include invasive mole (chorioadenoma destruens), choriocarcinoma, and placental site trophoblastic tumour.[1-6] Hydatidiform moles are abnormal conceptions with excessive placental and some or no fetal development. Complete and partial hydatidiform moles have distinctive histological and genetic features, but both overexpress paternal genes.[1,2,7] Gestational trophoblastic neoplasia can develop after any type of pregnancy,[1,2,6] although the incidence is greater after premalignant complete or partial molar pregnancies;[3] the risk of malignancy after a complete or partial hydatidiform mole is about 15% and 0.5%, respectively.[3,5,7]

All these tumours secrete human chorionic gonadotrophin (hCG), and measurement of the urinary or serum concentrations is important in diagnosis of disease and monitoring of treatment.[1,4,5,7]

The trophoblastic tumours vary in aggressiveness but some, such as choriocarcinoma, are highly invasive; however, appropriate **treatment**, based on the perceived risk category, can result in an excellent prognosis. Prognostic factors for increased risk include high titres of hCG, liver or brain metastases, and failure of previous single-agent chemotherapy as well as greater age.[3-5,8] With current treatment, including local irradiation for metastases, virtually 100% of patients with localised disease should be cured, as are over 80% of patients with more advanced stages.

Prophylactic chemotherapy has been used in women considered at particular risk of persistent gestational trophoblastic tumour after evacuation of a complete molar pregnancy, but the practice is controversial, with anecdotal reports of fatalities; most consider the risk to be too high, especially given the low morbidity and mortality achieved with monitoring.[1,4]

In patients with ***low-risk disease***, the treatment of choice is single-agent therapy with methotrexate or dactinomycin.[1-3,5,6,9] The choice of regimen usually depends on geographical location and local experience,[9,10] as comparative data are lacking.[3] Intramuscular methotrexate is often given on alternate days, or weekly, with or without folinic acid rescue.[3-6,9,10] Several intravenous dactinomycin schedules have been used; there is some suggestion that a daily regimen may be more effective than pulsed treatment.[3,5] A systematic review that included 4 randomised studies concluded that pulsed dactinomycin was superior to weekly methotrexate.[10] However, while dactinomycin may provide slightly higher remission rates, toxicity may be greater,[4] and since methotrexate is easier to give some favour methotrexate with folinic acid as first-line treatment.[5] Alternating cycles or sequential use of both drugs have also been tried.[4,9]

Irrespective of which drug is used first-line, a switch to the alternate drug is considered appropriate in cases of resistance.[3,5] If this also fails, then combination chemotherapy is indicated; regimens are similar to those used in high-risk disease.[4]

The combination EMA-CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, and vincristine) is the preferred treatment in ***high-risk*** patients.[2-6,8,11] Methotrexate, dactinomycin, and etoposide is also used.[2,3,5] Triple therapy with methotrexate, dactinomycin, and either cyclophosphamide or chlorambucil was the standard regimen for many years in the USA,[1,4] but was associated with toxicity and poor survival.[2,4] However, comparative data are lacking, and the superiority of any individual combination regimen remains to be established.[1,4,8] In

refractory disease, the salvage regimen EMA-EP uses etoposide and cisplatin in place of cyclophosphamide and vincristine in EMA-CO.[3,5,11,12] Other regimens have used etoposide and cisplatin with either bleomycin (BEP) or ifosfamide (VIP).[3,11,12]

Brain *metastases* are generally treated by local irradiation, given with systemic chemotherapy. Modified EMA-CO, using a higher dose of systemic methotrexate and adding intrathecal methotrexate, is also used.[1,2,4,5,11] Liver metastases have been treated with irradiation, local chemoembolisation, or surgical resection.[2,4,11]

Patients with placental site trophoblastic tumour, which is relatively insensitive to chemotherapy, may be best treated by hysterectomy in the early stages.[2,5] In patients with metastatic or recurrent disease, EMA-EP may be more effective than EMA-CO.[13] For further information on these and other common chemotherapy regimens, see Table I, p. 719.

1. Soper JT, *et al.* American College of Obstetricians and Gynecologists. Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. *Gynecol Oncol* 2004; 93: 575–85.
2. El-Helw LM, Hancock BW. Treatment of metastatic gestational trophoblastic neoplasia. *Lancet Oncol* 2007; 8: 715–24.
3. Ngan S, Seckl MJ. Gestational trophoblastic neoplasia management: an update. *Curr Opin Oncol* 2007; 19: 486–91.
4. Soper JT. Gestational trophoblastic disease. *Obstet Gynecol* 2006; 108: 176–87.
5. Sarwar N, *et al.* Gestational trophoblastic neoplasia: the management of relapsing patients and other recent advances. *Curr Oncol Rep* 2004; 6: 476–82.
6. Royal College of Obstetricians and Gynaecologists. Guideline no. 38: the management of gestational trophoblastic disease (issued February 2010). Available at: http://www.rcog.org.uk/files/rcog-corp/GT38ManagementGestational0210.pdf (accessed 12/07/10)
7. Sebire NJ, Seckl MJ. Gestational trophoblastic disease: current management of hydatidiform mole. Abridged version: *BMJ* 2008; 337: a1193. Full version: http://www.bmj.com/cgi/content/full/337/aug15_1/a1193 (accessed 18/03/09) Correction. *ibid.*: a1473.
8. Deng L, *et al.* Combination chemotherapy for high-risk gestational trophoblastic tumour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 13/07/09).
9. Osborne R, Gerulath A. What is the best regimen for low-risk gestational trophoblastic neoplasia? A review. *J Reprod Med* 2004; 49: 602–16.
10. Alazzam M, *et al.* First line chemotherapy in low risk gestational trophoblastic neoplasia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 18/03/09).
11. Lurain JR. Advances in management of high-risk gestational trophoblastic tumors. *J Reprod Med* 2002; 47: 451–9.
12. Lurain JR, Nejad B. Secondary chemotherapy for high-risk gestational trophoblastic neoplasia. *Gynecol Oncol* 2005; 97: 618–23.
13. Behtash N, Karimi Zarchi M. Placental site trophoblastic tumor. *J Cancer Res Clin Oncol* 2008; 134: 1–6.

Histiocytic syndromes. Histiocytic syndromes cover a broad range of proliferative disorders of histiocytes (such as macrophages and dendritic cells).[1] Langerhans-cell histiocytosis is one such disorder characterised by proliferation of CD1a-positive Langerhans cells (a form of dendritic cell).[2] Terms that were formerly used for different clinical manifestations of Langerhans-cell histiocytosis include histiocytosis X, type II histiocytosis, eosinophilic granuloma, Hand-Schüller-Christian syndrome, and Letterer-Siwe disease, but these are considered obsolete.[3] Langerhans-cell histiocytosis mainly presents in childhood, and is of uncertain aetiology: it is not clear whether it should be considered a malignancy.[2,4,5]

The clinical presentation of Langerhans-cell histiocytosis is highly variable and can include bone pain, weight loss, fever, skin rash, dyspnoea or tachypnoea, polydipsia and polyuria, lymphadenopathy, gingival hypertrophy, ataxia, and memory problems.[2,5] Depending on the organs involved, it has been categorised into localised or single-system disease, and disseminated or multisystem disease.[1,4,5] Single-system disease can be further categorised based on the number of sites involved (unifocal or multifocal).[1] Multisystem disease may be further subdivided into low-risk and high-risk groups depending upon which organs are involved; risk organs include the haematopoietic system, lungs, liver, and spleen.[1,5,6] Sequelae to the disease include diabetes insipidus, growth retardation, cognitive dysfunction, and orthopaedic handicap.[1,2,4] The morbidity and prognosis depends upon the number of organ systems involved, and whether normal function of these organs is affected.[1] Patients with **single-system disease** have a generally benign course, and single lesions often regress spontaneously. However, if a bone lesion does not resolve, or risks causing fracture or deformity before it resolves, or is causing disabling symptoms, it may be treated with curettage, intralesional corticosteroids, or radiotherapy.[1,4,5] Systemic chemotherapy may be suitable in some patients with multifocal bone disease; vinblastine with prednisone or prednisolone is a suggested regimen,[2,4,6] and may also be used for high-risk single lesions.[6] Similarly, single skin lesions may be allowed to resolve without treatment or treated with surgery, topical corticosteroids, methoxsalen plus UV light (PUVA), or topical chlormethine.[1,4,5,7]

Treatment for **multisystem disease** is controversial. Some advocate high-dose prednisone or single-agent chemotherapy as first-line options. Combination chemotherapy regimens may give greater response rates with fewer recurrences.[1] Corticosteroids and vinblastine for about 6 to 12 months are the most commonly used drugs; mercaptopurine and methotrexate have also been used with reports of efficacy.[4] A comparative study in children with multisystem disease found treatment with vinblastine or etoposide for 6 months to be equally effective.[8] Subsequent study showed that vinblastine with etoposide was not superior to vinblastine alone (when combined with corticosteroids and mercaptopurine).[2,4,6] Systemic corticosteroids have also been used for recalcitrant skin disease or multisystem disease in children[7] and for pulmonary Langerhans-cell histiocytosis in adults.[9] In patients who have not responded to combination chemotherapy, a number of treatments may be considered including ciclosporin,[4,7] thalidomide,[7] and high-dose chemotherapy with haematopoietic stem cell transplantation.[2,4,5] Cladribine has been used for multisystem disease with varying results;[5,7] an intensive regimen of cladribine and high-dose cytarabine may be effective for recurrent or refractory disease.[2] Anti-CD1 monoclonal antibodies[1,5] may offer improved therapeutic or diagnostic options in the future.

1. Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. *Pediatr Dermatol* 2008; 25: 291–5.
2. Gasent Blesa JM, *et al.* Langerhans cell histiocytosis. *Clin Transl Oncol* 2008; 10: 688–96.
3. Favara BE, *et al.* Contemporary classification of histiocytic disorders. The WHO Committee on Histiocytic/Reticulum Cell Proliferations and Reclassification Working Group of the Histiocyte Society. *Med Pediatr Oncol* 1997; 29: 157–66.
4. Henter JI, *et al.* Histiocyte disorders. *Crit Rev Oncol Hematol* 2004; 50: 157–74.
5. Stockschlaeder M, Sucker C. Adult Langerhans cell histiocytosis. *Eur J Haematol* 2006; 76: 363–8.
6. Windebank K, Nanduri V. Langerhans cell histiocytosis. *Arch Dis Child* 2009; 94: 904–8.
7. Chu T. Langerhans cell histiocytosis. *Australas J Dermatol* 2001; 42: 237–42.
8. Gadner H, *et al.* A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001; 138: 728–34. Correction. *ibid.*; 139: 170.
9. Vassallo R, *et al.* Pulmonary Langerhans'-cell histiocytosis. *N Engl J Med* 2000; 342: 1969–78.

Leukaemias, acute. The acute leukaemias are malignancies affecting haematopoietic precursor cells. They are relatively rare (about 1 to 3 cases per 100 000 of population), and of uncertain cause in the majority of cases, although radiation, carcinogenic substances, or oncogenic retroviruses have been implicated in some types, and certain individuals appear to have a genetic predisposition to these diseases.

After the initiating event or events the progeny of the affected cell do not differentiate normally but proliferate in an uncontrolled fashion. The result is the accumulation in the blood and bone marrow of immature cell types (blasts) at the expense of normal functional blood cells.

The acute leukaemias may be broadly divided into **acute lymphoblastic leukaemia** (ALL), in which the neoplastic proliferation affects lymphoid cell lines, and the **acute myeloid leukaemias** (AML), variously known as acute myelogenous leukaemias or acute non-lymphoblastic leukaemias, which affect myeloid cell lines. These broad groups can be divided in various ways. ALL is subdivided by an immunophenotypic classification that distinguishes disease of B- and T-cell lineage; it was formerly divided morphologically into L1, L2, and L3 subtypes. For AML the French-American-British (FAB) classification has been widely used. This distinguishes, by lineage and estimated degree of differentiation:

- M0, undifferentiated AML
- M1, AML with minimal maturation
- M2, AML with maturation
- M3, acute promyelocytic leukaemia
- M4, acute myelomonocytic leukaemia
- M5, acute monocytic leukaemia
- M6, erythroid leukaemia
- M7, megakaryocytic leukaemia.

However, knowledge of the genotype, via cytogenetic or molecular analysis, is becoming increasingly important in the treatment of leukaemia. Consequently, a revised classification system has been proposed under the auspices of WHO, which uses a combination of morphology, immunophenotype, genetic, biological, and clinical features. In this classification,[1,2] AML is divided into 4 main groups:

- AML with recurrent cytogenic translocations
- AML with myelodysplasia-related features
- AML, therapy-related
- AML not otherwise specified.

The terms *de novo* and secondary AML are widely used but are without standardised definitions. It has been proposed that *de novo* AML should refer to AML in patients with no clinical history of myelodysplastic syndrome, myeloproliferative disorder, or exposure to potentially leukaemogenic agents; secondary AML should refer to patients with AML secondary to these disorders or proven leukaemogenic exposure.[3]

In the WHO classification of lymphoid neoplasms, the Revised European-American Lymphoma (REAL) classification has been adopted, in which acute lymphoblastic leukaemias and lymphoblastic lymphomas are considered to be a single disease with different presentations.[1]

Acute leukaemia usually presents with fatigue, anaemia, infection (due to granulocytopenia), and easy bruisability or bleeding (mainly due to thrombocytopenia). Onset is usually rapid with ALL, although AML may be preceded by myelodysplasia lasting months or years. Bone pain, and enlargement of liver, spleen and lymph nodes (due to infiltration of leukaemic cells may occur. Other organs may also be affected, and various metabolic disturbances, including hyperuricaemia, hyponatraemia, and hypokalaemia may be present.

If untreated the acute leukaemias are normally fatal, usually within months. However, these malignancies are among those in which medical treatment can make a substantial difference to life expectancy, and in some cases a permanent remission may be effected.

1. Harris NL, *et al.* World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting–Airlie House, Virginia, November 1997. *J Clin Oncol* 1999; 17: 3835–49.
2. Vardiman JW, *et al.* The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood* 2002; 100: 2292–2302. Also available at: http://bloodjournal.hematologylibrary.org/cgi/reprint/100/7/2292.pdf (accessed 06/08/09)
3. Cheson BD, *et al.* Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003; 21: 4642–9.

ACUTE LYMPHOBLASTIC LEUKAEMIA. Treatment of acute lymphoblastic leukaemia (ALL) is usually stratified according to risk, with the intensity of therapy tailored to the predicted risk of relapse. Factors associated with a poor prognosis or high risk include age (infant or age greater than 10 years), high white cell count at diagnosis, poor response to induction therapy, and some genetic abnormalities such as the Philadelphia chromosome.[1-5]

Standard chemotherapy treatment regimens for T-cell and precursor B-cell ALL generally consist of 2 to 3 years of therapy divided into several phases:

- **Remission induction**
  Induction regimens are typically based around a regimen that includes vincristine, a corticosteroid (dexamethasone, prednisolone, or prednisone), an anthracycline (doxorubicin or daunorubicin), with or without asparaginase or pegaspargase, and/or cyclophosphamide.
- **Consolidation (intensification)**
  Although the importance of this phase is rarely disputed, consensus is lacking on the best regimens and duration of treatment. Drugs used include high-dose cytarabine, high-dose methotrexate, mercaptopurine, vincristine, and other antineoplastics used in induction regimens; often 4- to 5-drug combinations are used. Re-induction can further improve outcomes.
- **Maintenance (continuation)**
  Maintenance therapy is generally given for some 2 to 3 years after remission. The standard combination of drugs consists of daily mercaptopurine and weekly methotrexate.

In order to clear leukaemic cells from harbour sites, **CNS-directed therapy** is given throughout the course of ALL treatment, and may include:

- intrathecal chemotherapy (methotrexate either alone or as part of triple therapy with cytarabine and corticosteroids)
- systemic chemotherapy (high-dose methotrexate)
- cranial irradiation (usually reserved for high-risk adult patients)

Targeted drug therapy may be used in patients with specific genetic abnormalities in addition to chemotherapy regimens and CNS prophylaxis. In patients with Philadelphia chromosome-positive ALL, the addition of a tyrosine kinase inhibitor, such as imatinib or dasatinib, to standard chemotherapy regimens has greatly enhanced remission-induction rates and duration of disease-free survival. In Philadelphia chromosome-negative disease that is CD20-positive, the monoclonal antibody rituximab can be included in the treatment regimen.

In **relapsed/refractory** Philadelphia chromosome-negative ALL, second-line therapy with an induction regimen not previously used, or salvage regimens containing clofarabine or cytarabine, alkylator combinations, or liposomal vincristine may be considered; nelarabine may be used in T-cell ALL. In Philadelphia chromosome-positive disease, targeted therapy with dasatinib, nilotinib, or ponatinib can be considered, with or without chemotherapy or a corticosteroid.

Allogeneic **haematopoietic stem cell transplantation** may be a treatment option in adults who are in remission after initial induction therapy, or for relapsed or refractory disease.

Treatments that are **under investigation** include novel monoclonal antibodies, the proteasome inhibitor bortezomib, and inhibitors of the mammalian target of rapamycin, such as sirolimus and temsirolimus.

References.
1. Stanulla M, Schrappe M. Treatment of childhood acute lymphoblastic leukemia. *Semin Hematol* 2009; 46: 52–63.
2. Gökbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. *Semin Hematol* 2009; 46: 64–75.
3. Carroll WL, Raetz EA. Clinical and laboratory biology of childhood acute lymphoblastic leukemia. *J Pediatr* 2012; 160: 10–18.
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: acute lymphoblastic leukemia (version 1.2013). Available at: http://www.nccn.org/professionals/physician_gls/pdf/all.pdf (accessed 27/03/13)
5. Inaba H, *et al.* Acute lymphoblastic leukaemia. *Lancet* 2013; 381: 1943–55.

ACUTE MYELOID LEUKAEMIAS. Treatment of acute myeloid leukaemias (AML) is problematic because normal stem-cell precursors are sensitive to the drugs used, and therapy aimed at myeloid leukaemic clones results in destruction of part of the normal stem-cell pool. Wherever possible, treatment of AML should be in the context of clinical studies.[1-3] Treatment consists of induction and consolidation chemotherapy. Candidates for haematopoietic stem cell transplantation should be identified as early as possible.[3]

Induction of remission is usually possible with intensive chemotherapy. Complete remission has been stated to be achievable in up to 80% of younger patients and about 50% of older patients (who form the majority of those with AML), but patients suffer severe neutropenia during induction and remission rate is to some extent dependent upon the standard of supportive care. Remission rates are lower in those with adverse prognostic factors such as poor performance status, AML secondary to myelodysplasia or antineoplastics, high white cell count, features of multidrug resistance, and unfavourable cytogenetics.[4,5] Established regimens are based on cytarabine with an anthracycline, usually daunorubicin.[1-4,6-9] Although idarubicin may be preferred to daunorubicin,[10] especially in younger adult patients,[8] in children it is no more effective but may be associated with more toxicity.[11,12] Mitoxantrone is another alternative to daunorubicin,[8,10] and there is little evidence[1,4,10,12] that one anthracycline is better than another for induction protocols. Addition of etoposide or tioguanine to induction protocols of cytarabine and daunorubicin appears to be equally effective in younger adults and children,[13,14] but in older patients an induction regimen which added tioguanine was found to be more effective than one with etoposide.[15]

As in acute lymphoblastic leukaemia (see p. 692.3) there is a trend towards the use of more intensive induction regimens.[6,14] Use of high-dose cytarabine compared with standard doses potentially improves survival in younger patients with favourable cytogenetics, but in the elderly neurotoxicity outweighs any benefit;[10] a combination of cytarabine with fludarabine may be an alternative in these patients.[5] Some guidelines include low-intensity (with subcutaneous cytarabine, azacitidine, or decitabine) or intermediate-intensity induction therapy (with clofarabine) as treatment options for patients older than 60 years.[8] The use of haematopoietic growth factors is controversial; some allow for their use as an optional adjunct to intensive chemotherapy,[3,8] while others recommend against their routine use in AML.[1]

Once remission is induced, consolidation or **postremission therapy** is essential in preventing relapse.[1,6,10] Options include further chemotherapy, or allogeneic or autologous bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1937.1).[1,3,7-9] There is no consensus on the best postremission therapy.[3,7,8] Some advocate the use of high-dose cytarabine in those with favourable or intermediate risk; others are candidates for allogeneic stem cell transplantation.[3,7,8] Non-myeloablative chemotherapy with allogeneic transplantation may be an alternative in older patients.[3,5,7-9,16]

Patients who relapse or who fail to achieve complete remission will require **salvage** therapy. Standard salvage regimens can include high-dose cytarabine or fludarabine plus cytarabine.[7,8] Allogeneic stem cell transplantation can also be used for salvage therapy or for those in second or subsequent remission.[3,7,8] Decitabine may be an alternative for elderly patients who are not candidates for standard remission induction chemotherapy.[17] Investigational therapy is also an option.[7,8] Gemtuzumab ozogamicin has been used in elderly patients,[1,9] but is now withdrawn from the US market. Low-dose **maintenance** chemotherapy (with cytarabine and tioguanine) may improve disease-free survival but not overall survival,[8] and prolonged maintenance therapy is generally considered unnecessary in patients with AML.[1,6,12,14] Where debility or other medical conditions make standard or investigational therapy impossible in the elderly, **palliative** treatment with oral hydroxycarbamide is often given; low-dose cytarabine may also be of benefit.[1,2,7-9] Good results have been reported with a combination of idarubicin and etoposide in elderly patients.[5]

Other experimental therapies under investigation for AML include clofarabine, azacitidine, and imatinib.[2,7-9,12,14] The ciclosporin analogue valspodar, an inhibitor of multidrug resistance, has been investigated, but was associated with excessive early mortality.[18]

Acute promyelocytic leukaemia (APL) is a subtype of AML accounting for 10% of AML cases in adults.[19] It is important to distinguish APL from other forms since appropriate treatment is curative in most patients.[10] Most patients with APL can achieve complete remission after treatment with tretinoin alone, but remission durations are short and most patients relapse.[20] *Induction* therapy with tretinoin and chemotherapy (an anthracycline and cytarabine) improved event-free survival compared with chemotherapy alone.[19,21] It was also shown that cytarabine could be omitted for most patients,[20,22] and standard induction for low- and intermediate risk disease consists of concomitant tretinoin and an anthracycline.[8,10,23] There are few data to suggest that one anthracycline is vastly superior to another.[20,23] The addition of cytarabine can still be considered for high-risk patients.[8]

Consolidation therapy is given after complete remission,[8,20,21] and is usually anthracycline-based. Again, although most studies have included cytarabine, its role has been questioned,[19,20,22] and standard consolidation consists of concomitant tretinoin and an anthracycline.[8] As with induction, cytarabine may be added for high-risk disease.[8,23] Arsenic trioxide has been successfully combined with tretinoin for induction and consolidation,[8,10] and this combination is an alternative for those who cannot tolerate anthracyclines.[8,23] Arsenic trioxide has also been used alone as first-line therapy, but such use tends to be restricted to patients for whom chemotherapy is contra-indicated.[21]

For those in molecular remission after consolidation therapy, *maintenance* therapy with up to 2 years of tretinoin, with or without continuous low-dose chemotherapy (mercaptopurine plus methotrexate), is recommended.[8,21,22] Maintenance therapy is particularly beneficial for those at high risk of recurrence, such as those with a high leucocyte count and older adults.[20,22] Arsenic trioxide is recommended for those who remain molecularly positive at the end of consolidation.[8,21] It is also the treatment of choice for patients who relapse,[8,19-23] particularly those treated with tretinoin within the previous year. Patients who then achieve a second remission may be considered for autologous or allogeneic haematopoietic stem cell transplantation.[8,19,20,22,24] Gemtuzumab ozogamicin may also be an option for relapsed patients, although its precise role has not been determined,[21,24] and it should be used with caution in potential transplant candidates.[8] The synthetic retinoid, tamibarotene (AM-80), has been used to induce remission in patients who relapsed after successful remission induction with tretinoin.[25]

The efficacy of tretinoin appears to be achievable only because the characteristic chromosomal abnormalities in APL result in an abnormal retinoic acid receptor. The development of drugs that can effect differentiation in other forms of AML, and indeed in other neoplasms, seems likely to be a long and difficult task.

1. Milligan DW, *et al.* British Committee for Standards in Haematology. Guidelines on the management of acute myeloid leukaemia in adults. *Br J Haematol* 2006; 135: 450–74. Also available at: http://www.bcshguidelines.com/pdf/bjh_6314.pdf (accessed 07/08/09)
2. Estey E. Acute myeloid leukemia and myelodysplastic syndromes in older patients. *J Clin Oncol* 2007; 25: 1908–15.
3. Fey MF, Dreyling M. ESMO Guidelines Working Group. Acute myeloblastic leukaemias and myelodysplastic syndromes in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v158–v161. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v158.full.pdf+html (accessed 11/10/10)
4. Tallman MS. Therapy of acute myeloid leukemia. *Cancer Control* 2001; 8: 62–78.
5. Jackson GH, Taylor PRA. Acute myeloid leukaemia: optimising treatment in elderly patients. *Drugs Aging* 2002; 19: 571–81.
6. Arceci RJ. Progress and controversies in the treatment of pediatric acute myelogenous leukemia. *Curr Opin Hematol* 2002; 9: 353–60.
7. Estey E, Döhner H. Acute myeloid leukaemia. *Lancet* 2006; 368: 1894–1907.
8. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: acute myeloid leukaemia (version 3.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf (accessed 13/07/10)
9. Craig CM, Schiller GJ. Acute myeloid leukemia in the elderly: conventional and novel treatment approaches. *Blood Rev* 2008; 22: 221–34.
10. Jabbour EJ, *et al.* Adult acute myeloid leukemia. *Mayo Clin Proc* 2006; 81: 247–60.
11. O'Brien TA, *et al.* Results of consecutive trials for children newly diagnosed with acute myeloid leukemia from the Australian and New Zealand Children's Cancer Study Group. *Blood* 2002; 100: 2708–16.
12. Rubnitz JE, *et al.* Acute myeloid leukemia. *Pediatr Clin North Am* 2008; 55: 21–51.
13. Hann IM, *et al.* Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia: results of the Medical Research Council's 10th AML trial (MRC AML10). *Blood* 1997; 89: 2311–18.
14. Loeb DM, Arceci RJ. What is the optimal therapy for childhood AML? *Oncology (Huntingt)* 2002; 16: 1057–66.
15. Goldstone AH, *et al.* Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. *Blood* 2001; 98: 1302–11.
16. Stone RM. The difficult problem of acute myeloid leukemia in the older adult. *CA Cancer J Clin* 2002; 52: 363–71.
17. Ganetsky A. The role of decitabine for the treatment of acute myeloid leukemia. *Ann Pharmacother* 2012; 46: 1511–17.
18. Baer MR, *et al.* Phase 3 study of the multidrug resistance modulator PSC-833 in previously untreated patients 60 years of age and older with acute myeloid leukemia: Cancer and Leukemia Group B Study 9720. *Blood* 2002; 100: 1224–32.
19. Jurcic JG, *et al.* Diagnosis and treatment of acute promyelocytic leukemia. *Curr Oncol Rep* 2007; 9: 337–44.
20. Tallman MS, *et al.* Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood* 2002; 99: 759–67.
21. Sanz MA. Treatment of acute promyelocytic leukemia. *Hematology (Am Soc Hematol Educ Program)* 2006; 147–55.
22. Tallman MS, Nabhan C. Management of acute promyelocytic leukemia. *Curr Oncol Rep* 2002; 4: 381–9.
23. Sanz MA, *et al.* Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2009; 113: 1875–91.
24. Mantadakis E, *et al.* A comprehensive review of acute promyelocytic leukemia in children. *Acta Haematol (Basel)* 2008; 119: 73–82.
25. Tobita T, *et al.* Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. *Blood* 1997; 90: 967–73.

Leukaemias, chronic. The chronic leukaemias may be broadly divided into those in which the neoplastic proliferation affects lymphoid cell lines, and those affecting the myeloid cell lines.

Chronic leukaemias affecting the *lymphoid cell lines* include chronic lymphocytic leukaemia (CLL), which is B-cell in about 95% of cases and T-cell in about 5%, and hairy-cell leukaemia, which affects B-cells. The revised European-American lymphoma classification,[1] and a proposed WHO classification of haematologic malignancies,[2] consider lymphoid leukaemias and lymphomas of the same cell type to be one disease with different clinical presentations. Thus B-cell CLL is the same disease as B-cell small lymphocytic lymphoma.

Chronic neoplasms affecting the *myeloid cell lines* include the myeloproliferative disorders chronic myeloid leukaemia (CML), polycythaemia vera, and primary (essential) thrombocythaemia, and the myelodysplastic syndromes. All of these may undergo transformation to acute myeloid leukaemia.

1. Harris NL, *et al.* A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; 84: 1361–92. Also available at: http://bloodjournal.hematologylibrary.org/cgi/reprint/84/5/1361.pdf (accessed 07/08/09)
2. Harris NL, *et al.* World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting–Airlie House, Virginia, November 1997. *J Clin Oncol* 1999; 17: 3835–49.

CHRONIC LYMPHOCYTIC LEUKAEMIA. Chronic lymphocytic leukaemia (CLL) typically occurs in people over 60 years of age, and accounts for about 30% of leukaemias in the West although it is rarer in the Far East. CLL and small lymphocytic lymphoma (SLL) have been described as the same disease manifesting in different ways.[1] Stages of CLL are defined according to the American Rai system or the European Binet system, with both having prognostic value.[1-8] The clinical course is variable: low-risk patients (Rai stage 0; Binet stage A) have a median survival of about 10 years, while high-risk patients (Rai stage III/IV; Binet stage C) have a median survival of about 1.5 years; median survival in the intermediate stages is about 6 years.[2,3,9] The mutational status of the immunoglobulin IGHV gene also affects prognosis; attempts to use surrogate markers of this status included CD38 and ZAP-70, and these have assisted in further risk stratification.[7,10-13]

In patients at low risk and those at intermediate risk with indolent disease cytotoxic chemotherapy is usually deferred until signs and symptoms of disease progression occur.[2,3,5-10,13] In these patient groups, studies of immediate versus deferred chemotherapy for early-stage CLL have shown no significant advantage, or disadvantage, for immediate chemotherapy in terms of 10-year survival.[14] Patients with high-risk or progressive disease are usually treated with immediate chemotherapy.

When **treatment** is required, several options exist. For many years, chlorambucil, given either continuously or intermittently, and with or without prednisone, was the mainstay of chemotherapy for CLL, with response rates ranging from about 40 to 70%.[10,12,15] Alkylator-based combination regimens such as COP or CVP (cyclophosphamide, vincristine, and prednisone or prednisolone), CAP (cyclophosphamide, doxorubicin, and prednisone or prednisolone), or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) were found to have no advantage over chlorambucil alone.[4,6,15]

Subsequent study with fludarabine found response rates to be higher than with alkylator-based therapy, although no overall survival advantage was shown.[6-8,10-12,15] Fludarabine has been studied in combination with other agents. Use with chlorambucil showed excessive toxicity.[1,7,15] Fludarabine plus cyclophosphamide was found to have higher remission rates and longer progression-free survival than either chlorambucil or fludarabine monotherapy,[8,11,13,15] and as such this combination is often recommended as the initial treatment of choice,[10] especially in fitter patients. Chlorambucil or fludarabine monotherapy are still considered appropriate first-line options[1,9,12,13] in those with comorbidities or poorer performance status, and CVP

or CHOP regimens are still alternatives for those unable to tolerate fludarabine-based therapy.[1]

Bendamustine, an alkylating agent, produced better response rates and progression-free survival compared with chlorambucil, and is approved in some countries as initial monotherapy; efficacy compared with other first-line therapies has not been established.[1] Other purine analogues have been investigated for CLL. Cladribine, with or without corticosteroids, achieved comparable results to those with fludarabine monotherapy.[11] Cladribine plus cyclophosphamide was found to have similar results to cladribine alone.[11] However, some do not recommend cladribine as a routine alternative to fludarabine for initial therapy.[6]

The monoclonal antibodies alemtuzumab and rituximab have been studied with other drugs for the treatment of CLL.[5,6,10,11,16] The use of rituximab with fludarabine (FR regimen) especially has shown marked clinical efficacy,[7,10,12,15] and the FCR regimen (fludarabine, cyclophosphamide, and rituximab) has shown high overall response rates;[1,11,17] some consider FCR to be a suitable first-line option.[1,9,12,13] However, others have stated that the use of rituximab with fludarabine (with or without cyclophosphamide) requires further evaluation.[6] The use of the purine analogue pentostatin with cyclophosphamide and rituximab (PCR regimen) has also been shown to have high response rates and is also an option for initial therapy for CLL.[1,8,9,12,13] Although some consider rituximab monotherapy to be suitable initial therapy for older patients or for those with comorbidities,[1,12] others do not recommend it for untreated CLL.[6] Similarly, alemtuzumab may be used as first-line therapy in patients with certain cytogenetic abnormalities associated with a poor prognosis,[1,7,10] or as consolidation therapy after fludarabine-based induction therapy.[10,11,17] However, some do not recommend alemtuzumab for untreated CLL[6] and others advise against its use in the consolidative setting given the risks of infectious complications and possible CMV reactivation.[15]

There is no definitive evidence that consolidation or maintenance therapy is better than treatment at the time of relapse, although investigation is ongoing and participation in clinical studies is encouraged.[8] Treatment of relapses depends upon response to initial therapy.[6,7,11] After long remissions, patients will usually respond again to induction treatment.[7,9] Alternative agents, or combination chemotherapy with or without monoclonal antibodies may then be tried.[1,7,9,11] Monoclonal antibody monotherapy is an option,[1,9] especially in patients refractory to chemotherapy; alemtuzumab, ofatumumab, or dose-dense rituximab may be used. Alemtuzumab with rituximab is also an option.[1] For further information on common chemotherapy regimens, see Table 1, p. 719.

Haematopoietic stem cell transplantation (HSCT) has been investigated for CLL.[7] Autologous HSCT is unlikely to provide a cure[11,13,15] and relapse is inevitable.[10] The principles of allogeneic HSCT, which is potentially curative,[6,13] include the graft-versus-leukaemia effect and the absence of stem cell contamination.[11] However, transplant-related mortality has been high. Non-myeloablative conditioning protocols are under investigation.[6,7,10,11,15] Allogeneic HSCT is suggested for younger patients with non-response or early relapse after purine analogues, or those who relapse within 2 years of an initial response with purine-analogue based therapy or autologous HSCT, or in patients with certain cytogenetic abnormalities with a poor prognosis.[10]

Other drugs that have been investigated for CLL include bortezomib,[10] denileukin diftitox,[10] lenalidomide,[7,10,18] lumiliximab,[7,10] oblimersen sodium,[10] and thalidomide.[18]

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-Hodgkin's lymphomas (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf (accessed 26/05/10)
2. Hamblin TJ. Achieving optimal outcomes in chronic lymphocytic leukaemia. *Drugs* 2001; 61: 593–611.
3. Schriever F, Huhn D. New directions in the diagnosis and treatment of chronic lymphocytic leukaemia. *Drugs* 2003; 63: 953–69.
4. Andritsos L, Khoury H. Chronic lymphocytic leukemia. *Curr Treat Options Oncol* 2002; 3: 225–31.
5. Shanafelt TD, Call TG. Current approach to diagnosis and management of chronic lymphocytic leukemia. *Mayo Clin Proc* 2004; 79: 388–98.
6. British Society of Haematology. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. *Br J Haematol* 2004; 125: 294–317. Also available at: http://www.bcshguidelines.com/pdf/chronicLL_050504.pdf (accessed 15/05/09)
7. Dighiero G, Hamblin TJ. Chronic lymphocytic leukaemia. *Lancet* 2008; 371: 1017–29.
8. Nabhan C, *et al.* Controversies in the front-line management of chronic lymphocytic leukemia. *Leuk Res* 2008; 32: 679–88.
9. Eichhorst B, *et al.* ESMO Guidelines Working Group. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v162–v164. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v162.full.pdf+html (accessed 11/10/10)
10. Auer RL, *et al.* Emerging therapy for chronic lymphocytic leukaemia. *Br J Haematol* 2007; 139: 635–44.
11. Yee KWL, O'Brien SM. Chronic lymphocytic leukemia: diagnosis and treatment. *Mayo Clin Proc* 2006; 81: 1105–29.
12. Shanafelt TD, *et al.* Narrative review: initial management of newly diagnosed, early-stage chronic lymphocytic leukemia. *Ann Intern Med* 2006; 145: 435–47.
13. Zent CS, Kay NE. Chronic lymphocytic leukemia: biology and current treatment. *Curr Oncol Rep* 2007; 9: 345–52.
14. CLL Trialists' Collaborative Group. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. *J Natl Cancer Inst* 1999; 91: 861–8.
15. Kasamon YL, Flinn IW. Management of symptomatic, untreated chronic lymphocytic leukemia. *Blood Rev* 2007; 21: 143–56.
16. Mavromatis B, Cheson BD. Monoclonal antibody therapy of chronic lymphocytic leukemia. *J Clin Oncol* 2003; 21: 1874–81.
17. Wierda WG, *et al.* Novel immune-based treatment strategies for chronic lymphocytic leukemia. *J Clin Oncol* 2005; 23: 6325–32.
18. Chanan-Khan A, Porter CW. Immunomodulating drugs for chronic lymphocytic leukaemia. *Lancet Oncol* 2006; 7: 480–8.

CHRONIC MYELOID LEUKAEMIA. Chronic myeloid (myelogenous) or chronic granulocytic leukaemia (CML) is a rare disease, occurring usually in older patients, and representing about 15% of all adult leukaemias. It is associated in over 90% of cases with the presence in blood cells of an abnormal chromosome, the Philadelphia chromosome (Ph), which results from a reciprocal translocation between the long arms of chromosomes 9 and 22, with the fusion of the BCR gene and the ABL gene. The product of this gene, the protein BCR-ABL, is leukaemogenic. Ph-negative disease (atypical CML) carries a worse prognosis, and some classification systems consider it to be a separate disease.

CML occurs in 3 different phases. It is usually diagnosed in the chronic phase, which may last for several years, which when untreated, progresses to an advanced phase; this consists of an often rapidly fatal blastic phase (blast crisis), which is often preceded by a transition period, the accelerated phase.

The development of imatinib, an inhibitor of the BCR-ABL protein tyrosine kinase, constituted a revolutionary change in the management of CML.[1-7] The International Randomized Study of Interferon and STI571 (IRIS), found imatinib to be better than interferon alfa with low-dose cytarabine for newly diagnosed CML in **chronic phase.**[8,9] Follow-up study found responses to be durable in a high proportion of patients,[10] and a tyrosine kinase inhibitor such as imatinib has become established as standard initial therapy for chronic phase CML.[1,5,11] Since relapse is common after stopping imatinib, therapy should be continued indefinitely in responsive patients.[1,5,7] Resistance may also be a problem.[2-6,12-15] For patients who do not respond to first-line therapy or who relapse, the preferred second-line treatment is an alternative tyrosine kinase inhibitor such as dasatinib, nilotinib, bosutinib, or ponatinib. Omacetaxine mepesuccinate, allogeneic haematopoietic stem cell transplantation (HSCT), or investigational therapies (see below) are further options in patients who are resistant to or have failed treatment with tyrosine kinase inhibitors. These therapies or an alfa interferon such as peginterferon alfa may also be tried in patients who are unable to tolerate tyrosine kinase inhibitors.For patients who only partially respond or who relapse after first-line imatinib and who are not able to take an alternative tyrosine kinase inhibitor or omacetaxine mepesuccinate, high-dose imatinib may be considered.[1]

Early allogeneic HSCT (p. 1937.1) has the potential to cure CML due to a graft-versus-leukaemia effect, but it is still associated with appreciable morbidity and mortality, including graft-versus-host disease,[6] and results with imatinib have challenged the role of HSCT as first-line therapy for chronic phase CML.[1,11] While HSCT is still an option in suitable patients such as younger patients with HLA-identical sibling donors,[4,7] or those with high-risk disease and low transplantation risk,[2] most recommend an initial period of therapy with imatinib since the response can either reinforce or weaken the indication for HSCT.[5-7,16] Ongoing advances in alternative donor sources (such as the use of HLA-matched unrelated donors and cord blood), improved HLA typing techniques, and less toxic non-myeloablative regimens are broadening the use of HSCT.[1,4] Options in patients who relapse after HSCT include the use of donor lymphocyte infusions, tyrosine kinase inhibitors, or interferon alfa.[1,2,7]

Tyrosine kinase inhibitors induce favourable response rates in those with **advanced phase** CML. In those whose disease has progressed after initial tyrosine kinase inhibitor therapy, an alternative tyrosine kinase inhibitor is used, and then allogeneic HSCT can be considered. Post-transplant tyrosine kinase treatment is continued for at least 1 year. Omacetaxine mepesuccinate is an option for patients whose disease has progressed to advanced phase due to resistance and/or intolerance to 2 or more tyrosine kinase inhibitors. For those whose disease has progressed to blast-phase, treatment includes a tyrosine kinase inhibitor, either alone or with chemotherapy, followed by allogeneic HSCT.[1]

Novel therapies for CML include farnesyl transferase inhibitors such as lonafarnib and tipifarnib, hypomethylating agents such as azacitidine and decitabine, histone deacetylase inhibitors, and vaccines.[4,15,17] Combinations of imatinib with other drugs are also under investigation.[2]

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: chronic myelogenous leukemia (version 4.2013). Available at: http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf (accessed 13/03/13)
2. Hehlmann R, *et al.* European LeukemiaNet. Chronic myeloid leukaemia. *Lancet* 2007; 370: 342–50.
3. Kantarjian HM, *et al.* New insights into the pathophysiology of chronic myeloid leukemia and imatinib resistance. *Ann Intern Med* 2006; 145: 913–23.
4. Quintás-Cardama A, Cortes JE. Chronic myeloid leukemia: diagnosis and treatment. *Mayo Clin Proc* 2006; 81: 973–88.
5. Baccarani M, *et al.* European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol* 2009; 27: 6041–51.
6. Goldman JM, Melo JV. Chronic myeloid leukemia—advances in biology and new approaches to treatment. *N Engl J Med* 2003; 349: 1451–64.
7. Goldman JM. How I treat chronic myeloid leukemia in the imatinib era. *Blood* 2007; 110: 2828–37.
8. O'Brien SG, *et al.* Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003; 348: 994–1004.
9. Hughes TP, *et al.* Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2003; 349: 1423–32.
10. Druker BJ, *et al.* IRIS Investigators. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006; 355: 2408–17.
11. Baccarani M, Dreyling M. ESMO Guidelines Working Group. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v165–v167. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v165.full.pdf+html (accessed 11/10/10)
12. Marshall HM, Hammond JM. Treatment options in imatinib-resistant chronic myelogenous leukemia. *Ann Pharmacother* 2008; 42: 259–64.
13. Paterson SC, *et al.* Is there a cloud in the silver lining for imatinib? *Br J Cancer* 2003; 88: 983–7.
14. Gambacorti-Passerini CB, *et al.* Molecular mechanisms of resistance to imatinib in Philadelphia-chromosome-positive leukaemias. *Lancet Oncol* 2003; 4: 75–85.
15. Cortes J, Kantarjian H. New targeted approaches in chronic myeloid leukemia. *J Clin Oncol* 2005; 23: 6316–24. Correction. *ibid.*; 9034.
16. Schiffer CA. BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia. *N Engl J Med* 2007; 357: 258–65.
17. Jabbour E, *et al.* Suboptimal response to or failure of imatinib treatment for chronic myeloid leukemia: what is the optimal strategy? *Mayo Clin Proc* 2009; 84: 161–9.

HAIRY-CELL LEUKAEMIA. Hairy-cell leukaemia is a rare, chronic, B-cell lymphoproliferative disorder marked by the presence of white blood cells with prominent cytoplasmic villi, pancytopenia, and splenomegaly. Many patients are asymptomatic and there is no clear advantage to early treatment before symptoms appear.[1,2] Splenectomy was formerly used as initial therapy, but response duration tended to be short. Interferon alfa-2a or -2b given for one year produced at least a partial response in most cases but patients had a tendency to relapse once therapy was stopped.[1,3,4]

Better results were obtained with the purine analogues cladribine and pentostatin, and these are now considered first-line treatments for this disease.[1,3-8] Durable complete remission rates of 50% or more are seen after relatively short courses of therapy.[3,4,7-10] Toxicity is generally acceptable.[3] These drugs do not appear to show cross-resistance; cladribine has been used successfully in patients resistant to, or intolerant of, pentostatin,[1,3] and others[6] have used pentostatin in patients who do not respond to cladribine. Despite long disease-free survival rates associated with purine analogue therapy, they are not curative, and relapses occur in many patients, which suggests the presence of residual disease.[7,10] For patients who relapse, retreatment with initial therapy is advocated.[1,7] Interferon alfa is an option in those patients relapsing after, or refractory to, treatment with a purine analogue.[1,4] There are reports of remission after use of rituximab in patients with relapsed or refractory disease,[1,3,4,7,8,10,11] or for residual disease,[10] and it has been suggested for use in those who fail cladribine and pentostatin.[6,7] Other immunotherapy under investigation for hairy-cell leukaemia includes alemtuzumab, and the recombinant immunotoxins LMB-2 and BL22.[4,7,8,10]

1. Mey U, *et al.* Advances in the treatment of hairy-cell leukaemia. *Lancet Oncol* 2003; 4: 86–94.
2. Goodman GR, *et al.* Hairy cell leukemia: an update. *Curr Opin Hematol* 2003; 10: 258–66.
3. Savoie L, Johnston JB. Hairy cell leukemia. *Curr Treat Options Oncol* 2000; 2: 217–24.
4. Riccioni R, *et al.* Hairy cell leukemia. *Curr Treat Options Oncol* 2007; 8: 129–34.
5. Ravandi F, O'Brien S. Chronic lymphoid leukemias other than chronic lymphocytic leukemia: diagnosis and treatment. *Mayo Clin Proc* 2005; 80: 1660–74.
6. Golomb HM. Hairy cell leukemia: treatment successes in the past 2 years. *J Clin Oncol* 2008; 26: 2607–9.
7. Gidron A, Tallman MS. Hairy cell leukemia: towards a curative strategy. *Hematol Oncol Clin North Am* 2006; 20: 1153–62.
8. Dearden C, Else M. Hairy cell leukemia. *Curr Oncol Rep* 2006; 8: 337–43.
9. Goodman GR, *et al.* Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. *J Clin Oncol* 2003; 21: 891–6
10. Grever MR. How I treat hairy cell leukemia. *Blood* 2010; 115: 21–8.
11. Thomas DA, *et al.* Rituximab in relapsed or refractory hairy cell leukemia. *Blood* 2003; 102: 3906–11.

MYELODYSPLASTIC SYNDROMES. Myelodysplastic syndromes are low-grade neoplasms of haematopoietic stem cells characterised by ineffective haematopoiesis that results in anaemia, neutropenia, or thrombocytopenia in various combinations. They have been described as smouldering leukaemia or preleukaemia, and transformation to acute myeloid leukaemia (AML) occurs in some patients.

The clinical course of myelodysplastic syndromes is variable, and a precise individual determination of prognostic score is important in planning **treatment.**[1,2] In the few younger patients with suitable HLA-matched

donors, allogeneic haematopoietic stem cell transplantation (HSCT) has curative potential.[1,3-8] As most patients are older, with medical conditions precluding the use of standard conditioning regimens, novel transplant conditioning regimens of reduced intensity are being investigated.[5,7-9] Autologous HSCT may be an option for those without a suitable donor.[7]

Patients who are likely to have an ***indolent*** course are best treated conservatively with observation and supportive care (transfusions, antibacterials, or epoetins plus colony-stimulating factors).[1-4,7-9] Iron chelation therapy may be needed in patients who develop iron overload (p. 1545.2) from blood transfusions.[2,7,9] Azacitidine, decitabine, or lenalidomide may be considered where a low serum-erythropoietin concentration does not respond to epoetins (with or without colony-stimulating factors). Lenalidomide is effective for patients with chromosome 5q deletions,[6,8,10-13] and is recommended as first-line therapy in these patients.[2,9] Patients with serum-erythropoietin above 500 milliunits/mL and a good probability of response to immunosuppressive therapy should be given antilymphocyte immunoglobulins with or without ciclosporin, or possibly ciclosporin alone.[2,9] Those likely to have a poor response to immunosuppressants should be given treatment with azacitidine, decitabine, lenalidomide, investigational agents, or considered for allogeneic HSCT.[2] Azacitidine or decitabine are also treatment options for patients with serious cytopenias; if not responsive, immunosuppressive therapy, investigational agents, or allogeneic HSCT can be tried.[2]

The treatment of ***progressive*** or advanced myelodysplastic syndromes or those that have transformed to AML may involve intensive chemotherapy similar to that for AML (see p. 693.1), but remission rates are lower,[1,3,4] and relapse common.[9] However, many patients are elderly with poor performance status, and are unable to tolerate intensive chemotherapy. They may be treated with supportive care and haematopoietic growth factors alone.[9] Low-intensity chemotherapy such as azacitidine or decitabine may be tried in such patients,[2] but has had limited success.[1,3] Other antineoplastics and immunomodulating agents investigated for use in myelodysplastic syndromes include histone deacetylase inhibitors such as valproic acid and vorinostat, farnesyl transferase inhibitors, amifostine, arsenic trioxide, thalidomide, and topotecan.[1,3-5,7,9,14,15] Attempts to induce cellular differentiation have generally been disappointing.[3]

1. Paquette RL. Diagnosis and management of aplastic anemia and myelodysplastic syndrome. *Oncology (Huntingt)* 2002; **16** (suppl): 153–61.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: myelodysplastic syndromes (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf (accessed 10/06/10)
3. Steensma DP, Tefferi A. The myelodysplastic syndrome(s): a perspective and review highlighting current controversies. *Leuk Res* 2003; **27**: 95–120.
4. List AF. New approaches to the treatment of myelodysplasia. *Oncologist* 2002; **7** (suppl 1): 39–49.
5. Mufti G, *et al.* Myelodysplastic syndrome. *Hematology (Am Soc Hematol Educ Program)* 2003; 176–99.
6. Koppel A, Schiller G. Myelodysplastic syndrome: an update on diagnosis and therapy. *Curr Oncol Rep* 2008; **10**: 372–8.
7. Santini V, *et al.* Treatment options in myelodysplastic syndromes: a new frontier. *J Chemother* 2008; **20**: 291–6.
8. Stone RM. How I treat patients with myelodysplastic syndromes. *Blood* 2009; **113**: 6296–6303.
9. Steensma DP, Bennett JM. The myelodysplastic syndromes: diagnosis and treatment. *Mayo Clin Proc* 2006; **81**: 104–30.
10. List A, *et al.* Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med* 2005; **352**: 549–57.
11. Nimer SD. Clinical management of myelodysplastic syndromes with interstitial deletion of chromosome 5q. *J Clin Oncol* 2006; **24**: 2576–82.
12. List A, *et al.* Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 2006; **355**: 1456–65.
13. Nimer SD. Myelodysplastic syndromes. *Blood* 2008; **111**: 4841–51.
14. Zorat F, Pozzato G. Thalidomide in myelodysplastic syndromes. *Biomed Pharmacother* 2002; **56**: 20–30.
15. Gore SD, Hermes-DeSantis ER. Future directions in myelodysplastic syndrome: newer agents and the role of combination approaches. *Cancer Control* 2008; **15** (suppl): 40–9.

MYELOFIBROSIS. Myelofibrosis is a chronic Philadelphia-negative myeloproliferative disorder, associated with a mutation in the Janus kinase 2 (JAK2) gene in over 50% of patients. Bone marrow is replaced by collagen fibrosis. The disease may present as idiopathic or primary, or as transformation of an antecedent polycythaemia vera (below) or essential thrombocythaemia (below). Median survival after diagnosis is about 5 years, although this may be longer in younger patients with good prognostic features. Older age, anaemia, leucocytosis, peripheral blasts, and the presence of constitutional symptoms are the major risk factors. Symptoms include fatigue, night sweats, pruritus, bone pain, weight loss, and fever; patients typically develop cytopenia and splenomegaly.[1-4]

Allogeneic stem cell transplantation is the only potentially curative **treatment** approach. However, many patients are ineligible.[1,2,5] Hydroxycarbamide is used to treat splenomegaly; splenectomy may be performed for painful splenomegaly in those with good performance status.[5] Anti-angiogenic therapy with thalidomide or lenalidomide, usually given with corticosteroids, has shown response rates of between 20 and 30%.[1,4,5] Pomalidomide is under investigation.[2,4] JAK2-inhibitors such as ruxolitinib are under development.[1-3]

1. Hoffman R, Rondelli D. Biology and treatment of primary myelofibrosis. *Hematology Am Soc Hematol Educ Program* 2007; 346–54.
2. Rambaldi A, *et al.* From palliation to epigenetic therapy in myelofibrosis. *Hematology Am Soc Hematol Educ Program* 2008; 83–91.
3. Verstovsek S. Therapeutic potential of Janus-activated kinase-2 inhibitors for the management of myelofibrosis. *Clin Cancer Res* 2010; **16**: 1988–96.
4. Holle N, *et al.* Thalidomide and lenalidomide in primary myelofibrosis. *Neth J Med* 2010; **68**: 293–8.
5. Barbui T, *et al.* European LeukemiaNet. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011; **29**: 761–70.

POLYCYTHAEMIA VERA. Polycythaemia vera (polycythaemia rubra vera) is a Philadelphia-negative chronic myeloproliferative disorder,[1] associated in about 95% of patients with a mutation in the Janus kinase 2 (JAK2) gene.[1-3] It is characterised by an increased red cell mass and packed cell volume, and is often associated with increases in white cell and platelet counts and splenomegaly.[1,4] It is a disease of later life, with a median age at presentation of about 60 years.[4] The symptoms are related to hyperviscosity due to the increased number of cells in the blood; patients often present with either arterial or venous thrombosis (cerebrovascular accident, myocardial infarction, pulmonary embolism) or occasionally, with haemorrhage, particularly involving the skin and gastrointestinal tract.[1,4]

Untreated, the disease is associated with a high risk of morbidity and mortality, and patients can undergo myelofibrotic transformation into blast crisis and acute myeloid leukaemia.[1,4] The aims of **treatment** are therefore to reduce the risk of thrombosis and haemorrhage, minimise transformation risk, and manage complications, or pregnancy.[4]

The mainstay of treatment is periodic phlebotomy to maintain the haematocrit within normal values,[5,6] along with aspirin in low doses (40 to 100 mg daily)[1,7] sufficient to reduce thrombosis without increasing the risk of major bleeding.[8] This may be all that is required in younger patients at low risk of thrombosis. In patients at high risk of thrombosis, including those who have a high phlebotomy requirement, some form of myelosuppressive therapy may also be considered. Chlorambucil, which was formerly used for this purpose, has largely been stopped because of a high incidence of leukaemia in patients so treated.[4-6] In patients with a life expectancy of less than 10 years, radioactive phosphorus-32 is probably appropriate, and produces good results with few immediate adverse effects.[5] However, like the alkylating agents it is associated with an increased risk of secondary malignancies.[6] In younger patients hydroxycarbamide,[1,4,6] busulfan,[5,6] or in some countries pipobroman,[5] have been preferred because they were considered to have lower risk of inducing leukaemia. However, there is some evidence[9] that they too may have leukaemogenic potential, especially when used in combination,[7,10] and some recommend that busulfan and pipobroman be reserved for elderly patients.[1,4] Non-cytotoxic therapies that have been shown to be effective include interferon alfa.[1,4-7,9] This may be preferred in younger patients requiring treatment.[4,5] Anagrelide, another antiplatelet drug, has also been tried in polycythaemia vera. It is effective in controlling the platelet count, but does not control progression of polycythaemia vera, and its adverse effects may make it difficult for some patients to tolerate.[4]

1. Penninga EI, Bjerrum OW. Polycythaemia vera and essential thrombocythaemia: current treatment strategies. *Drugs* 2006; **66**: 2173–87.
2. Campbell PJ, Green AR. The myeloproliferative disorders. *N Engl J Med* 2006; **355**: 2452–66.
3. McMullin MF, *et al.* National Cancer Research Institute, Myeloproliferative Disorder Subgroup; British Committee for Standards in Haematology. Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis. *Br J Haematol* 2007; **138**: 821–2. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_amendment_07.pdf (accessed 02/04/09)
4. McMullin MF, *et al.* General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130**: 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 02/04/09)
5. Tefferi A. Polycythemia vera: a comprehensive review and clinical recommendations. *Mayo Clin Proc* 2003; **78**: 174–94.
6. Solberg LA. Therapeutic options for essential thrombocythemia and polycythemia vera. *Semin Oncol* 2002; **29** (suppl 10): 10–15.
7. Finazzi G, Barbui T. Evidence and expertise in the management of polycythemia vera and essential thrombocythemia. *Leukemia* 2008; **22**: 1494–1502.
8. Squizzato A, *et al.* Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 06/06/08).
9. Spivak JL. The optimal management of polycythaemia vera. *Br J Haematol* 2002; **116**: 243–54.
10. Tefferi A, *et al.* A clinical update in polycythemia vera and essential thrombocythemia. *Am J Med* 2000; **109**: 141–9.

PRIMARY THROMBOCYTHAEMIA. Primary thrombocythaemia (essential thrombocythaemia) is a rare Philadelphia-negative myeloproliferative disorder in which abnormal platelet production results in elevated platelet counts.[1] The Janus kinase 2 (JAK2) genetic mutation occurs in about 50 to 60% of patients.[2] The disorder occurs mainly during later life[3] and unlike other myeloproliferative disorders, is associated with generally near-normal life expectancy.[3,4] However, microvascular occlusion marked by conditions such as erythromelalgia (burning pain and erythema of the hands and feet), paraesthesia, or migraine, and arterial or venous thrombosis (e.g. cerebrovascular accident, myocardial infarction, pulmonary embolism) may occur. The risk for thrombosis is highest in patients with a history of thrombosis and in those aged over 60 years. In less than 10% of patients the disease eventually enters a spent phase marked by fibrosis and marrow hypoplasia, or transforms to acute leukaemia.

Asymptomatic patients and those at low risk of thrombosis are generally not treated,[5] but when to begin **treatment** is controversial.[6] Some consider that primary antithrombotic prophylaxis seems rational even in asymptomatic patients if there are no contra-indications to this therapy. Low-dose aspirin (40 to 100 mg daily) is considered to be effective, without increasing the risk of major bleeding. Acute microvascular symptoms may be managed with higher doses of aspirin (100 to 300 mg daily).[1] In patients at risk of thrombosis, drugs that lower platelet counts are used, including cytotoxics.[1,4,7] Phosphorus-32 and alkylating agents such as busulfan or pipobroman are little used now because of their known potential to induce leukaemia.[1,3,7] Hydroxycarbamide can reduce thrombotic events,[3,7,8] and has tended to be preferred because it was thought to have lower risk of inducing leukaemia, but it too appears to have leukaemogenic potential.[3,4,6-9] The increased risk of leukaemia from therapy is particularly relevant in younger patients, for whom non-cytotoxic drugs may be preferred. Some non-cytotoxic therapies have also been shown to reduce platelet counts. Anagrelide[3,4] is often substituted for hydroxycarbamide,[1,5-8] but its value has been questioned by a comparison[10] of 2 regimens using aspirin with either anagrelide or hydroxycarbamide. Although the reductions in platelet count were similar for both groups, patients taking anagrelide were found to be at greater risk of arterial thrombosis, serious haemorrhage, and transformation to myelofibrosis (but the rate of venous thromboembolism was lower). Interferon alfa can also effectively reduce platelet counts;[4-7] it is a good alternative for younger patients who face lifelong treatment,[1] and is the treatment of choice in pregnant women.[1,3,5,6,8] Haematopoietic stem cell transplantation may be considered in younger patients who have advanced, complicated disease.[6]

1. Penninga EI, Bjerrum OW. Polycythaemia vera and essential thrombocythaemia: current treatment strategies. *Drugs* 2006; **66**: 2173–87.
2. Campbell PJ, Green AR. The myeloproliferative disorders. *N Engl J Med* 2006; **355**: 2452–66.
3. Andersson BS. Essential thrombocythemia: diagnosis and treatment, with special emphasis on the use of anagrelide. *Hematology* 2002; **7**: 173–7.
4. Briere J, Guilmin F. Management of patients with essential thrombocythemia: current concepts and perspectives. *Pathol Biol (Paris)* 2001; **49**: 178–83.
5. Finazzi G, Barbui T. Evidence and expertise in the management of polycythemia vera and essential thrombocythemia. *Leukemia* 2008; **22**: 1494–1502.
6. Schafer AI. Thrombocytosis. *N Engl J Med* 2004; **350**: 1211–19.
7. Tefferi A, Murphy S. Current opinion in essential thrombocythemia: pathogenesis, diagnosis, and management. *Blood Rev* 2001; **15**: 121–31.
8. Solberg LA. Therapeutic options for essential thrombocythemia and polycythemia vera. *Semin Oncol* 2002; **29** (suppl 10): 10–15.
9. Finazzi G, Barbui T. Efficacy and safety of hydroxyurea in patients with essential thrombocythemia. *Pathol Biol (Paris)* 2001; **49**: 167–9.
10. Harrison CN, *et al.* Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med* 2005; **353**: 33–45.

Lymphomas. The malignant lymphomas are neoplastic disorders of the lymphoreticular cells. These cells are primarily located in the lymph nodes, but because of their wide distribution in the body lymphomas may arise in extranodal and extralymphatic tissues such as lung, gastrointestinal tract, and skin.

The term covers a heterogeneous group of diseases, comprising two main subgroups: Hodgkin's disease, and the non-Hodgkin's lymphomas (NHL). The cellular origin of Hodgkin's disease is uncertain; the NHL are monoclonal malignancies arising from B cells in about 80% of cases, with the remainder from cells of T lineage and from undifferentiated cells.

Management of patients with malignant lymphoma is largely determined by interpretation of histological features, and, especially for NHL, by an allocation of subtype and grade. Various classification systems have been proposed for NHL of which the National Cancer Institute Working Formulation has been widely used.[1] Under the Working Formulation, NHL are divided into:

- *low grade*, including small lymphocytic, follicular small cleaved cell, and follicular mixed small cleaved and large cell lymphoma
- *intermediate grade*, including follicular large cell, diffuse large cell, diffuse small cleaved cell, and diffuse mixed types

- *high grade*, including large cell immunoblastic, lymphoblastic, and small non-cleaved cell (including Burkitt's) lymphomas

The International Lymphoma Study Group has proposed a revised European-American lymphoma (REAL) classification,[2] and this has subsequently also been published under the auspices of WHO.[3] It is based on a division into B-cell, T-cell and natural killer cell, and Hodgkin's neoplasms. In this classification, B-cell lymphomas include B-cell small lymphocytic lymphoma, MALT lymphoma, follicular lymphoma (35% of adult NHL, rare in children), diffuse large B-cell lymphoma (30% of adult NHL, 5% of NHL in children), and Burkitt's lymphoma (rare in adults; 30% of NHL in children) and Waldenström's macroglobulinaemia (lymphoplasmacytic lymphoma). Plasma-cell myeloma (multiple myeloma) is also a B-cell neoplasm. T-cell lymphomas include precursor T-cell lymphoblastic lymphoma (rare in adults; 45% of NHL in children) and mycosis fungoides; and Hodgkin's lymphoma is subdivided into nodular lymphocyte-predominant and classical (nodular sclerosis and mixed cellularity) forms.

1. Anonymous. Lymphoma classification—where now? *Lancet* 1992; 339: 1084–5.
2. Harris NL, *et al.* A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; 84: 1361–92.
3. Harris NL, *et al.* World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting—Airlie House, Virginia, November 1997. *J Clin Oncol* 1999; 17: 3835–49.

HODGKIN'S DISEASE. Hodgkin's disease (Hodgkin's lymphoma) is characterised histologically in most cases by the presence of a particular type of giant cell, the Reed-Sternberg cell. It is more common in males than in females, and in the West is seen particularly in young adults and in the elderly, although the age distribution differs elsewhere.

It usually presents as painless enlargement of one or more lymph nodes, particularly in the neck or axillae. About a third of all patients also have constitutional symptoms of fever, weight loss, and night sweats, which indicate poorer prognosis. In advanced disease, signs of organ infiltration may occur, as may infectious complications. The mass of the tumour may result in compression of vital organs.

Hodgkin's disease can be treated by radiotherapy or chemotherapy or both, and the choice of treatment depends on the volume and histological subtype of the tumour, the age of the patient, and, particularly, the stage of the disease.[1] The Ann Arbor classification (with Cotswold modifications) recognises 4 stages:

- Stage I, with involvement of a single lymph node region or extralymphatic site
- Stage II, in which spread is restricted to lymph nodes and sites on one side of the diaphragm only
- Stage III, involving spread on both sides of the diaphragm with possible splenic and extralymphatic involvement
- Stage IV, where the patient has diffuse or disseminated disease in one or more extralymphatic organs or tissues.

Stages are subclassified A or B according to the absence or presence respectively of the aforementioned constitutional symptoms.[1-3] X indicates bulky disease and E the involvement of single extranodal sites.[2,3] Survival rates after treatment for Hodgkin's disease are generally excellent, and there is increasing emphasis on tailoring therapy to decrease early and late treatment-related morbidity while not compromising survival.[1] For prognostic and therapeutic considerations, patients are grouped into early-stage favourable (limited) disease (IA or IIA, no bulky disease); early-stage unfavourable (intermediate) disease (IB or IIB, bulky disease); and advanced disease (stages III and IV).

In the treatment of stages I, II, and IIIA disease, **radiotherapy** alone was standard therapy for adult patients with limited disease, especially in those with good prognosis. However, there have been concerns about relapse rates and an increased risk of secondary malignancy after radiotherapy. Adding chemotherapy to radiotherapy was found to reduce recurrence rates, although this does not translate to an increase in overall survival.[4] Nonetheless, **combined modality** treatment is now the preferred treatment for favourable early stage disease.[1-3,5-10] Although the optimal chemotherapy regimen and radiation dose have yet to be determined, the ABVD or Stanford V regimens (see below) are commonly used.[1,7] Chemotherapy with ABVD alone is also used[1,8,11] and radiotherapy alone is still an option for highly selected patients unable to tolerate chemotherapy due to comorbidities.[1] Combined modality treatment is also generally accepted as the treatment of choice in those with unfavourable early stage disease, again using the ABVD[1,2,5-10] or Stanford V regimens.[1]

Chemotherapy alone is generally considered to be the treatment of choice in advanced disease although radiotherapy may be added for consolidation with some regimens.[1,7] Meta-analyses or systematic reviews of combined modality therapy in advanced disease have found no survival benefit from additional radiotherapy, although it may have a role in initial bulky or residual disease.[4,7,12]

There are several 4-drug standard **regimens** available and the choice lies between one of these, alternating cycles of 2 different regimens, or a hybrid cycle that involves giving 7 or 8 drugs in the same course of treatment. However, the single most important factor governing the outcome of chemotherapy is thought to be dose intensity of the drugs given.

The earliest of the successful 4-drug regimens was MOPP combination chemotherapy (chlormethine, vincristine, procarbazine, and prednisone or prednisolone). There are several MOPP-variant regimens that may be as effective and less toxic; these include substitution of chlorambucil or cyclophosphamide for chlormethine (LOPP or COPP, respectively), vinblastine for vincristine (MVPP), and both chlorambucil and vinblastine substituted in one regimen (ChlVPP). However, an alternative to the MOPP-based regimens, a non-cross resistant combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was found to be as effective as MOPP with a reduced risk of inducing sterility or secondary leukaemia. Better results were later reported with ABVD alone, or with MOPP/ABVD, than with MOPP alone, and ABVD has become the basis of standard treatment for advanced stage Hodgkin's disease.[1,3,7-11,13,14] The Stanford V regimen (doxorubicin, vinblastine, chlormethine, vincristine, bleomycin, etoposide and prednisone, with consolidative radiotherapy) is also used as primary treatment for advanced disease.[1]

Attempts to improve the results of ABVD or MOPP have centred on dose intensified hybrid regimens. The German Hodgkin's Lymphoma study group found improved results with a hybrid regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) compared with COPP/ABVD; overall survival was highest with an increased dose of BEACOPP, although toxicity was increased.[15] Escalated-dose BEACOPP may be considered for patients with high-risk disease.[1,7,11]

Salvage treatment options for patients who relapse depend on the initial treatment and the interval between treatment and relapse. Patients who are candidates for salvage therapy can be divided into 4 groups:

- those initially treated with radiotherapy who have a recurrence, in whom standard chemotherapy regimens are effective
- those who never achieve complete remission with standard chemotherapy, in whom prognosis is very poor, and who are candidates for an intensive salvage chemotherapy regimen with autologous haematopoietic stem cell transplantation (HSCT)
- those whose original remission lasted for over a year, of whom some will respond to re-treatment with standard therapy, but in whom intensive salvage chemotherapy regimens with HSCT may be considered
- and those whose remission is short, less than one year, in whom standard chemotherapy may be used to reduce tumour volume before intensive salvage chemotherapy and HSCT.[2,16]

Common salvage regimens include BEAM or mini-BEAM (carmustine, etoposide, cytarabine, and melphalan), DHAP (dexamethasone, high-dose cytarabine, and cisplatin), ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin), ICE (ifosfamide, carboplatin, and etoposide), or gemcitabine-based regimens.[1,7,11,17] For further information on common chemotherapy regimens, see Table 1, p. 719. Although intensive chemotherapy and autologous HSCT is considered by some[2,7,11,14,17] to be the treatment of choice in relapsed patients, others[4] note that benefit on overall survival remains to be established.

Immunotherapy with brentuximab vedotin (a antibody-drug conjugate consisting of a CD30-specific monoclonal antibody and a microtubule disrupting agent) may be an option when autologous haematopoietic stem cell transplantation has failed, or when other therapies have failed in those deemed unsuitable for transplantation. Other immunotherapies under investigation for Hodgkin's disease include the anti-CD20 monoclonal antibody rituximab, and other monoclonal antibodies, some radiolabelled, to CD25 and CD30.[3,5,7,11,17]

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: Hodgkin lymphoma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/hodgkins.pdf (accessed 27/05/10)
2. Fung HC, Nademanee AP. Approach to Hodgkin's lymphoma in the new millennium. *Hematol Oncol* 2002; 20: 1–15.
3. Yung L, Linch D. Hodgkin's lymphoma. *Lancet* 2003; 361: 943–51.
4. Brandt L, *et al.* A systematic overview of chemotherapy effects in Hodgkin's disease. *Acta Oncol* 2001; 40: 185–97.
5. Connors JM, *et al.* Hodgkin's lymphoma: basing the treatment on the evidence. *Hematology (Am Soc Hematol Educ Program)* 2001; 1: 178–93.
6. Josting A, Diehl V. Early-stage Hodgkin's disease. *Curr Oncol Rep* 2001; 3: 279–84.
7. Engert A, *et al.* ESMO Guidelines Working Group. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v168–v171. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v168.full.pdf+html (accessed 11/10/10)
8. Evens AM, *et al.* Treatment of Hodgkin lymphoma: the past, present, and future. *Nat Clin Pract Oncol* 2008; 5: 543–56.
9. Raemaekers JMM, van der Maazen RWM. Hodgkin's lymphoma: new views from an old disease. *Neth J Med* 2008; 66: 457–66.
10. Diehl V, Fuchs M. Early, intermediate and advanced Hodgkin's lymphoma: modern treatment strategies. *Ann Oncol* 2007; 18 (suppl 1): i71–i79.
11. Bartlett NL. Modern treatment of Hodgkin lymphoma. *Curr Opin Hematol* 2008; 15: 408–14.
12. Loeffler M, *et al.* Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. *J Clin Oncol* 1998; 16: 818–29.
13. Tesch H, *et al.* Treatment of advanced stage Hodgkin's disease. *Oncology* 2001; 60: 101–9.
14. Connors JM. State-of-the-art therapeutics: Hodgkin's lymphoma. *J Clin Oncol* 2005; 23: 6400–8.
15. Diehl V, *et al.* Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 2003; 348: 2386–95. Correction. *ibid.* 2005; 353: 744.
16. Glossmann J-P, *et al.* New treatments for Hodgkin's disease. *Curr Treat Options Oncol* 2002; 3: 283–90.
17. Cashen AF, Bartlett NL. Salvage regimens for Hodgkin lymphoma. *Clin Adv Hematol Oncol* 2008; 6: 517–24.

NON-HODGKIN'S LYMPHOMAS. The non-Hodgkin's lymphomas are a heterogeneous group of malignancies that vary considerably in their behaviour, prognosis, and management. Classifications have grouped them by grade (low, intermediate, or high) or cellular origin (B-cell, T-cell, or NK-cell), and histology (see Lymphomas, p. 695.3). The most recent WHO classification, while still considering cell of origin, does not group the non-Hodgkin's lymphomas into a distinct clinical framework.[1] The non-Hodgkin's lymphomas include Burkitt's lymphoma, MALT lymphoma, and mycosis fungoides, all of which are discussed separately.

The usual presentation of lymphomas is lymphadenopathy, which in low-grade lymphoma may develop insidiously over a long period. There may be constitutional symptoms of fever, night sweats, and weight loss. Extranodal involvement may occur, as may symptoms due to organ compression by the tumour mass. Lymphomas of T-cell origin have a worse prognosis than B-cell lymphomas of the same type, and excess tumour bulk, involvement of bone marrow or gastrointestinal tract, and elevated serum lactic dehydrogenase concentrations are also adverse prognostic factors. Staging is of somewhat less importance as a determinant of treatment and prognosis than in Hodgkin's disease.

Follicular lymphoma is the commonest form of *indolent* non-Hodgkin's lymphoma.[2,3] Follicular lymphomas may be subclassified histologically into 3 grades according to the number of centroblasts, and grade 3, which is more aggressive, should be treated as for diffuse large B-cell lymphoma[1,4,5] (see below). The approach to therapy of other follicular lymphoma differs dramatically in patients with localised or disseminated (advanced) disease.[1]

In the few patients with limited disease at presentation, radiotherapy is potentially curative,[2,5-10] with most patients achieving long-term freedom from disease, and low rates of relapse.[2] The addition of chemotherapy to radiotherapy has not thus far convincingly prolonged remission or improved overall survival.[1,7] Patients who do not respond after therapy should be treated as those with more disseminated disease.[1] Even in more advanced disease, which is rarely curable,[2,6,8,10] follicular lymphoma may follow a fairly chronic course, with a median survival of 8 or more years[4,6,9] although transformation to more aggressive forms may occur.[2]

Treatment in advanced disease has not been shown to affect survival, and a conservative approach of withholding treatment until symptoms require it is considered viable.[1,3,6,7,9,11] The addition of rituximab to combination chemotherapy has increased overall response rate, response duration, and progression-free survival and hence some[1,10] recommend rituximab with chemotherapy (chemoimmunotherapy) for first-line treatment; caution is advised in patients with hepatitis B.[1]

Rituximab may be combined with either bendamustine or fludarabine.[1] Established regimens to which rituximab may be added include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or fludarabine-based regimens such as FCM (fludarabine, cyclophosphamide, and mitoxantrone) or FND (fludarabine, mitoxantrone, and dexamethasone).[1,3,5,10] Rituximab monotherapy is also an option for patients with a low-risk profile or who cannot tolerate more intensive chemoimmunotherapy or for the elderly and infirm.[1,10] Single-agent alkylators such as chlorambucil or cyclophosphamide are an option for these patients.[1] Rituximab maintenance therapy is under investigation; although benefits have been reported, the optimal dose and duration have not been established.[12]

The use of interferon alfa with chemotherapy for first-line treatment has produced conflicting results. However, when interferon alfa was used with anthracycline-containing regimens, improvements in response rate and prolonged remission were reported;[6,11] prolonged survival has not

been proven.[7] Interferon alfa as maintenance therapy appears to improve disease-free survival, but only if complete remission has been obtained with initial chemotherapy.[2,6] Overall, a *meta-analysis*[13] of 10 studies found that the ability of interferon alfa to prolong remission duration and survival may depend on it being used with relatively intensive chemotherapy and given in unit doses of at least 5 million units (at least 36 million units/month).

Radioimmunotherapy with radiolabelled monoclonal antibodies such as tositumomab and ibritumomab may also be considered first-line,[1,3] although myelosuppression may be a problem[9,14] and there may be practical difficulties associated with their use. Some consider radioimmunotherapy as an initial option for the elderly or infirm.[1]

Relapse of indolent lymphomas is generally inevitable. Selection of salvage therapy depends on the efficacy of initial regimens.[10] Options include chemoimmunotherapy with a different chemotherapy option to that used first-line, radioimmunotherapy (as discussed above), rituximab alone, or alkylator monotherapy.[1,3,5,10] High-dose chemotherapy followed by autologous or allogeneic haematopoietic stem cell transplantation (HSCT) may be an appropriate option for relapsed patients.[1,3,4,7,10] In the case of allogeneic HSCT, nonmyeloablative approaches may be considered.[1,3,10]

Intermediate- to high-grade lymphomas, of which **diffuse large B-cell lymphoma** (DLCL) is the most common form,[1] are *aggressive*. About one third of patients with DLCL have localised disease at presentation,[15] and treatment with CHOP (see above) and rituximab with or without radiotherapy is the treatment of choice.[1,4,16,17] Many also consider CHOP plus rituximab (R-CHOP) to be the standard of care in advanced disease,[1,4,16] although other, generally anthracycline-based, regimens are also considered acceptable, such as dose-adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin).[1] High-dose chemotherapy with autologous HSCT has been tried for initial therapy in patients with diffuse aggressive non-Hodgkin's lymphoma, but remains investigational.[1,11,15,18]

On relapse, patients are treated with salvage chemotherapy regimens such as DHAP (dexamethasone, cytarabine, and cisplatin), ICE (ifosfamide, carboplatin, etoposide), ESHP or ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, and cisplatin), GemOx (gemcitabine and oxaliplatin), or MINE (mitoxantrone, ifosfamide, mesna, etoposide); all these regimens may be given with or without rituximab.[1] Monotherapy with pixantrone may also be considered in patients with B-cell lymphomas. Patients are then evaluated for high-dose chemotherapy and autologous HSCT, which is considered the treatment of choice in suitable patients who respond to the salvage regimens.[1,2,17,19] However, in disease resistant to salvage chemotherapy, its role has not been established,[19] and patients whose disease progresses are considered not likely to benefit from currently available standard therapy.[1] In an effort to improve outcomes after autologous HSCT, the addition of radioimmunotherapy (as above) to conditioning regimens is being investigated. Allogeneic HSCT is also under investigation.

There is no standard approach for those patients ineligible for transplant;[19] options include rituximab monotherapy, second-line chemotherapy regimens such as R-EPOCH or EPOCH, CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) with or without rituximab, lenalidomide, palliative radiotherapy, or investigational treatment.[1]

For further information on common chemotherapy regimens, see Table 1, p. 719.

High-grade lymphomas such as **precursor T-lymphoblastic lymphoma** (T-LBL) and Burkitt's lymphoma (see below) are *highly aggressive* and untreated patients survive only weeks. They occur mainly in children and young adults, and are often widely disseminated with bone marrow, peripheral blood, and CNS involvement. Lymphoblastic lymphoma is generally treated with protocols based on those used for acute lymphoblastic leukaemia (see p. 692.3), including the use of CNS prophylaxis.[1]

Vaccines for B-cell lymphomas are under investigation.

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-Hodgkin's lymphoma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf (accessed 27/05/10)
2. Hauke RJ, Armitage JO. A new approach to non-Hodgkin's lymphoma. *Intern Med* 2000; 39: 197–208.
3. Van Hende V, Offner F. Treatment of follicular lymphoma—a review. *Acta Clin Belg* 2007; 62: 408–18.
4. Ansell SM, Armitage J. Non-Hodgkin lymphoma: diagnosis and treatment. *Mayo Clin Proc* 2005; 80: 1087–97.
5. Bendandi M. Aiming at a curative strategy for follicular lymphoma. *CA Cancer J Clin* 2008; 58: 305–17.
6. Reiser M, Diehl V. Current treatment of follicular non-Hodgkin's lymphoma. *Eur J Cancer* 2002; 38: 1167–72.
7. Brandt L, *et al.* A systematic overview of chemotherapy effects in indolent non-Hodgkin's lymphoma. *Acta Oncol* 2001; 40: 213–23.
8. Evans LS, Hancock BW. Non-Hodgkin lymphoma. *Lancet* 2003; 362: 139–46.
9. Hiddemann W, *et al.* Treatment strategies in follicular lymphomas: current status and future perspectives. *J Clin Oncol* 2005; 23: 6394–9.
10. Dreyling M. ESMO Guidelines Working Group. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v181–v183. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v181.full.pdf+html (accessed 11/10/10)
11. Fisher RI. Overview of non-Hodgkin's lymphoma: biology, staging, and treatment. *Semin Oncol* 2003; 30 (suppl 4): 3–9.
12. van Oers MHJ. Rituximab maintenance therapy: a step forward in follicular lymphoma. *Haematologica* 2007; 92: 826–33.
13. Rohatiner AZS, *et al.* Meta-analysis to evaluate the role of interferon in follicular lymphoma. *J Clin Oncol* 2005; 23: 2215–23.
14. Fanale MA, Younes A. Monoclonal antibodies in the treatment of non-Hodgkin's lymphoma. *Drugs* 2007; 67: 333–50.
15. Ng AK. Diffuse large B-cell lymphoma. *Semin Radiat Oncol* 2007; 17: 169–75.
16. Coiffier B. State-of-the-art therapeutics: diffuse large B-cell lymphoma. *J Clin Oncol* 2005; 23: 6387–93.
17. Tilly H, Dreyling M. ESMO Guidelines Working Group. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v172–v174. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v172.full.pdf+html (accessed 11/10/10)
18. Godwin JE, Fisher RI. Diffuse large-cell lymphomas: a review of therapy. *Clin Lymphoma* 2001; 2: 155–63.
19. Kenkre VP, Smith SM. Management of relapsed diffuse large B-cell lymphoma. *Curr Oncol Rep* 2008; 10: 393–403.

AIDS-related lymphomas. Non-Hodgkin's lymphoma is often a late complication of AIDS and its incidence in HIV-infected individuals is about 60 times greater than in the general population.[1] Histologically, it is usually diffuse large cell lymphoma (see Non-Hodgkin's Lymphomas, p. 696.3) or small non-cleaved lymphoma (Burkitt's lymphoma—see below).[1-3] About 50% of these are associated with the presence of Epstein-Barr virus.[4] The other common HIV-associated lymphoma is primary CNS lymphoma (p. 698.1), which is invariably associated with Epstein-Barr virus.[1,2] More recently, primary effusion lymphoma or body cavity-based lymphoma has been identified,[1,2] which is associated with human herpes virus 8. Although Hodgkin's disease (see p. 696.1) is not considered an AIDS-defining illness, epidemiological studies have shown it to be associated with HIV infection.[2]

It was unclear if the introduction of HAART for HIV infection (p. 957.2) would reduce the risk of lymphomas by improving immune function,[5] or, conversely, increase the incidence by allowing patients to survive long enough for lymphoma to develop.[1] However, it has become apparent that the incidence of AIDS-related lymphoma has decreased with the advent of HAART.[1,3,5] There is some evidence of tumour response when antiretroviral therapy is started in a patient who already has a lymphoma.[4]

Most patients with AIDS-related non-Hodgkin's lymphomas have disseminated disease, often extranodal, at presentation.[1,2] Optimal management is not established.[3] Combination chemotherapy regimens used include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CDE (cyclophosphamide, doxorubicin, and etoposide) and a dose-adjusted EPOCH regimen (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin).[1,3,5,6] M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) has also been used;[1] a low-dose modification of this regimen produced responses comparable to the standard-dose regimen.[7] There is some controversy about whether HAART should be given with or after chemotherapy,[2,6] although most seem to recommend concomitant treatment[2,6] as it results in a more modest decrease in immune function than when chemotherapy is given alone.[5] The addition of rituximab has been investigated, but results have been disappointing and an increased risk of neutropenic sepsis and death has been reported.[3,5] However, some consider the use of rituximab with chemotherapy to be more effective than chemotherapy alone, and safe in these patients provided appropriate antibacterial prophylaxis is used.[6] The use of colony-stimulating factors with chemotherapy has reduced neutropenia and febrile episodes, but there has been no effect on remission rates or overall survival.[1] Most studies used granulocyte-macrophage colony-stimulating factor, but this may increase HIV-1 replication.[1]

Patients with relapsed AIDS-related lymphoma who are responsive to salvage chemotherapy may be treated successfully with high-dose chemotherapy and autologous haematopoietic stem cell transplantation.[6]

HIV-positive patients with Hodgkin's disease are more likely to present with constitutional symptoms, at an advanced stage, with extranodal disease, and concomitant Epstein-Barr virus infection than HIV-negative individuals. Bone marrow involvement may be found in more than 50% of patients. Before HAART, patients with Hodgkin's disease and infected with HIV had a median survival of 1 to 2 years. Outcomes in the HAART era may be improving, although optimal treatment is undecided. Regimens that have been tried include the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) and Stanford V regimens.[2]

For further information on common chemotherapy regimens, see Table 1, p. 719.

1. Kersten MJ, Van Oers RHJ. Management of AIDS-related non-Hodgkin's lymphomas. *Drugs* 2001; 61: 1301–15.
2. Cheung MC, *et al.* AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy. *Oncologist* 2005; 10: 412–26.
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-Hodgkin's lymphoma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf (accessed 28/05/10)
4. Hermans P. Opportunistic AIDS-associated malignancies in HIV-infected patients. *Biomed Pharmacother* 2000; 54: 32–40.
5. Stebbing J, *et al.* The evidence-based treatment of AIDS-related non-Hodgkin's lymphoma. *Cancer Treat Rev* 2004; 30: 249–53.
6. Levine AM. Management of AIDS-related lymphoma. *Curr Opin Oncol* 2008; 20: 522–8.
7. Kaplan LD, *et al.* Low-dose compared with standard-dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. *N Engl J Med* 1997; 336: 1641–8.

Burkitt's lymphoma. Burkitt's lymphoma is a small non-cleaved cell lymphoma (SNCL) of B-cell origin, which is highly aggressive and with a characteristic chromosomal translocation involving the *c-myc* oncogene. The disease accounts for up to 50% of childhood non-Hodgkin's lymphoma in non-endemic areas. Three clinical variants have been described. The endemic form occurs most commonly in equatorial Africa and Papua New Guinea, in young children, and is almost always associated with Epstein-Barr virus (EBV) infection. It frequently involves the jaws and other facial bones; bone marrow and CNS involvement can occur. In contrast, the sporadic form, seen most commonly in developed countries, arises in the lymphoid tissues of the gut and upper respiratory tract. The immunodeficiency subtype is seen in the setting of HIV infection, and to a lesser extent post-transplantation. Adult patients with the latter 2 subtypes typically present with extranodal disease, and the abdomen is the most common site of involvement. Symptoms include abdominal pain, gastrointestinal bleeding, nausea, and vomiting, and may mimic appendicitis. Bone marrow and CNS involvement can occur. Jaw involvement is rare, and only about a third of patients are EBV-positive.

The main **treatment** for Burkitt's lymphoma is chemotherapy. Shorter duration, dose-intensive chemotherapy regimens have resulted in improved survival and in children complete remission is common and prognosis good: probability of long-term disease-free survival is usually greater than 80%.[1] Prognosis has been less good in adults, but with the increasing use of more intensive regimens similar to those used in children, is improving. About half of all adult cases are reported to be curable with intensive chemotherapy regimens.[2,3]

Commonly used regimens include CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate) for low-risk patients; it is given in an alternating regimen with IVAC (ifosfamide, etoposide, and high-dose cytarabine) in high-risk patients.[2-5] Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with methotrexate plus cytarabine) is also given to adult patients.[2-6] A dose-adjusted EPOCH regimen (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) is also recommended for use in low-risk patients or in high-risk patients unable to tolerate more aggressive treatment.[4] Rituximab has been added to these regimens in an attempt to improve response and long-term survival;[2-7] initial results have been promising. Cytarabine and methotrexate are also given intrathecally for CNS prophylaxis.[2-4]

Relapsed or ***refractory*** Burkitt's lymphoma has not been well-studied and the optimal treatment regimen is unknown.[2,3] Drugs used for salvage chemotherapy include high-dose methotrexate and high-dose cytarabine or etoposide plus cisplatin;[2] combination regimens incorporating cisplatin, cytarabine, or ifosfamide may be of benefit, particularly if these were not used first-line.[3] Autologous or allogeneic haematopoietic stem cell transplantation may be considered for relapsed or refractory disease,[2-4] although its role in Burkitt's lymphoma remains controversial.[5,7] There are reports of improved survival with high-dose chemotherapy followed by autologous stem cell transplantation compared with chemotherapy alone. Allogeneic transplantation has been reported to lower relapse rates when compared with autologous transplantation, but transplant-related mortality is higher.[7]

1. Cairo MS, *et al.* Burkitt's and Burkitt-like lymphoma in children and adolescents: a review of the Children's Cancer Group experience. *Br J Haematol* 2003; 120: 660–70.
2. Evens AM, Gordon LI. Burkitt's and Burkitt-like lymphoma. *Curr Treat Options Oncol* 2002; 3: 291–305.
3. Blum KA, *et al.* Adult Burkitt leukemia and lymphoma. *Blood* 2004; 104: 3009–20.
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-Hodgkin's lymphomas (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf (accessed 28/05/10)
5. Aldoss IT, *et al.* Adult Burkitt lymphoma: advances in diagnosis and treatment. *Oncology (Williston Park)* 2008; 22: 1508–17.
6. Levine AM. Management of AIDS-related lymphoma. *Curr Opin Oncol* 2008; 20: 522–8.

7. Yustein JT, Dang CV. Biology and treatment of Burkitt's lymphoma. *Curr Opin Hematol* 2007; 14: 375–81.

Primary CNS lymphoma. Primary CNS lymphoma is an aggressive form of non-Hodgkin's lymphoma that develops in the brain, spinal cord, leptomeninges, or the eye.[1,2] It accounts for some 0.5 to 5% of all primary brain tumours (see also Malignant Neoplasms of the Brain, p. 701.2). There is a strong association with HIV infection (see AIDS-related Lymphomas, p. 697.2). Patients usually present with neurological symptoms such as hemiparesis or dysphasia, mental status changes, symptoms of increased intracranial pressure, and behavioural changes.[1,2] The ocular manifestation is termed primary intra-ocular lymphoma; it is often misdiagnosed as uveitis, and should be distinguished from systemic lymphoma with orbital involvement.[1,3,4]

Treatment options for primary CNS lymphoma include corticosteroids, radiotherapy, and chemotherapy. Corticosteroids such as dexamethasone, although the treatment of choice for short-term palliation, should be avoided before tissue biopsy since they can interfere with the histopathology.[1,2] These tumours are radiosensitive, but the timing of radiotherapy is controversial. Most recommend some form of radiation after chemotherapy; drug delivery may be optimal before radiation, when the blood-brain barrier is maximally disrupted by the tumour.[2] Others advise against first-line radiotherapy, based on limited efficacy and potential delayed neurotoxicity; consolidation radiotherapy may be beneficial in younger patients who achieve a complete response after methotrexate-based chemotherapy.[1,5]

While the optimum chemotherapy combination remains unclear,[1,5] chemotherapy has significantly improved disease-free and overall survival.[2] High-dose methotrexate appears to be the most effective drug and is recommended first-line, with or without other drugs such as cytarabine.[1,2,5] Regimens based on CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) have been associated with increased neurotoxicity and found ineffective, probably due to poor penetration across the intact blood-brain barrier;[1,2] as a consequence, CHOP-like chemotherapy is considered to have no role in the treatment of primary CNS lymphoma.[1]

In patients who relapse after a relatively long-term response (longer than 1 year), then re-treatment with a methotrexate-based regimen is considered reasonable. For those who do not respond to initial chemotherapy or who relapse quickly, recommendations include radiotherapy with or without chemotherapy.[2] Alternative agents include rituximab, temozolomide, topotecan, and the combination regimen of cisplatin, cytarabine, and dexamethasone.[2] High-dose chemotherapy followed by autologous haematopoietic stem cell transplantation (HSCT) has been investigated, but evidence to support its use first-line is considered to be lacking.[1] However, it has been reported as being an effective treatment for relapsed and refractory disease.[6]

Optimal treatment for primary intra-ocular lymphoma is not known,[3] and recommendations for therapy remain controversial.[1] Options include ocular radiotherapy, intravitreal methotrexate, combined modality treatment, and systemic methotrexate-based chemotherapy.[1,3,4] High-dose chemotherapy with autologous HSCT has been tried,[1,4] and agents under investigation include rituximab and trofosfamide.[1]

1. Marcus R, *et al.* British Committee for Standards in Haematology. Guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL). Available at: http://www.bcshguidelines.com/pdf/PCNSL_guidelines.pdf (accessed 18/05/09)
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: central nervous system cancers (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf (accessed 28/05/10)
3. Grimm SA, *et al.* Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. *Ann Oncol* 2007; 18: 1851–5.
4. Grimm SA, *et al.* Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. *Neurology* 2008; 71: 1355–60.
5. DeAngelis LM. Primary central nervous system lymphoma: a curable brain tumor. *J Clin Oncol* 2003; 21: 4471–3.
6. Soussain C, *et al.* Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. *J Clin Oncol* 2008; 26: 2512–18.

MALT lymphoma. Marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) occur most commonly in the stomach, but may also occur in the salivary gland, breast, thyroid, eye, or lung. They tend to be indolent and remain localised for long periods of time, but can transform to a more aggressive type. Clinical symptoms of gastric MALT lymphoma are vague and varied and include abdominal pain, dyspepsia, vomiting, and gastric bleeding.

Most gastric MALT lymphomas are associated with *Helicobacter pylori* infection.[1-4] The bacterium stimulates the formation of MALT in the stomach, which normally lacks organised lymphoid tissue, and there is evidence that it indirectly stimulates tumour growth. Eradication of *H. pylori* infection using antibacterial and antisecretory therapy, as described in Peptic Ulcer Disease, p. 1816.2, has been shown to result in regression of gastric MALT lymphoma in most patients.[1,2,4,5] Tumour response may be slow,[2] and lymphoma regression after *H.pylori* eradication is not always complete; eradication suppresses but does not necessarily eradicate the neoplastic clone. Only lymphomas limited to the mucosa or submucosa regress after eradication and lymphoma can recur.[1] Thus, patients who are *H. pylori*-positive with early stage primary gastric MALT lymphomas may be treated solely with *H. pylori* eradication regimens and long-term endoscopic follow-up.[2,4,6,7] The best treatment for patients without *H. pylori* infection, those whose tumours do not respond to eradication, and those with more advanced tumour stage at presentation remains to be established.

Radiation therapy is the treatment of choice for localised disease.[2,4,6,7] Rituximab monotherapy may be considered for early stage disease if radiation therapy is contra-indicated.[2] Surgical resection is generally limited to specific clinical situations,[2] such as the management of complications or for cases of locally persistent disease.[3,4] Single-agent or combination chemotherapy is recommended in advanced disease.[2,7] No standard chemotherapy regimen has been established.[4] Regimens that may be tried include alkylating agents such as cyclophosphamide or chlorambucil, purine analogues such as cladribine or fludarabine,[3,4,7] and occasionally anthracycline-based chemotherapy for younger patients with more aggressive disease.[3] Rituximab is also an option, given either alone or with chemotherapy.[2-4,7]

It has been suggested that screening for and eradication of *H. pylori* is worth investigating as a means of preventing gastric cancer.[8]

Non-gastrointestinal low-grade MALT lymphomas have been treated with surgery or radiation therapy if localised, and with single-agent or combination chemotherapy (similar to that used for other low-grade non-Hodgkin's lymphomas—see p. 696.3) if advanced.[2-4,6]

1. Schechter NR, Yahalom J. Low-grade MALT lymphoma of the stomach: a review of treatment options. *Int J Radiat Oncol Biol Phys* 2000; 46: 1093–1103.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-Hodgkin's lymphoma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf (accessed 28/05/10)
3. Cohen SM, *et al.* Non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue. *Oncologist* 2006; 11: 1100–1117.
4. Morgner A, *et al.* Therapy of gastric mucosa associated lymphoid tissue lymphoma. *World J Gastroenterol* 2007; 13: 3554–66.
5. Wotherspoon AC, *et al.* Mucosa-associated lymphoid tissue lymphoma. *Curr Opin Hematol* 2002; 9: 50–5.
6. Bertoni F, Zucca E. State-of-the-art therapeutics: marginal-zone lymphoma. *J Clin Oncol* 2005; 23: 6415–20.
7. Zucca E, Dreyling M. ESMO Guidelines Working Group. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v175–v176. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v175.full.pdf+html (accessed 12/10/10)
8. Peterson WL, *et al.* Helicobacter pylori-related disease. *Arch Intern Med* 2000; 160: 1285–91.

Mantle cell lymphoma. Mantle cell lymphoma is a rare, aggressive lymphoma of B-cell origin, characterised in most cases by a chromosomal t(11;14) translocation. Patients are often elderly and more often male. Most patients present with advanced stage disease. Clinical features include fever, weight loss, drenching night sweats, and gastrointestinal symptoms.[1,2]

There is no established standard **treatment** for mantle cell lymphoma.[3,4] For the few patients presenting with *localised* disease, radiotherapy significantly improves progression-free survival, and is recommended first-line, with or without chemotherapy.[1,3]

Systemic combination chemotherapy, although non-curative, is recommended in *advanced* disease.[1,3] Rituximab plus chemotherapy is recommended first-line.[1,3,5] Chemotherapy options include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), HyperCVAD/MA (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine), and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin).[1-3,5] For further information on these and other common chemotherapy regimens, see Table 1, p. 719. An alternative treatment in younger patients, without significant comorbidities, is high-dose radiochemotherapy consolidated by autologous haematopoietic stem cell transplantation (HSCT).[1,3,5,6] Allogeneic HSCT may be curative, but only a few patients are suitable and it is associated with considerable morbidity and mortality.[1,2,6] For patients who cannot tolerate more intensive therapy, some recommend CHOP with or without rituximab[3] or anthracycline- or fludarabine-containing regimens.[1]

Patients who *relapse* after initial therapy or with progressive disease may be treated with bendamustine (with or without rituximab), bortezomib, lenalidomide, purine analogue-containing regimens (with or without rituximab), temsirolimus, thalidomide (alone or with rituximab),[1,3,5,6] or ibrutinib. Radioimmunotherapy, with radiolabelled monoclonal antibodies ibritumomab and tositumomab, has also been investigated for relapsed or refractory disease.[1,2,5,6] Allogeneic HSCT may be considered in suitable patients with relapsed disease after first-line therapy.[1,2,6]

1. Weigert O, *et al.* Current management of mantle cell lymphoma. *Drugs* 2007; 67: 1689–1702.
2. Schmidt C, Dreyling M. Therapy of mantle cell lymphoma: current standards and future strategies. *Hematol Oncol Clin North Am* 2008; 22: 953–63.
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-Hodgkin's lymphoma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf (accessed 28/05/10)
4. Gill S, Ritchie D. Therapeutic options in mantle cell lymphoma. *Leuk Lymphoma* 2008; 49: 398–409.
5. Witzig TE. Current treatment approaches for mantle-cell lymphoma. *J Clin Oncol* 2005; 23: 6409–14.
6. Dreyling M, *et al.* European MCL Network. Current treatment standards and future strategies in mantle cell lymphoma. *Ann Oncol* 2008; 19 (suppl 4): iv41–iv44. Also available at: http://annonc.oxfordjournals.org/cgi/reprint/19/suppl_4/iv41.pdf (accessed 10/08/09)

Mycosis fungoides. Mycosis fungoides is the most common of the cutaneous T-cell lymphomas. It is considered to have 3 stages which may overlap or occur simultaneously:

- a premycotic erythematous or patch phase, characterised by a pruritic rash resembling psoriasis, which may persist for years or even decades
- an infiltrative or plaque phase, in which some patches become thickened, darker plaques with marked T-cell infiltration
- a tumour phase where lesions enlarge and ulcerate. Ultimately there may be visceral involvement or potentially fatal sepsis secondary to skin breakdown

A leukaemic variant of mycosis fungoides presents as widespread pruritic erythroderma, accompanied by abnormal T-cells in the blood, and is known as the Sézary syndrome.

There are many therapeutic options for mycosis fungoides, but few have been evaluated in controlled studies. **Treatment** depends on disease stage and spread.[1-5] Patients with limited and slowly progressive *patch phase disease* have a good prognosis (median survival similar to age-matched controls) and may be managed with topical and local therapies. Topical therapies include emollients, corticosteroids, chlormethine, carmustine, the retinoids bexarotene or tazarotene, and imiquimod.[1,2,6-10] Phototherapy, using UV B light, or a psoralen plus UV A light (PUVA), is a useful alternative when topical treatments are ineffective or not tolerated.[1,2,8] Mycosis fungoides is very radiosensitive, and for clearly localised patches, or isolated patches that have failed to respond to other treatments, local x-ray or electron beam radiotherapy may be used.[2,3,6-8]

The initial therapy for patients with widespread *patch/plaque phase disease* is also topical, using chlormethine or PUVA.[1,6] Topical retinoids are not recommended for generalised skin involvement, as they can cause irritation.[6] Patients who fail to respond to a single drug may be treated with combinations such as chlormethine with phototherapy,[1] PUVA with interferon alfa,[1,3,7] or PUVA with retinoids.[7] Total skin electron beam therapy may be used, but it may not be widely available and is usually only given once;[3] it is generally used for thickened plaques or for disease that has not responded to other local therapies.[1-3]

In the *tumour phase*, combination therapy as described above is often used initially.[1,4,7] Alternatively, systemic retinoids (such as acitretin, bexarotene, isotretinoin, or tretinoin), interferons, vorinostat, romidepsin, denileukin diftitox, or low-dose methotrexate may be tried.[6] Systemic chemotherapy may be used for palliation in recalcitrant disease and advanced disease with extracutaneous involvement, but responses are often of short duration.[1,2,6] Options include single-agent liposomal doxorubicin, gemcitabine, chlorambucil, pentostatin, etoposide, cyclophosphamide, and temozolomide.[6] Combination regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (CHOP without doxorubicin), CAVE (cyclophosphamide, doxorubicin, vincristine, etoposide),[1] or EPOCH (etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide).[8] For further information on common chemotherapy regimens, see Table 1, p. 719.

Mycosis fungoides with erythrodermic features is treated similarly except that skin irradiation tends to be avoided or used in very low doses as it causes severe desquamation.[1] Extracorporeal photopheresis may be useful for disease with erythrodermic features.[1,3,5,6,10]

Therapies for *persistent or recurrent* mycosis fungoides include denileukin diftitox, bexarotene, and vorinostat.[2,4,5] Experience with autologous haematopoietic stem cell transplantation (HSCT) is limited, but allogeneic HSCT may be considered for patients with advanced disease that is progressive or refractory to multiple treatment options.[6,7] Alemtuzumab has been used in patients with advanced or refractory mycosis fungoides or Sézary syndrome.[4,6,8]

1. Kim YH, Hoppe RT. Mycosis fungoides and the Sézary syndrome. *Semin Oncol* 1999; 26: 276–89.

2. Siegel RS, *et al.* Primary cutaneous T-cell lymphoma: review and current concepts. *J Clin Oncol* 2000; **18**: 2908–25.
3. Whittaker SJ, *et al.* Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003; **149**: 1095–1107. Also available at: http://bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Cutaneous%20T%20Cell%20Lymphoma.pdf (accessed 15/04/09)
4. Hwang ST, *et al.* Mycosis fungoides and Sézary syndrome. *Lancet* 2008; **371**: 945–57.
5. Perez A, Whittaker S. Cutaneous T-cell lymphoma. *Br J Haem Med* 2006; **67**: 178–83.
6. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-Hodgkin's lymphoma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf (accessed 28/05/10)
7. Willemze R, Dreyling M, ESMO Guidelines Working Group. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v177–v180. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v177.full.pdf+html (accessed 13/10/10)
8. Keehn CA, *et al.* The diagnosis, staging, and treatment options for mycosis fungoides. *Cancer Control* 2007; **14**: 102–11.
9. Berthelot C, *et al.* Skin directed therapy for mycosis fungoides: a review. *J Drugs Dermatol* 2008; **7**: 655–66.
10. Lansigan F, Foss FM. Current and emerging treatment strategies for cutaneous T-cell lymphoma. *Drugs* 2010; **70**: 273–86.

Waldenström's macroglobulinaemia. Waldenström's macroglobulinaemia (primary macroglobulinaemia) is an uncommon B-cell lymphoproliferative disorder characterised by lymphoplasmacytic cells that infiltrate the bone marrow and by hypersecretion of immunoglobulin M (IgM). Patients are mainly elderly, and more often male. Although often asymptomatic, patients can present with weakness and fatigue, peripheral neuropathy, anaemia, hepatosplenomegaly, and lymphadenopathy. Some develop the hyperviscosity syndrome (characterised by oronasal bleeding, visual disturbances and retinal haemorrhage, neurological disturbances such as headache, vertigo, and hearing loss, and, rarely, heart failure).

Asymptomatic patients require no treatment and may remain stable for some years. Where **treatment** is required, first-line options include the use of alkylating agents, nucleoside analogues (such as cladribine or fludarabine), or the monoclonal antibody rituximab, as well as combinations of these.[1-9] Combination regimens include nucleoside analogues with either rituximab or cyclophosphamide, or a combination of all three drugs. Cyclophosphamide-based therapy with rituxumab may also be an option, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or DRC (dexamethasone, rituximab, and cyclophosphamide). Rituximab may also be used with thalidomide, and this combination or the DRC regimen may be useful for those whose main indication for treatment is cytopenias.

Rituximab-based therapies may be the preferred ***initial therapy*** for most patients; cyclophosphamide-based regimens are appropriate if rapid disease control is needed.[7] Rituximab monotherapy is discouraged in those patients with higher IgM concentrations and at risk of hyperviscosity,[2,3,5] although it is an appropriate choice for those patients with low-risk disease and associated comorbidities.[7] The use of chlorambucil has decreased in Waldenström's macroglobulinaemia,[8] but it may also be considered as monotherapy in low-risk disease and in older patients with comorbidities.[7]

High-dose therapy followed by autologous haematopoietic stem cell transplantation (HSCT) has a role in the management of selected patients,[2,5] and non-myeloablative allogeneic HSCT has also been investigated.[2,7,9,10] Although many patients are too old to tolerate the high-dose therapy,[5,10] candidacy for autologous HSCT is a factor in the choice of initial therapy;[7] it is recommended that exposure to alkylating agents and nucleoside analogues be limited if HSCT is to be considered.[2,3,6,7,9] Alternatively, stem cells may be collected before treatment with these drugs.[2] A retrospective study[11] found that use of nucleoside analogues was associated with an increased risk of disease transformation to high-grade lymphoma.

When disease stabilises, treatment may be stopped and begun again on ***relapse***.[3] The choice of therapy depends on the first-line treatment used, the quality and duration of response, and other variables such as patient age, tolerance of therapy, and candidacy for HSCT.[7] Initial treatments that produce relatively long responses (6 to 12 months) may be repeated; alternate first-line agents or combination regimens are recommended for earlier progressions.[3,7] Appropriate second- or third-line choices include bortezomib, thalidomide (with or without dexamethasone), HSCT, or alemtuzumab,[3,7] although some consider the use of the latter unacceptable in this context because of high treatment-related mortality.[8] Lenalidomide is under investigation for Waldenström's macroglobulinaemia[3,8,9] and small studies have reported benefit with interferon alfa.[2,6,10]

Plasmapheresis is indicated for the treatment of symptomatic hyperviscosity,[1,3-6,10] and high-dose corticosteroids may be used to treat systemic vasculitis arising from deposition of paraproteins.[6] Splenectomy, although rarely indicated, may be used to manage painful splenomegaly and hypersplenic syndromes.[1,6]

1. Desikan R, *et al.* Waldenström's macroglobulinaemia: current therapy and future approaches. *BioDrugs* 2002; **16**: 201–7.
2. Dimopoulos MA, *et al.* Diagnosis and management of Waldenstrom's macroglobulinemia. *J Clin Oncol* 2005; **23**: 1564–77.
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: multiple myeloma (version 2.2009). Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf (accessed 17/04/09)
4. Rajkumar SV, *et al.* Monoclonal gammopathy of undetermined significance, Waldenström macroglobulinemia, AL amyloidosis, and related plasma cell disorders: diagnosis and treatment. *Mayo Clin Proc* 2006; **81**: 693–703. Correction. *ibid.*; 1509.
5. Johnson SA, *et al.* Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Guidelines on the management of Waldenström macroglobulinaemia. *Br J Haematol* 2006; **132**: 683–97. Also available at: http://www.bcshguidelines.com/pdf/waldenstroms_151106.pdf (accessed 21/04/09)
6. Gertz MA. Waldenström's macroglobulinemia: a review of therapy. *Leuk Lymphoma* 2002; **43**: 1517–26.
7. Dimopoulos MA, *et al.* Update on treatment recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia. *J Clin Oncol* 2009; **27**: 120–6.
8. Leleu X, *et al.* Update on therapeutic options in Waldenström macroglobulinemia. *Eur J Haematol* 2009; **82**: 1–12.
9. Vijay A, Gertz MA. Waldenström macroglobulinemia. *Blood* 2007; **109**: 5096–5103.
10. Johnson SA, *et al.* Waldenström's macroglobulinaemia. *Blood Rev* 2002; **16**: 175–84.
11. Leleu X, *et al.* Increased incidence of transformation and myelodysplasia/acute leukemia in patients with Waldenström macroglobulinemia treated with nucleoside analogs. *J Clin Oncol* 2009; **27**: 250–5.

PLASMA CELL NEOPLASMS. Multiple myeloma. Multiple myeloma (myelomatosis) is a lymphoproliferative disorder of B-cell origin, involving the development of an abnormal plasma-cell precursor. It occurs mainly in the elderly, and accounts for about 1% of all malignancies. It is more common in black than in white patients and in men than in women.

The proliferation of the abnormal clone tends to suppress normal haematopoiesis, resulting in anaemia and immunosuppression, with an increased risk of serious infection. Perhaps the most characteristic complication, however, is skeletal destruction, apparently due to release of an osteoclast stimulating factor, resulting in osteoporosis, lytic lesions and fractures, and bone pain, as well as consequent hypercalcaemia. In addition, the plasma cells release large quantities of monoclonal immunoglobulins, known as paraproteins, which can produce a hyperviscosity syndrome and in some cases may interfere with platelet function. Renal failure of various causes and neurological problems due to compression are also common.

Multiple myeloma is not curable with presently-available treatment, and **therapy** is concerned with prolongation of survival and alleviation of symptoms.[1,2] Those patients with stable, indolent or smouldering myeloma, or benign monoclonal gammopathy, are followed carefully but not treated until overt progressive disease occurs.[1-3] Early treatment may inhibit disease progression, but overall survival and response rates are not affected.[4]

The treatment of overt disease depends on eligibility for haematopoietic stem cell transplantation (HSCT) and risk assessment.[3] High-dose chemotherapy combined with autologous HSCT improves response rate, event-free survival, and overall survival compared with standard chemotherapy.[6] Evidence for these benefits is strongest for patients younger than 55 years old.[7] Although some[8] consider standard-dose chemotherapy to be the preferred initial treatment in patients older than 70 years, other reviews[6,9] have concluded that autologous HSCT is safe for the majority of patients older than 65 years, and guidelines have suggested its consideration in this group[2] if they have good functional status and limited comorbidity. With tandem transplantation, patients receive a second planned autologous HSCT,[1,10] since it was shown that patients who did not enter remission after one transplant could achieve remission after another.[11] Some recommend tandem transplants in those who do not have at least a very good partial response after the first,[12] and as such, some centres routinely collect enough stem cells for two transplants.[1,10,13,14] However, the benefit of a second transplantation has been challenged by the high efficacy of novel induction agents followed by one autologous HSCT, with these agents then used as consolidation therapy.[15] Allogeneic HSCT has been used for multiple myeloma, sometimes after autologous HSCT, but few patients are suitable, and transplant-related morbidity and mortality are high with conventional myeloablative chemotherapy regimens; non-myeloablative regimens (miniallogeneic HSCT) are under investigation.[5,10-13]

Although the VAD regimen (vincristine, doxorubicin, and dexamethasone) was used for many years as induction therapy, newer regimens are now recommended in preference.[3,5,10,15,16] Dexamethasone, which may be used alone, forms part of most recommended regimens.[1,16] Options include thalidomide plus dexamethasone, lenalidomide plus dexamethasone, and bortezomib-based regimens.[1,3,5,10,12,15,16] Although considered by some to be less favourable than the newer regimens,[16] the DVD regimen uses liposomal doxorubicin instead of doxorubicin in the VAD regimen.[1,16]

Peripheral stem cells are collected after giving high-dose cyclophosphamide and granulocyte colony-stimulating factor.[6,8] Although some suggest the use of alkylating agents and interferon alfa after stem cell collection,[8] earlier alkylator or nitrosurea therapy interferes with stem cell mobilisation,[1,10,12,13] and can result in poor engraftment.[7,9] The standard conditioning regimen before transplantation is considered to be high-dose melphalan.[2,3,6,8-10,13] Total body irradiation is no longer recommended, as combined with lower dose melphalan, it resulted in higher toxicity and no significant survival benefit compared with high-dose melphalan alone.[6,7,9] Similarly, stem cells are not purged of contaminating myeloma cells as a randomised study[17] showed no benefit.

Where transplantation is infeasible or inappropriate, ***chemotherapy*** may be given to induce remission and prolong survival. The standard first-line regimen has long been a combination of oral melphalan and corticosteroids, usually prednisolone or prednisone.[1-3,9,10,13-16] This MP regimen produces an objective response in about half of all patients, and prolongs median survival to between 2 and 3 years.[9] The contribution of corticosteroids to the regimen has been controversial although a trend towards increased survival was noted[6] compared with melphalan alone, and high-dose dexamethasone given alone has been reported to be effective in producing remissions.[9] Cyclophosphamide is active,[6] and has been substituted for melphalan.[2] The addition of thalidomide to melphalan and prednisone (the MPT regimen) has led to better response rates and progression-free survival, and it is recommended as standard induction for elderly patients ineligible for HSCT;[3,5] however, toxicity is higher than with the MP regimen.[12,16,18] Similarly, the MPV or MPB regimen (bortezomib added to melphalan and prednisone) was found to have improved response rates and overall survival compared with MP alone,[1,5,16] and it is also a recommended induction regimen. Lenalidomide added to melphalan plus prednisone is another option.[1] Other induction regimens include bortezomib plus dexamethasone, thalidomide plus dexamethasone, lenalidomide plus dexamethasone, the VAD or DVD regimens,[1] or bendamustine plus prednisone.

Maintenance chemotherapy with thalidomide has been used after autologous HSCT,[1,19] and may be offered to patients not achieving a complete response after tandem HSCT,[15,18] although optimal duration of maintenance therapy is not known.[3,19] Bortezomib and lenalidomide can also be used for maintenance,[1,12] although there may be an increased risk of secondary cancer with the latter. Other options include thalidomide plus prednisone.[1] Corticosteroids or interferon do not appear to provide significant clinical benefit,[3,10,15,19] although some guidelines suggest second-line use.[1]

In patients who fail to respond to initial treatment, or who subsequently ***relapse***, various regimens may be tried.[1] If relapse occurs more than 6 months after initial induction therapy, re-use of the initial regimen is recommended. However, a different regimen should be considered if disease recurs within 6 months of completing induction therapy.[1,16] Good responses have been achieved with bortezomib,[1,2] and it is recommended either as monotherapy, or with dexamethasone, or liposomal doxorubicin.[1,16] Other regimens include:[1,16]

- monotherapy with either bendamustine, thalidomide, lenalidomide, pomalidomide, high-dose cyclophosphamide, or carfilzomib
- dexamethasone plus either thalidomide, lenalidomide, or pomalidomide
- dexamethasone plus bortezomib and either thalidomide or lenalidomide
- dexamethasone plus cyclophosphamide and either bortezomib or lenalidomide
- dexamethasone plus lenalidomide and bendamustine
- bortezomib plus vorinostat
- cyclophosphamide-VAD
- DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin)
- DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide)

For further information on common chemotherapy regimens, see Table 1, p. 719.

Although chemotherapy aimed at the myelomatous clone will produce symptomatic relief as disease is brought under control, ***supportive and symptomatic care*** is also important. Bisphosphonates such as clodronate, pamidronate, and zoledronate have been found to be effective in reducing skeletal complications,[20,21] and are recommended in those patients with bone disease.[1,2,14,22] Some recommend that bisphosphonate therapy be stopped after 2 years in patients with responsive or stable disease.[22,23] (For further discussion, see Malignant Neoplasms of the Bone, under Bisphosphonates, p. 1174.1.) Radiotherapy is used for impending fracture or impending spinal cord compression, and is often effective in relieving uncontrolled bone pain.[1,9]

Erythropoietin therapy can improve anaemia and reduce the need for transfusion.[1,6,8,9] A high fluid intake is essential in patients with renal dysfunction or hypercalcaemia (for the appropriate management of the latter, see p. 1778.1). Vigorous antibacterial treatment may be needed if infection occurs (see Infections in Immunocompromised Patients, p. 186.3) and plasma exchange may alleviate the hyperviscosity syndrome.[1,8,10]

Drugs under investigation for the treatment of multiple myeloma include oblimersen, vorinostat, and arsenic trioxide.[13,14]

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: multiple myeloma (version 1.2013). Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf (accessed 08/11/12)
2. Smith A, *et al.* UK Myeloma Forum; Nordic Myeloma Study Group; British Committee for Standards in Haematology. Guidelines on the diagnosis and management of multiple myeloma 2005. *Br J Haematol* 2006; 132: 410–51. Also available at: http://www.bcshguidelines.com/pdf/multiplemyeloma0206.pdf (accessed 23/04/09)
3. Harousseau J-L, Dreyling M. ESMO Guidelines Working Group. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v155–v157. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v155.full.pdf+html (accessed 13/10/10)
4. He Y, *et al.* Early versus deferred treatment for early stage multiple myeloma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 23/04/09).
5. Kyle RA, Rajkumar SV. Multiple myeloma. *Blood* 2008; 111: 2962–72.
6. Kumar A, *et al.* Management of multiple myeloma: a systematic review and critical appraisal of published studies. *Lancet Oncol* 2003; 4: 293–304.
7. Imrie K, *et al.* The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. *Ann Intern Med* 2002; 136: 619–29.
8. Kyle RA. Update on the treatment of multiple myeloma. *Oncologist* 2001; 6: 119–24.
9. Rajkumar SV, *et al.* Current therapy for multiple myeloma. *Mayo Clin Proc* 2002; 77: 813–22.
10. Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc* 2005; 80: 1371–82.
11. Sirohi B, Powles R. Multiple myeloma. *Lancet* 2004; 363: 875–87.
12. Kumar SK, *et al.* Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc* 2009; 84: 1095–1110.
13. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med* 2004; 351: 1860–73. Correction. *ibid.* 2005; 352: 1163.
14. Schwartz RN, Vozniak M. Current and emerging treatments for multiple myeloma. *J Manag Care Pharm* 2008; 14 (suppl S): S12–S18.
15. San-Miguel J, *et al.* Individualizing treatment of patients with myeloma in the era of novel agents. *J Clin Oncol* 2008; 26: 2761–6.
16. Saad AA, *et al.* Treatment of multiple myeloma in the targeted therapy era. *Ann Pharmacother* 2009; 43: 329–38.
17. Stewart AK, *et al.* Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: results of a multicenter randomized controlled trial. *J Clin Oncol* 2001; 19: 3771–9.
18. Palumbo A, *et al.* Thalidomide for treatment of multiple myeloma: 10 years later. *Blood* 2008; 111: 3968–77.
19. Harousseau JL. Maintenance treatment in multiple myeloma. *Ann Oncol* 2008; 19 (suppl 4): iv54–iv55.
20. McCloskey EV, *et al.* The clinical and cost considerations of bisphosphonates in preventing bone complications in patients with metastatic breast cancer or multiple myeloma. *Drugs* 2001; 61: 1253–74.
21. Mhaskar R, *et al.* Bisphosphonates in multiple myeloma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 02/06/10).
22. Kyle RA, *et al.* 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/25/17/2464 (accessed 23/04/09)
23. Lacy MQ, *et al.* Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. *Mayo Clin Proc* 2006; 81: 1047–53.

Malignant effusions. The amount of interstitial fluid is normally regulated by a complex equilibrium between capillary filtration, osmotic pressure, and physical hydrostatic or hydraulic forces. Malignant neoplasms can disturb this equilibrium by obstruction of capillary or lymphatic drainage as well as causing active exudation of additional fluid after metastatic implantation. Malignant effusions are associated most often with lung, breast, and ovarian malignancies and lymphomas. Symptoms vary, and the fluid build-up may be asymptomatic; both pleural and pericardial effusions can produce cough, pleuritic chest pain, and dyspnoea and pericardial effusions may progress to cardiac tamponade. Peritoneal effusions may lead to malignant ascites.

The main aim of **treatment** for malignant effusions is effective palliation of symptoms, and depends in part on the tumour type, patient performance status, and prognosis.[1-4] If the tumour is chemosensitive, systemic chemotherapy may resolve the effusion.[1,4,5] Similarly, radiotherapy can be effective for pericardial effusions associated with radiosensitive tumours.[3] Simple fluid drainage (thoracentesis, paracentesis, or pericardiocentesis) will relieve symptoms until fluid build-up recurs,[2,3] and in patients with very poor prognosis and a limited life expectancy, may suffice for palliation.[4] Use of an indwelling pleural catheter allows convenient and minimally invasive fluid drainage in patients with pleural effusions, and may result in spontaneous pleurodesis.[4] In malignant ascites, paracentesis is usually effective temporarily; evidence for the value of diuretics is weak, but spironolactone may be of benefit in some patients, either alone or with a loop diuretic.[6] In other patients with refractory tumours, fluid drainage followed by sclerotherapy is likely to be preferred.

The principle of *sclerotherapy* is the instillation of an irritant agent into the pleural or pericardial cavity to promote inflammatory and fibrotic changes which result in the membranes adhering together and abolition of the space between the membranes in which fluid accumulates. When this is done to treat pleural effusions (pleurodesis) success is dependent on adequate fluid drainage beforehand and full re-expansion of the lung to bring the pleural surfaces together. Intrapleural thrombolytics such as streptokinase have been used to improve fluid drainage in cases of loculation of the effusion.[1,7]

Many drugs have been used for sclerotherapy, and the most common are a tetracycline (doxycycline or tetracycline), bleomycin, or talc. The choice between these three remains controversial, and opinions on the preferred option differ.[1,2,4,7,8] However, a systematic review[9] found talc to be the sclerosant of choice for malignant pleural effusions. Other sclerosants that have been used, with varying reported rates of success, include interferon alfa, mepacrine, mitoxantrone, picibanil, povidone-iodine, silver nitrate, *Corynebacterium parvum*, and *Staphylococcus aureus* superantigen.[8] After drainage of the effusions the sclerosant is instilled in a small volume (50 to 100 mL) of liquid through the drainage tube.[5] Talc may also be given as a powder insufflation (rather than slurry), but this involves a surgical procedure under general anaesthesia. Sclerotherapy results in painful inflammation, and local anaesthetics or analgesics should be given.[2,7] For patients who fail sclerotherapy, or for whom this is not considered suitable, there are various surgical options to manage effusions.[1,3,6]

1. Antunes G, *et al.* British Thoracic Society. BTS guidelines for the management of malignant pleural effusions. *Thorax* 2003; 58 (suppl 2): ii29–ii38. Also available at: http://thorax.bmj.com/cgi/reprint/58/suppl_2/ii29.pdf (accessed 27/04/09)
2. Heffner JE, Klein JS. Recent advances in the diagnosis and management of malignant pleural effusions. *Mayo Clin Proc* 2008; 83: 235–50.
3. Karam N, *et al.* Diagnosis and management of chronic pericardial effusions. *Am J Med Sci* 2001; 322: 79–87.
4. Uzbeck MH, *et al.* Management of malignant pleural effusions. *Adv Therapy* 2010; 27: 334–47.
5. Khaleeq G, Musani AI. Emerging paradigms in the management of malignant pleural effusions. *Respir Med* 2008; 102: 939–48.
6. Becker G, *et al.* Malignant ascites: systematic review and guideline for treatment. *Eur J Cancer* 2006; 42: 589–97.
7. Spector M, Pollak JS. Management of malignant pleural effusions. *Semin Respir Crit Care Med* 2008; 29: 405–13.
8. Heffner JE. Diagnosis and management of malignant pleural effusions. *Respirology* 2008; 13: 5–20.
9. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 27/04/09).

Malignant neoplasms of the bladder. Cancer of the bladder is the fourth or fifth most common cancer in Europe and the USA, where over 90% of bladder cancers are transitional cell in type. About two-thirds of all cases occur in men, and the median age at diagnosis is 65 years. Known risk factors include tobacco smoking, exposure to chemicals such as aniline dyes, and previous radiotherapy; in countries where it is endemic, schistosomiasis is also an important cause of squamous cell bladder cancer. Most patients present with haematuria; there may also be urinary frequency or dysuria.

Urothelial tumours fall into 3 major groups, non-invasive, invasive, and metastatic, which differ in prognosis and management.[1] About 70% of cases are non-muscle-invasive (superficial), 25% are muscle-invasive, and 5% are metastatic.[2]

The **non-muscle invasive** tumours are divided into low-grade carcinomas or papillomas confined to the mucosa (Ta), those that have invaded the submucosa (T1), and high-grade carcinoma *in situ* (CIS).[1,2] The standard initial treatment for primary or recurrent disease is surgery, in the form of transurethral resection (TUR). In an attempt to prolong remission and reduce the recurrence rate antineoplastics are instilled into the bladder soon after TUR (prophylactic or adjuvant intravesical therapy).[1-3] Effective agents include mitomycin, doxorubicin, epirubicin, and thiotepa; efficacy is similar in terms of outcome and choice depends on adverse effects.[2,4] The immunomodulator BCG is also used intravesically, with good results.[2] A single dose of intravesical chemotherapy is usually given within 24 hours of TUR, which may be sufficient for low-grade Ta tumours.[1,3,4] The need for further adjuvant intravesical therapy depends on the patient's prognosis and risk of tumour recurrence.[3,4] The ideal duration and intensity of the schedule remains undefined.[4]

Chemotherapy reduces recurrence, but not progression,[2,4] and BCG is considered by some to be the preferred option for high-grade tumours or those at high risk of progression.[1,3] Mitomycin is an alternative.[1] BCG is also generally preferred to antineoplastics for CIS,[1,5] and may be considered as maintenance therapy in those showing a complete response.[1,5] Those with recurrent or persistent disease can be given a second course of BCG or mitomycin.

If residual disease is still present, cystectomy should be considered; intravesical therapy with a different agent (mitomycin, valrubicin, or BCG plus interferon alfa) is an alternative to cystectomy. Radical cystectomy is recommended if disease progresses.[1] Photodynamic therapy using porfimer sodium or 5-aminolevulinic acid has also been investigated.[6]

Management of **muscle-invasive** bladder cancer that has not yet metastasised is a matter of some controversy, but conventional therapy has revolved around radical surgery.[1,2,7] Patients are usually also given systemic chemotherapy before (neoadjuvant) or after (adjuvant) complete cystectomy, in an attempt to prolong survival.[1,5,7] Neoadjuvant chemotherapy apparently favours survival,[3] there is insufficient evidence for routine use of adjuvant chemotherapy,[3,5] and use of the latter usually depends on prognosis, and whether or not neoadjuvant chemotherapy was given.[1] Some recommend considering the use of adjuvant chemotherapy in node-positive patients.[3] Selected patients may be considered for bladder-sparing approaches such as partial cystectomy followed by radiotherapy, chemotherapy, or both.[1,7]

The optimal chemotherapy regimen remains to be defined but regimens incorporating cisplatin, gemcitabine, or methotrexate are usually preferred. Typical regimens include gemcitabine plus cisplatin, CMV (cisplatin, methotrexate, and vinblastine), or MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin).[1,3] For further information on common chemotherapy regimens, see Table 1, p. 719.

Patients with unresectable or **metastatic** disease, or who subsequently develop metastatic disease, are usually treated with systemic chemotherapy with or without radiotherapy.[1,3] For patients with good prognosis, a combination regimen such as MVAC or CMV may be used. Various combinations of gemcitabine, taxanes, and cisplatin have shown clinical benefit,[1,7] and gemcitabine plus cisplatin has been shown to provide similar survival advantage to MVAC with better tolerability: some now consider that it should be the preferred regimen in advanced disease.[1,8] Taxane-based regimens may be considered in patients unable to receive cisplatin.[1] No standard second-line therapy exists and participation in clinical studies is encouraged; depending on first-line therapy, palliative options include monotherapy with bleomycin, fluorouracil, cisplatin, carboplatin, docetaxel, doxorubicin, gemcitabine, ifosfamide, methotrexate, paclitaxel, pemetrexed, or vinblastine.[1] Vinflunine is an option for those who progress on first-line platinum-based therapy.[3] Newer drugs under investigation include epidermal growth factor receptor inhibitors such as cetuximab and inhibitors of angiogenesis such as bevacizumab and sunitinib.[9]

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: bladder cancer including upper tract tumors and urothelial carcinoma of the prostate (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf (accessed 02/06/10)
2. Parekh DJ, *et al.* Superficial and muscle-invasive bladder cancer: principles of management for outcomes assessments. *J Clin Oncol* 2006; 24: 5519–27.
3. Bellmunt J, *et al.* ESMO Guidelines Working Group. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v134–v136. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v134.full.pdf+html (accessed 14/10/10)
4. Babjuk M, *et al.* European Association of Urology. Guidelines on TaT1 (non-muscle invasive) bladder cancer (updated March 2009). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full_TaT1_BC.pdf (accessed 21/08/09)
5. Scottish Intercollegiate Guidelines Network. Management of transitional cell carcinoma of the bladder (guideline number 85, issued December 2005). Available at: http://www.sign.ac.uk/pdf/sign85.pdf (accessed 11/06/08)
6. Hall MC, *et al.* Bladder cancer clinical guideline update panel. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. Available at: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bladcan07/chapter1.pdf (accessed 13/07/10)
7. Stenzl A, *et al.* European Association of Urology. Guidelines on bladder cancer: muscle-invasive and metastatic (updated March 2008). Available at: http://www.uroweb.org/fileadmin/tx_eauguidelines/2008/Full/Muscle-Invasive_BC.pdf (accessed 01/12/08)
8. Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. *J Clin Oncol* 2006; 24: 5545–51.
9. Agarwal N, Hussain M. Management of bladder cancer: current and emerging strategies. *Drugs* 2009; 69: 1173–87.

Malignant neoplasms of the bone. Skeletal complications may result from primary cancers or from bone metastases secondary to other cancers. Primary bone malignancies are rare, and are usually sarcomas (see Bone Sarcoma, p. 717.3). Multiple myeloma (p. 699.2) also produces bone involvement. Metastatic bone disease is a common problem with cancers of the breast, prostate, and lung.

Skeletal malignancies cause considerable morbidity, including cancer pain (the general management of which is discussed on p. 7.1) and also result in immobility, bone fractures, bone-marrow infiltration, spinal cord or nerve root compression, and hypercalcaemia.[1-3] The most common sites of metastasis are the axial skeleton including the spine and ribs, and the proximal ends of the long bones.

The goals of management of **bone metastases** are essentially palliative: to relieve pain, preserve and restore function, and to reduce the risk of fracture and stabilise the

skeleton. Treatment often requires a multi-disciplinary approach that includes radiation, surgery, and systemic therapy.[2,4-6]

Radiotherapy provides excellent palliation of localised metastatic bone pain,[2,3] with responses occurring in over 70% of patients treated with external beam irradiation. Radiation can also be used to prevent or treat fractures, or to prevent spinal cord compression.[2] Bone-seeking radiopharmaceuticals such as rhenium-186, phosphorus-32, samarium-153, or strontium-89 may be used as an alternative for pain palliation, or as an adjunct to external beam radiotherapy.[2,4,5,7] Radiofrequency ablation has also been reported to be effective for pain, but is contra-indicated in the spine owing to proximity of the spinal cord and nerve roots.[3]

Structural weakness due to extensive bone loss may require ***structural support***; external fixation with cast or brace immobilisation is an option. Internal surgical fixation or stabilisation can treat or prevent fractures.[2] Surgical excision and reconstruction with methylmethacrylate bone cement may also be required. Postoperative radiotherapy is used to prevent fractures[2] and improve mobility.[3]

Bone metastases cause local osteolysis and various bone-modifying agents (such as the bisphosphonates and denosumab) that ***inhibit bone resorption*** have been tried, not only to correct hypercalcaemia of malignancy (p. 1167.2), but also to relieve bone pain and reduce the risk of fractures. Bisphosphonates are of benefit in patients with severe bone pain that is too widespread for local use of radiotherapy and does not respond to other analgesics.[8] Reviews[9,10] concluded that bisphosphonates significantly decrease skeletal morbidity, except for spinal cord compression. Benefits in terms of skeletal events are only seen after about 6 months of treatment.[9] Despite the integration of bisphosphonate use into clinical practice for bone metastases, the optimal timing, schedule, or duration of treatment remains to be determined.[3,6,9,11,12] It has been suggested that bone-modifying treatment should start when bone metastases are diagnosed and continue until no longer clinically relevant; they do not affect survival.[10,13] While some continue bisphosphonate treatment despite disease progression, others advocate changing to a more potent bisphosphonate, or stopping treatment altogether.[9] There are no data about the consequences of stopping bone-modifying treatment after one or more skeletal-related events. Starting bone-modifying agents in women with breast cancer without evidence of bone metastases is not recommended.[13] There is little evidence supporting the efficacy of one bone-modifying agent over another;[13] denosumab and the bisphosphonates clodronate, ibandronate, pamidronate, and zoledronate have all been used.[1,2,6,9,12,13] Of the bisphosphonates, those given intravenously have shown a more significant reduction in skeletal-related events than those given orally.[3,10] Denosumab has shown some benefit over zoledronate at delaying or preventing skeletal events in advanced breast cancer,[14] and was noninferior to zoledronate in other cancers or multiple myeloma.[15]

There is much interest in the use of bisphosphonates to *prevent* the development of bone metastases.[11,12] However, preliminary evidence of their efficacy was conflicting.

Systemic ***antineoplastic therapy*** should also be given if the primary tumour is chemosensitive. Endocrine treatment is usually preferred for patients with breast and prostatic cancers,[2] and can produce useful control of symptoms from bone metastases.

Atrasentan is a new drug under investigation.[1,6]

1. Cremers S, Garnero P. Biochemical markers of bone turnover in the clinical development of drugs for osteoporosis and metastatic bone disease: potential uses and pitfalls. *Drugs* 2006; 66: 2031–58.
2. Berenson JR, *et al.* Treatment strategies for skeletal complications of cancer. *Cancer Biol Ther* 2006; 5: 1074–7.
3. Wilkinson AN, *et al.* Managing skeletal related events resulting from bone metastases. Abridged version: *BMJ* 2008; 337: a2041. Full version: http://www.bmj.com/cgi/section_pdf/337/nov03_1/a2041.pdf (accessed 13/01/09)
4. McEwan AJB. Use of radionuclides for the palliation of bone metastases. *Semin Radiat Oncol* 2000; 10: 103–114.
5. Dewar JA. Managing metastatic bone pain. *BMJ* 2004; 329: 812–13.
6. Petrut B, *et al.* Pharmacotherapy of bone metastases in breast cancer patients. *Expert Opin Pharmacother* 2008; 9: 937–45.
7. Finlay IG, *et al.* Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol* 2005; 6: 392–400.
8. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 12/05/05).
9. Gainford MC, *et al.* Recent developments in bisphosphonates for patients with metastatic breast cancer. *BMJ* 2005; 330: 769–73.
10. Ross JR, *et al.* Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. Abridged version: *BMJ* 2003; 327: 469. Full version: http://www.bmj.com/cgi/reprint/327/7413/469 (accessed 12/06/08) Correction. *ibid.* 2004; 328: 384.
11. Aapro M, *et al.* Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol* 2008; 19: 420–32.
12. Michaelson MD, Smith MR. Bisphosphonates for treatment and prevention of bone metastases. *J Clin Oncol* 2005; 23: 8219–24.
13. Van Poznak CH, *et al.* American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *J Clin Oncol* 2011; 29: 1221–7.
14. 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.
15. Henry DH, *et al.* Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011; 29: 1125–32.

Malignant neoplasms of the brain. Metastatic brain cancer is the most common cause of intracranial tumours in adults, being up to ten times more common than primary brain tumours.[1] The cancers that most often metastasise to the brain are lung cancer, breast cancer, and melanoma,[1] as well as colorectal cancer, renal cell carcinoma, and adenocarcinoma.[2,3] CNS involvement in patients with acute leukaemia (see Acute Lymphoblastic Leukaemia, p. 692.3) or lymphoma (see CNS Lymphomas, p. 698.1) is also quite common. The frequency and natural history of *primary* brain tumours differ between children and adults. In adults, they are usually gliomas,[4] which are classified histologically into astrocytomas, oligodendrogliomas, and oligo-astrocytomas.[5] Astrocytomas are defined by grades: I (pilocytic), II (diffuse), III (anaplastic astrocytoma), and IV (glioblastoma multiforme), the latter two of which are the most common and are considered malignant.[4,6] Low-grade astrocytomas[7] and malignant medulloblastomas are the commonest primary brain tumours in children.[8]

The symptoms of primary and metastatic cranial neoplasms are those of local pressure and damage to the brain (such as focal seizures and neurological defects), of displacement of brain structures (like oculomotor paresis with tentorial herniation), and of raised intracranial pressure (such as impaired consciousness and papilloedema). Memory loss and personality changes may occur, and headache, nausea and vomiting are common symptoms.

The standard therapy for **primary brain tumours** involves surgery and radiotherapy.[4,5,8,9] General medical management includes control of seizures with antiepileptics, the use of corticosteroids such as dexamethasone to control peritumoral oedema, anticoagulation to manage venous thromboembolism, and treatment for fatigue.[4,6]

Surgery is generally used to relieve compression and cerebral oedema, establish diagnosis, decrease the need for corticosteroids, and where feasible resect as much of the tumour as possible.[1,4,6,10] Progress in image-guided resection has improved safety, and although some consider it to have increased the extent of resection,[4,8] others note it has not been as beneficial as expected for gliomas.[10] The value of surgery in prolonging survival is controversial;[4,10] there is some evidence that extensive resection prolongs survival,[1,4] but this may be biased[10] by the selection of younger fitter patients for surgery.

Adjuvant *radiotherapy* is widely used after surgical resection for malignant tumours in adults and children.[1,4-6,8,10] There is no consensus on the timing of the start of radiotherapy.[10] Strategies to increase the dose of radiation delivered to the tumour by using brachytherapy (radioactive implants) or stereotactic radiosurgery (a technique using highly focused beams of radiation) have failed to improve survival.[4]

Local chemotherapy using biodegradable polymers impregnated with carmustine, placed intraoperatively into the surgical cavity, has been shown to improve survival in patients with either newly diagnosed or recurrent malignant glioma.[1,9,10] While some recommend this after maximal resection in high-grade disease,[1] others consider it to have only marginal benefit over adjuvant radiotherapy alone.[6]

The role of adjuvant *systemic chemotherapy* for primary brain malignancies has been unclear, in part because of the difficulty in finding drugs that can cross the blood-brain barrier; until the advent of temozolomide, treatment was usually based on nitrosoureas such as carmustine and lomustine.[1,3,11] The PCV regimen (procarbazine, lomustine, and vincristine) has been widely used in the treatment of gliomas after surgical resection and radiation therapy.[5,10] The value of this regimen was called into question by a large randomised study of adjuvant PCV plus radiotherapy versus radiotherapy alone in high-grade astrocytoma, in which PCV provided no additional survival benefit.[12] However, a meta-analysis including this and 11 smaller studies found that giving some form of adjuvant chemotherapy (usually based on nitrosoureas) modestly improved survival in adults with high-grade glioma.[13] Temozolomide, an oral alkylating agent, was initially used for the treatment of recurrent gliomas.[5] Its use during and after radiotherapy in newly diagnosed glioblastoma, usually after debulking surgery, has improved survival,[14] and this regimen has largely replaced the nitrosoureas in the management of glioma.[1,4,6,9-11,15,16] For patients who progress after chemotherapy, there is no established second-line regimen.[6] Second-line agents include irinotecan, cisplatin or carboplatin, and platinum-based regimens.[1,5] Bevacizumab plus irinotecan may be tried for recurrent disease.[1,16]

In *children*, the extent of resection correlates with survival and maximal safe resection is a major therapeutic goal.[17,18] The biology of brain tumours in very young children appears to differ from that seen in older children.[17,19] Chemotherapy is used to delay radiotherapy, reduce its dose or frequency, or even eliminate the need for it altogether, as it can cause neurodevelopmental damage.[7,17-21] Generally, in children older than 3 years, surgery can be followed by a reduced dose of craniospinal irradiation, while although those younger than 3 years are considered high-risk, radiotherapy is avoided if at all possible in this group.[18]

Common combination chemotherapy regimens used in children have included cisplatin or carboplatin, cyclophosphamide, etoposide, ifosfamide, lomustine, methotrexate, procarbazine, topotecan, vincristine, or vinblastine.[17,19,20] Temozolomide and oxaliplatin warrant further investigation.[19] Different tumour types vary in their sensitivity to chemotherapy.

Autologous haematopoietic stem cell transplantation (p. 1937.1) is also used for various paediatric brain tumours to limit the adverse effects of chemotherapy, and to maximise the dose of chemotherapy that can be used;[17-21] results have been conflicting and appear to depend on the type of tumour. Preparative regimens used have been based on thiotepa, busulfan, or melphalan, as well as high-dose combination chemotherapy regimens.[17,20,21] Intrathecal chemotherapy with drugs such as methotrexate, is also used.[19]

Since present regimens for primary brain tumours are far from optimal, alternatives continue to be tried.[1] Strategies include optimising current regimens, investigating different combinations of drugs, as well as methods to improve delivery across the blood-brain barrier.[5] Other treatments investigated include single or multitargeted kinase inhibitors, ligand-toxin conjugates, antisense oligonucleotides, and gene therapy.

Whole-brain radiation therapy (WBRT) is the common choice for most patients with **brain metastases**.[1,2,22] Surgery plus WBRT may be suitable for those with a single brain metastasis, especially if prognosis is favourable and systemic disease controlled.[1,2] Stereotactic radiosurgery (with or without WBRT) may be an alternative for patients with isolated metastases and for whom surgery is not an option.[1,2,22,23]

Chemotherapy has traditionally had a limited role in the treatment of brain metastases.[2,23] The blood-brain barrier was thought to limit delivery of drugs to the site of disease, especially those drugs that are large and less lipid-soluble. However, the blood-brain barrier appears to be partially dysfunctional in cerebral metastatic disease, and systemic therapy has led to responses in patients, especially in those who are chemotherapy-naive or who have not been heavily pre-treated.[2,3,22,23] It has been noted that the use of corticosteroids should be limited as they may restore an otherwise disrupted blood-brain barrier.[3] The chemosensitivity of the primary tumour may also be an important factor in determining response,[2,3,22,23] although many tumours that metastasise to the brain are not very chemosensitive.[1] In addition, metastases may progress and be resistant to further therapy simply due to prior exposure to the drugs used.[3,22] Thus the choice of drug needs to take previous treatment regimens into consideration.[3] Aside from common chemotherapy regimens used to treat the primary tumour (see Table 1, p. 719), other agents used for brain metastases include temozolomide (with or without radiotherapy), capecitabine, high-dose methotrexate, gefitinib, irinotecan, and topotecan. Radiosensitisers used include the platinum analogues and motexafin gadolinium.[1-3,22,23]

A brain cancer vaccine (DCVax-Brain) is also being investigated.

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: central nervous system cancers (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf (accessed 02/06/10)
2. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. *J Clin Oncol* 2005; 23: 6207–19.
3. Shah GD, Abrey LE. Chemotherapy for brain metastases: breast, gynecologic and non-melanoma skin malignancies. *Cancer Treat Res* 2007; 136: 185–97.
4. Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med* 2008; 359: 492–507. Correction. *ibid.*: 877.
5. Mathieu D, Fortin D. Chemotherapy and delivery in the treatment of primary brain tumors. *Curr Clin Pharmacol* 2007; 2: 197–211.
6. Stupp R, *et al.* ESMO Guidelines Working Group. High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v190–v193. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v190.full.pdf+html (accessed 14/10/10)
7. Karajannis M, *et al.* Treatment of pediatric brain tumors. *J Cell Physiol* 2008; 217: 584–9.
8. Pizer B, Clifford S. Medulloblastoma: new insights into biology and treatment. *Arch Dis Child Educ Pract Ed* 2008; 93: 137–44.
9. Reardon DA, *et al.* Recent advances in the treatment of malignant astrocytoma. *J Clin Oncol* 2006; 24: 1253–65.
10. Aoki T, *et al.* Management of glioblastoma. *Expert Opin Pharmacother* 2007; 8: 3133–46.
11. Padul CE, *et al.* Cytotoxic chemotherapeutic management of newly diagnosed glioblastoma multiforme. *J Neurooncol* 2008; 89: 339–57.
12. Medical Research Council Brain Tumour Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council Trial. *J Clin Oncol* 2001; 19: 509–18.

13. Glioma Meta-analysis Trialists (GMT) Group. Chemotherapy for high-grade glioma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/05/05).
14. Stupp R, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; 352: 987–96.
15. van den Bent MJ, *et al.* Recent developments in the use of chemotherapy in brain tumours. *Eur J Cancer* 2006; 42: 582–8.
16. Stupp R, *et al.* Chemoradiotherapy in malignant glioma: standard of care and future directions. *J Clin Oncol* 2007; 25: 4127–36.
17. Kalifa C, Grill J. The therapy of infantile malignant brain tumors: current status? *J Neurooncol* 2005; 75: 279–85.
18. Puget S, Rutka JT. Malignant brain tumors: two steps forward. *Clin Neurosurg* 2007; 54: 4–9.
19. Grill J, Bhangoo R. Recent development in chemotherapy of paediatric brain tumours. *Curr Opin Oncol* 2007; 19: 612–15.
20. Wolff JEA, Finlay JL. High-dose chemotherapy in childhood brain tumors. *Onkologie* 2004; 27: 239–45.
21. Dallorso S, *et al.* EBMT-PDWP. Evolving role of myeloablative chemotherapy in the treatment of childhood brain tumours. *Bone Marrow Transplant* 2005; 35 (suppl 1): S31–S34.
22. Oh Y, Stewart DJ. Systemic therapy for lung cancer brain metastases: a rationale for clinical trials. *Oncology (Williston Park)* 2008; 22: 168–78.
23. Lin NU, *et al.* CNS metastases in breast cancer. *J Clin Oncol* 2004; 22: 3608–17.

Malignant neoplasms of the breast. Cancer of the breast is the most common malignant neoplasm in women. The disease is rare under the age of 25, and increases in incidence with age, although the rate of increase slows after the menopause. Risk factors include a family history (women with inherited BRCA1 or BRCA2 mutations are at higher risk), and reproductive hormonal factors such as early menarche, late menopause, nulliparity, and older age at birth of first child. Oral contraceptives and postmenopausal HRT are also associated with a small excess risk (see Carcinogenicity, Breast, on p. 2234.2 and p. 2246.3 respectively).

Ductal carcinoma in situ (DCIS) is a tumour localised to the breast ducts with no evidence of invasion. Invasive breast cancer can be divided into three main groups:

- early breast cancer (operable, primary, stage I/II)
- locally advanced disease (inoperable local, stage III)
- advanced disease (metastatic; stage IV)

Breast cancer is an extremely heterogeneous disorder, and the clinical course is consequently very variable; such factors as patient age and menopausal status, tumour size and grade, involvement of axillary lymph nodes or skin, and presence of hormone receptors within the tumour may be a guide to the extent and aggressiveness of disease, and hence have prognostic significance for treatment.[1] Early determination of oestrogen-receptor (ER) status and for overexpression of HER2 (human epidermal growth factor receptor-2) is recommended, since they are of value in determining response to certain treatments.[1-3] Progesterone-receptor (PR) status may also be measured, although UK guidelines recommend against routine assessment in patients with early breast cancer.[2]

About 20% of all cancers of the breast detected by mammographic screening are **ductal carcinoma in situ** (DCIS),[4-7] the management of which still has some areas of controversy. Most patients with DCIS will be offered breast-conserving surgery,[1,8,9] although mastectomy, which was historically preferred, is still the treatment of choice in high-risk patients.[1,4-6] Radiotherapy is usually recommended after successful breast-conserving surgery,[1,7-9] as it reduces the rate of recurrence and the risk of developing invasive disease (although it does not affect survival); there may be a subgroup of women in whom it is unnecessary, but there is controversy as to how to define the group. Studies examining the use of adjuvant tamoxifen have produced conflicting reports of benefit on recurrence,[5,6] and again, there is no proven effect on survival. UK guidelines recommend against use of adjuvant tamoxifen in patients with DCIS,[2] but some recommend it in selected patients such as those with ER-positive DCIS,[1,9] in young patients, and in those without risk factors for potential adverse effects.[7] Adjuvant use of newer oestrogen modulators such as anastrozole is also under investigation.[5-7]

In patients with **early disease** (stage I or II; a relatively small tumour with no or limited nodal involvement) the prognosis is fairly good. ***Primary treatment*** is surgical,[1,2,9,10] using breast-conserving surgery or mastectomy.[1,9,11] Neoadjuvant chemotherapy should be considered for those women with large tumours who are otherwise suitable for breast-conserving surgery, in order to downstage the tumour; there is no evidence of a survival benefit.[1,11,12] Chemotherapy regimens are the same as those recommended for adjuvant treatment (see below).[1] Adjuvant radiotherapy is recommended after breast-conserving surgery, as it reduces local recurrence rates. Radiotherapy is generally recommended after mastectomy in women with four or more positive lymph nodes, considered to be at high risk of recurrence.[1,9,11]

Further adjuvant therapy with cytotoxic chemotherapy or hormonal therapy as well as ovarian ablation or suppression has been tried in order to eradicate the micrometastases which cause relapses. Studies by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have confirmed the benefits of adjuvant therapy and attempted to determine which women derive most benefit and which regimens are most effective. Analyses from these[13] and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 studies[14] permitting up to 15 years of follow-up have shown that:

- all women with early-stage breast cancer benefit from adjuvant therapy (although the size of the benefit varies)
- the benefit continues to increase with time, suggesting that adjuvant therapy is curative in a proportion of women who would otherwise relapse
- about 6 months of anthracycline-based chemotherapy reduces the annual death rate due to breast cancer by about 38% in women under 50 years of age at diagnosis, and about 20% in those aged 50 to 69 at diagnosis (too few women over 70 were given chemotherapy to estimate benefit in this group)
- this survival advantage occurs largely independent of oestrogen receptor (ER) status, nodal status, or other tumour characteristics
- adjuvant regimens including an anthracycline are more effective than those without a drug of this class
- in women with ER-positive disease, about 5 years of treatment with adjuvant tamoxifen reduces the annual death rate due to breast cancer by around 31%, largely independent of age, other tumour characteristics, or the use of chemotherapy
- combined chemotherapy and tamoxifen therefore increases the survival benefit further: for middle-aged women with ER-positive disease the breast-cancer mortality rate over 15 years would be approximately halved by 6 months of anthracycline-based chemotherapy followed by 5 years of adjuvant tamoxifen
- ovarian ablation (by surgery or irradiation) or ovarian suppression with a gonadorelin analogue also appear to reduce the mortality due to breast cancer, but that the advantage only applies where other adjuvant therapies are not given

Although these data help in making therapeutic decisions, the size of the benefit will always be less in patients with good prognosis; in the most favourable cases (small tumours with no involved nodes) the incremental benefit may be too small to warrant adjuvant treatment.[1] Tailoring systemic adjuvant therapy to the patient is important, and age and clinical characteristics alone are not adequate grounds to make the judgement: appropriate prognostic markers should be considered.[14,15] Patients with tumours considered hormone-responsive (ER-positive or PR-positive) may receive hormonal therapy alone, or with chemotherapy. Patients with hormone non-responsive tumours (ER-negative or PR-negative) derive greater benefit from chemotherapy and should not receive hormonal therapy.[1,9] In addition, most patients with HER2 overexpression should receive adjuvant trastuzumab as well,[1,9] as studies have shown improvements in both disease-free and overall survival,[16,17] and the benefits are independent of ER status.[1] However, there are concerns about cardiotoxicity.[18,19]

Anthracycline-based regimens are widely used for adjuvant ***chemotherapy***, replacing earlier historical regimens such as CMF (cyclophosphamide, methotrexate, and fluorouracil) with those such as FAC or CAF (cyclophosphamide, doxorubicin, fluorouracil), AC (doxorubicin plus cyclophosphamide), and their many variants. Anthracycline-containing regimens appear to be superior to non-anthracycline-containing regimens for those with HER2-positive tumours.[1,19] The EBCTCG analysis could not show any difference in efficacy between anthracycline regimens,[13] but regimens based on epirubicin have gained in popularity in many centres, since its lower cardiotoxicity compared with doxorubicin means that higher doses can be given.[10] Addition of a taxane (docetaxel or paclitaxel) to an anthracycline-based regimen appears to improve disease-free and overall survival.[19-21] (UK guidelines recommend the use of docetaxel rather than paclitaxel.[2])

Reducing dose intensity of chemotherapy results in poorer survival, and this has led to the hypothesis that higher doses may offer more benefit, particularly in patients at high risk of recurrence. However, despite some positive reports of high-dose chemotherapy with stem-cell support, randomised studies have largely failed to show any benefit of high-dose over standard-dose therapy.[22,23]

Hormonal therapy is only effective in hormone-responsive disease and results of the analyses above established 5 years of tamoxifen as the standard of care in ER-positive disease.[1,10] However, in postmenopausal women, there is evidence that 5 years of anastrozole is an effective alternative to tamoxifen,[24] and treatment with letrozole was found to further reduce the risk of recurrence compared with tamoxifen after 2 years of follow-up.[25] Studies in which 2 to 3 years of tamoxifen were followed by an aromatase inhibitor (anastrozole, exemestane, or letrozole) compared with continued tamoxifen found that disease-free survival was improved with sequential therapy; overall survival was improved in some studies but unaffected in others.[1,26] In addition, although extending tamoxifen beyond 5 years is not generally advocated, there may be significant benefits to following a full course of tamoxifen with extended therapy with an aromatase inhibitor.[27] Thus, aromatase inhibitors can be recommended either as initial, sequential, or extended therapy in postmenopausal women,[1,2,9,26,28] and UK guidelines[2] suggest that tamoxifen should only be used for initial therapy in those with contra-indications to an aromatase inhibitor, although others have questioned the evidence for their routine initial use.[29]

The optimum length of extended or sequential therapy has yet to be determined, but US guidelines allow for 5 years of an aromatase inhibitor after a full course of tamoxifen.[1] Prolonged use of tamoxifen alone is considered an acceptable option by some in those women who cannot tolerate an aromatase inhibitor,[30] and there is some preliminary evidence that 10 years of tamoxifen may be superior to 5 years,[19] although women should be closely monitored for endometrial cancer development.[30] Aside from some suggestion that breast cancer may be sensitive to steroidal aromatase inhibitors (such as exemestane) even after failure of a nonsteroidal inhibitor (such as anastrozole or letrozole),[27] there is no compelling evidence for meaningful efficacy or toxicity differences between the aromatase inhibitors.[1]

Aromatase inhibitors are not effective for hormonal therapy in premenopausal women with ER-positive disease;[1,9,19] tamoxifen is either given alone or it may be combined with ovarian suppression (using a gonadorelin analogue) or ovarian ablation (via oophorectomy or irradiation).[1,2,9,31]

The optimum sequencing of surgery, radiotherapy, and chemotherapy/hormonal therapy has been investigated. Concurrent chemoradiotherapy (chemotherapy given with radiotherapy) is generally considered too toxic, although some allow for its use with the CMF regimen. Otherwise sequential therapy is preferred, with adjuvant chemotherapy given before radiotherapy.[1] Whether tamoxifen should be given concurrently or sequentially with radiotherapy remains unclear, despite several studies addressing the question;[32] US guidelines allow for either option.[1] Where both chemotherapy and hormonal therapy are given, it is recommended that chemotherapy should precede hormonal therapy.[1]

In **locally advanced** breast cancer (stage III) the few patients for whom initial surgery is feasible may be treated as those with high-risk early breast cancer (see above). However, for inoperable disease, anthracycline-based neoadjuvant chemotherapy is standard, which usually results in sufficient tumour shrinkage to allow surgical management, as well as allowing assessment of the responsiveness of the tumour to subsequent treatment.[1,8] Radiotherapy and adjuvant chemotherapy are used after surgery, followed by hormonal therapy if the disease is ER-positive. Adjuvant trastuzumab is also given for those patients with overexpression of HER2. Adjuvant chemotherapy regimens should take into account what was given neoadjuvantly. For disease that does not respond to neoadjuvant chemotherapy, thus remaining inoperable, additional systemic chemotherapy and/or radiotherapy may be tried.[1,2]

The aims of therapy in **advanced or metastatic disease** (stage IV) are palliation and prolongation of life; cure is generally not possible with current regimens,[1,33] and it is often appropriate to select therapy on the basis of previous therapy and patient factors.[19] In women with ER-positive, limited, or asymptomatic disease, ***hormonal therapy*** is preferred: US guidelines advocate an aromatase inhibitor (anastrozole, letrozole, or exemestane), or an anti-oestrogen (usually tamoxifen) for first-line hormonal therapy in postmenopausal patients; second-line therapy options include fulvestrant, toremifene, progestogens such as megestrol, androgens such as fluoxymesterone, or oestrogens such as ethinylestradiol.[1,28] Premenopausal women should undergo ovarian ablation (by surgery or irradiation) or suppression with a gonadorelin analogue, and then be treated as for postmenopausal women. Initial hormonal therapy is continued until disease progression or unacceptable adverse effects occur at which point up to 2 further hormonal regimens may be tried. If these fail, or symptomatic visceral disease develops, the patient is a candidate for chemotherapy. UK guidelines suggest similar management, with the use of an aromatase inhibitor in postmenopausal women, and tamoxifen and ovarian suppression in premenopausal women who have not previously had tamoxifen, or ovarian suppression alone in those who have.[3]

Patients with ER-negative disease, or tumours that are not localised, or who have symptomatic visceral metastasis, or women who have ER-positive tumours refractory to hormonal therapy, should receive ***chemotherapy***.[1,3,33] The taxanes, and in particular docetaxel (which is considered the reference drug in metastatic breast cancer[34]) are acknowledged to be effective,[35] and anthracyclines (doxorubicin, epirubicin, and the related drug mitoxantrone) are also widely used,[1] although a systematic review suggested that their benefits in terms of tumour response did not

extend to improved survival.[36] The benefits of platinum-based therapy have not been established.[37] Capecitabine, gemcitabine, and vinorelbine are also active single agents.[1,3,33]

There is considerable uncertainty as to whether combination regimens offer any substantial benefit over sequential use of single drugs. Although a systematic review of older regimens suggested benefit from combination chemotherapy,[38] and this is the usual standard of care where therapy has curative intent,[34] some do not consider the evidence of benefit from combination therapy persuasive, since toxicity is likely to be increased.[1,33] Nonetheless, established combination regimens, including CMF and various anthracycline- and taxane-based regimens are in use,[1,8] along with newer combinations, such as gemcitabine plus paclitaxel, vinorelbine plus epirubicin, or paclitaxel plus bevacizumab.[1,33] However, while time to progression is improved by paclitaxel plus bevacizumab,[1] no significant effect on overall survival has been shown with bevacizumab combinations, and which patients may benefit is as yet unclear.[33] Ixabepilone with or without capecitabine, is another option.[1,39] In patients with HER2-overexpressing tumours, trastuzumab may be added to chemotherapy:[1,33] the combination is markedly more effective in this group than chemotherapy alone,[34] although use with anthracyclines may be problematic because of the increased risk of cardiotoxicity.[1] Trastuzumab or lapatinib may also be added to hormonal therapy in those with hormone-receptor positive disease.[1,33] UK guidelines recommend stopping trastuzumab once disease progresses outside the CNS, although it should be continued if progression is confined to the CNS alone.[3] Capecitabine plus lapatinib is an option for those refractory to trastuzumab therapy.[1,33]

For further information on common chemotherapy regimens, see Table 1, p. 719.

Higher response rates have been achieved by intensive regimens, combined with autologous bone marrow transplants or stem cells in some studies. However, the results of randomised studies have been disappointing, and a systematic review found no improvement in overall survival with the use of stem-cell supported high-dose therapy in metastatic breast cancer.[40]

The use of bisphosphonates in women with bone metastases reduces bone pain and skeletal complications such as fracture, spinal cord compression, and hypercalcaemia (see Malignant Neoplasms of the Bone, p. 700.3). Radiotherapy is also used for bone pain, and for the treatment of brain metastases (see Malignant Neoplasms of the Brain, p. 701.2).

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: breast cancer (version 3.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf (accessed 29/10/10)
2. NICE. Early and locally advanced breast cancer: diagnosis and treatment (Clinical Guideline 80, issued February 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG80NICEGuideline.pdf (accessed 20/07/09)
3. NICE. Advanced breast cancer: diagnosis and treatment (Clinical Guideline 81, issued February 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG81NICEGuideline.pdf (accessed 20/07/09)
4. Burstein HJ, *et al.* Ductal carcinoma in situ of the breast. *N Engl J Med* 2004; 350: 1430–41.
5. Leonard GD, Swain SM. Ductal carcinoma in situ, complexities and challenges. *J Natl Cancer Inst* 2004; 96: 906–20.
6. Mokbel K. Contemporary treatment of ductal carcinoma in situ of the breast. *Med Sci Monit* 2005; 11: RA86–RA93.
7. Sakorafas GH, *et al.* Recent advances and current controversies in the management of DCIS of the breast. *Cancer Treat Rev* 2008; 34: 483–97.
8. Moulder S, Hortobagyi GN. Advances in the treatment of breast cancer. *Clin Pharmacol Ther* 2008; 83: 26–36.
9. Aebi S, *et al.* ESMO Guidelines Working Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v9–v14. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v9.full.pdf+html (accessed 29/10/10)
10. Melville S, Heycock L. Treatment of early breast cancer. *Pharm J* 2007; 279: 357–60.
11. Turner NC, Jones AL. Management of breast cancer—part I. Abridged version: *BMJ* 2008; 337: a421. Full version: http://www.bmj.com/cgi/section_pdf/337/jul04_1/a421.pdf (accessed 26/02/09)
12. Wolff AC, Davidson NE. Primary systemic therapy in operable breast cancer. *J Clin Oncol* 2000; 18: 1558–69.
13. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365: 1687–1717.
14. Fisher B, *et al.* Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. *Lancet* 2004; 364: 858–68.
15. Muss HB, *et al.* Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *JAMA* 2005; 293: 1073–81.
16. Engel RH, Kaklamani VG. HER2-positive breast cancer: current and future treatment strategies. *Drugs* 2007; 67: 1329–41.
17. Houssami N, *et al.* The prevention, detection, and management of breast cancer. *Med J Aust* 2006; 184: 230–4.
18. Hortobagyi GN. Trastuzumab in the treatment of breast cancer. *N Engl J Med* 2005; 353: 1734–6.
19. Turner NC, Jones AL. Management of breast cancer—part II. Abridged version: *BMJ* 2008; 337: a540. Full version: http://www.bmj.com/cgi/section_pdf/337/jul11_2/a540.pdf (accessed 26/02/09)
20. Nowak AK, *et al.* Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer. *Lancet Oncol* 2004; 5: 372–80.
21. Martin M, *et al.* Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005; 352: 2302–13.
22. Hortobagyi GN. What is the role of high-dose chemotherapy in the era of targeted therapies? *J Clin Oncol* 2004; 22: 2263–6.
23. Farquhar C, *et al.* High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 23/02/09).
24. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; 365: 60–2.
25. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005; 353: 2747–57.
26. Winer EP, *et al.* American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 2005; 23: 619–29. Also available at: http://www.jco.org/cgi/reprint/23/3/619.pdf (accessed 23/02/09)
27. Strasser-Weippl K, Goss PE. Advances in adjuvant hormonal therapy for postmenopausal women. *J Clin Oncol* 2005; 23: 1751–9.
28. Pruthi S, *et al.* A multidisciplinary approach to the management of breast cancer, part 2: therapeutic considerations. *Mayo Clin Proc* 2007; 82: 1131–40.
29. Seruga B, Tannock IF. Up-front use of aromatase inhibitors as adjuvant therapy for breast cancer: the emperor has no clothes. *J Clin Oncol* 2009; 27: 840–2.
30. Bedard PL, Cardoso F. Recent advances in adjuvant systemic therapy for early-stage breast cancer. *Ann Oncol* 2008; 19 (suppl 5): v122–v127.
31. Dellapasqua S, *et al.* Adjuvant endocrine therapy for premenopausal women with early breast cancer. *J Clin Oncol* 2005; 23: 1736–50.
32. Whelan T, Levine M. Radiation therapy and tamoxifen: concurrent or sequential? That is the question. *J Clin Oncol* 2005; 23: 1–4.
33. Cardoso F, *et al.* ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v15–v19. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v15.full.pdf+html (accessed 29/10/10)
34. Hamilton A, Hortobagyi G. Chemotherapy: what progress in the last 5 years? *J Clin Oncol* 2005; 23: 1760–75. Correction. *ibid.*; 5851.
35. Ghersi D, *et al.* Taxane containing regimens for metastatic breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 23/02/09).
36. Lord S, *et al.* Antitumour antibiotic containing regimens for metastatic breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/02/09).
37. Carrick S, *et al.* Platinum containing regimens for metastatic breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 23/02/09).
38. Carrick S, *et al.* Single agent versus combination chemotherapy for metastatic breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 20/07/09).
39. Pronzato P. New therapeutic options for chemotherapy-resistant metastatic breast cancer: the epothilones. *Drugs* 2008; 68: 139–46.
40. Farquhar C, *et al.* High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 23/02/09).

PROPHYLAXIS OF BREAST CANCER. The recognition of factors increasing the risk of breast cancer (p. 702.1), and particularly the identification of specific genes that confer a high risk, has spurred the search for effective ways of preventing the disease. Current options, other than regular screening to detect the cancer at early stages, include surgery, drug therapy (below), and possibly some life-style modifications.[1-7]

Prophylactic bilateral mastectomy and prophylactic salpingo-oophorectomy have both been shown to substantially decrease the incidence of breast cancer in moderate- and high-risk women and in known BRCA1/2 mutation carriers.[2,4-7] Mastectomy is recommended for women at high risk, such as those with genetic factors, or for women with a history of lobular carcinoma *in situ*, or thoracic radiation.[2] Bilateral salpingo-oophorectomy is generally limited to women with a known or strongly suspected BRCA1/2 mutation.[2,4,7]

The association between lifestyle modifications and breast cancer risk is not clear-cut,[2] and there is no evidence that specific dietary components can effectively reduce breast cancer risk.[7] Nevertheless, women judged to be at moderate or high risk may be advised to avoid alcohol or to decrease alcohol consumption, and postmenopausal women may benefit from weight loss.[2,7]

Treatment with tamoxifen as part of the adjuvant management of early breast cancer is associated with a reduced risk of developing cancer in the other breast. This led to the suggestion that prophylactic tamoxifen might prevent the development of breast cancer in women at risk, and to studies to test this hypothesis. These studies were not without controversy, since the risk/benefit for tamoxifen use in healthy women differed from that in women with breast cancer. The first study to be reported was the US National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study,[8] which randomised 13 388 women to 5 years of treatment with tamoxifen or placebo. Participants were either aged 60 years or older, had a history of lobular carcinoma in situ, or had a 5-year predicted risk of developing breast cancer of greater than 1.66% (as assessed by number of first-degree relatives with breast cancer, number of previous breast biopsies, presence of atypical hyperplasia, and reproductive factors). In this study there was a highly significant 49% reduction in the occurrence of invasive breast cancer in women given tamoxifen (21.4 cancers prevented per 1000 women treated). The incidence of non-invasive breast cancer was reduced to a similar extent. Tamoxifen reduced the incidence of oestrogen-receptor (ER) positive, but not ER-negative, tumours. Adverse effects of tamoxifen included a modest increase in the risk of endometrial cancer and vascular events (stroke and pulmonary embolism). Although this study was prematurely unblinded, and all women were offered a 5-year course of tamoxifen, follow-up continued for 7 years and the incidence of breast cancer remained relatively constant for the 2 years after tamoxifen therapy was stopped.[9] Preliminary results from 2 smaller randomised European studies did not confirm the benefit of tamoxifen in breast cancer prevention. The Italian study[10] was in hysterectomised women with no particular risk for breast cancer, and because of its size may not have been sufficiently powered to detect an effect of tamoxifen. The full follow-up[11] of 5 years of treatment in this study found no difference in breast cancer incidence between tamoxifen and placebo groups. A subgroup analysis of women at high risk of ER-positive breast cancer did find a protective effect from tamoxifen, and there was an apparent protective effect for women in this group who used HRT. However, this group was not identified at randomisation of the study and these results need to be confirmed. The British study[12] of 8 years of tamoxifen or placebo was in women with a first-degree family history of breast cancer, and their median age was younger than in the US study. Although preliminary results showed no benefit from tamoxifen, follow-up for a median of about 13 years did find a reduction in the risk of ER-positive tumours.[13] This reduced risk also appeared to improve with longer follow-up. Initial results of a further placebo-controlled study (IBIS-I)[14] of women at increased risk of breast cancer found that during 5 years of tamoxifen use, the risk of all breast cancers was reduced by 32%. As in other studies, the reduction occurred in ER-positive tumours. Similar adverse effects were found with tamoxifen use, but there was also an unexpected increase in deaths from all causes in tamoxifen users. This may be associated with the excess in thromboembolic events reported, although statistical variability could not be ruled out. Extended follow-up[15] for a further median of 8 years found that the beneficial effect of tamoxifen was maintained, and that reduction in the risk of ER-positive tumours increased with longer follow-up. However, the rate of adverse effects of tamoxifen reduced after treatment stopped. A retrospective analysis[16] of the NSABP P-1 data for women who had developed invasive breast cancer found that in carriers of the oncogene BRCA2, but not BRCA1 carriers, there was a reduction in breast cancer similar to the reduction in ER-positive cancer among all women in the study. The numbers available, however, were too small to be statistically significant, and it is therefore still not known if tamoxifen can reduce the risk of breast cancer in patients with these mutations.

Another anti-oestrogen, raloxifene, has reportedly shown a reduction in breast cancer risk while its effects on osteoporosis were being studied.[17] A further large placebo-controlled study[18] that included the incidence of breast cancer as a primary outcome also found a reduction with about 5 years of raloxifene use. There was a 55% lower risk of invasive ER-positive cancer (absolute risk reduction of 1.2 cancers per 1000 women treated for 1 year), but there was no effect on ER-negative disease. The effect of raloxifene has also been directly compared with tamoxifen in women with a predicted increased risk of breast cancer (STAR study).[19] After up to 5 years of use, the incidence of invasive disease was similar in both groups, suggesting that raloxifene is as effective as tamoxifen in reducing the risk of developing invasive breast cancer in this group of women. The aromatase inhibitors, anastrozole and exemestane, are also under investigation.[2,4,6,20]

From these studies, tamoxifen prophylaxis has been shown to reduce the incidence of ER-positive breast cancer in women at increased risk,[21] although there are limited data for women with BRCA1 and 2 mutations.[2] Tamoxifen remains the drug of choice for premenopausal women at increased risk of breast cancer;[2,5,6,22] raloxifene is not recommended for use in this population. In postmenopausal women, treatment is influenced by age, presence of uterus, and comorbidities.[2] Either tamoxifen or raloxifene is recommended for use in women at high risk;[2] some[5,6] recommend raloxifene over tamoxifen due to its more favourable adverse effect profile.

Other candidates for the prevention of breast cancer include plant oestrogens (phytoestrogens) such as those in soya.[6] Epidemiological evidence suggests that diets high in these compounds may be protective, but there are many confounding factors and inconsistencies in the data available.[23] It was thought that retinoids might also be protective, but a secondary prevention study of fenretinide failed to show any benefit.[24] Regular use of aspirin and other NSAIDs has been reported to decrease breast cancer risk, but this has not been supported in other studies.[4,6,7] Similarly, inconsistent associations have been reported with the use of statins; some suggest that additional study of lipophilic

statins is warranted.[6] Use of luteinising hormone releasing hormone (LHRH) agonists is also under investigation, although adverse effects may pose a problem.[6]

For the suggestion that bisphosphonates may reduce the risk of breast cancer, see Malignant Neoplasms of the Breast, under Bisphosphonates, p. 1174.2.

1. Chlebowski RT. Reducing the risk of breast cancer. *N Engl J Med* 2000; 343: 191–8.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: breast cancer risk reduction (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast_risk.pdf (accessed 04/06/10)
3. Guillem JG, *et al.* American Society of Clinical Oncology; Society of Surgical Oncology. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. *J Clin Oncol* 2006; 24: 4642–60. Also published in *Ann Surg Oncol* 2006; 13: 1296–1321.
4. Mahoney MC. Breast cancer risk reduction and counseling: lifestyle, chemoprevention, and surgery. *J Natl Compr Canc Netw* 2007; 5: 702–10.
5. Reeder JG, Vogel VG. Breast cancer prevention. *Cancer Treat Res* 2008; 141: 149–64.
6. Castrellon AB, Glück S. Chemoprevention of breast cancer. *Expert Rev Anticancer Ther* 2008; 8: 443–52.
7. Mahoney MC, *et al.* Opportunities and strategies for breast cancer prevention through risk reduction. *CA Cancer J Clin* 2008; 58: 347–71.
8. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; 90: 1371–88.
9. Fisher B, *et al.* Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005; 97: 1652–62.
10. Veronesi U, *et al.* Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet* 1998; 352: 93–7.
11. Veronesi U, *et al.* Italian randomized trial among women with hysterectomy: tamoxifen and hormone-dependent breast cancer in high-risk women. *J Natl Cancer Inst* 2002; 95: 160–5.
12. Powles T, *et al.* Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* 1998; 352: 98–101.
13. Powles TJ, *et al.* Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J Natl Cancer Inst* 2007; 99: 283–90.
14. IBIS Investigators. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. *Lancet* 2002; 360: 817–24.
15. Cuzick J, *et al.* Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 2007; 99: 272–82.
16. King M-C, *et al.* Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA* 2001; 286: 2251–6.
17. Martino S, *et al.* Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* 2004; 96: 1751–61.
18. Barrett-Connor E, *et al.* Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; 355: 125–37.
19. Vogel VG, *et al.* Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006; 295: 2727–41.
20. Cuzick J. Aromatase inhibitors for breast cancer prevention. *J Clin Oncol* 2005; 23: 1636–43.
21. Cuzick J, *et al.* Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003; 361: 296–300.
22. Chlebowski RT, *et al.* American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition. *J Clin Oncol* 2002; 20: 3328–43. Also available at: http://www.jco.org/cgi/reprint/20/15/3328.pdf (accessed 26/02/09)
23. Trock BJ, *et al.* Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst* 2006; 98: 459–71.
24. Veronesi U, *et al.* Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst* 1999; 91: 1847–56.

MALIGNANT NEOPLASMS OF THE MALE BREAST. Breast cancer can occur in men, although it has a much lower incidence than in women. Risk factors are not well understood, but it may sometimes be associated with abnormalities of sex hormone metabolism, including those acquired through liver disease or testicular trauma. In addition, the inherited mutation BRCA2, which is associated with an increased risk of breast cancer in women, also increases the risk of breast cancer in men; occasionally BRCA1 mutations are seen. Men with Klinefelter's syndrome, a sex chromosome anomaly, may be predisposed to development of breast cancer. Possible environmental risk factors include industrial exposure to chronic heat. Other risk factors include smoking, obesity, and alcohol consumption.

A painless mass is the most common presentation; nipple discharge may occur. Other less common symptoms include breast tenderness, swelling, or nipple itching. Diagnosis is often at a late stage. Breast cancer in men occurs at a slightly older median age than in women (60 to 70 years), and is more likely to be oestrogen-receptor (ER) positive. Survival by stage appears to be similar to that in women, with an overall 5-year survival about 40 to 65%.

Treatment is similar to that for women (see p. 702.1).[1-4] Primary management for *early* or *localised* disease is surgical and usually involves simple or radical mastectomy with axillary lymph node dissection, although breast-conserving surgery is also used. Because of the rarity of the disease large controlled studies are lacking but studies in limited numbers of men and extrapolation from results in women suggest that neoadjuvant and adjuvant therapy should be considered on the same basis as for women. Radiotherapy may be used to reduce the rate of local recurrence in those considered at high risk. As most male breast cancers are ER-positive, adjuvant hormonal therapy with tamoxifen is commonly used.[1-4] Use of aromatase inhibitors such as anastrozole or letrozole is considered controversial, since inhibition of oestrogen may be incomplete unless orchidectomy is also performed;[3,4] use with a gonadorelin analogue has been suggested.[4] Males with ER-negative disease should be offered chemotherapy. Regimens are usually anthracycline- or taxane-based; common combination regimens include CMF (cyclophosphamide, methotrexate, and fluorouracil) and FAC (fluorouracil, doxorubicin, and cyclophosphamide).[2-4] Adjuvant trastuzumab should be considered for men with high-risk HER2-positive disease.[2-4]

In *advanced* metastatic disease tamoxifen is generally the first choice treatment for ER-positive disease, although there is evidence of benefit from aromatase inhibitors such as anastrozole or letrozole. Again, combination with gonadorelin analogues has been suggested because of the risk of incomplete oestrogen inhibition.[3] Chemotherapy is used for patients with ER-negative disease, or for those who progress on hormonal therapy.[2-4] Regimens are usually doxorubicin-based, such as FAC.[2,4] For further information on common chemotherapy regimens, see Table 1, p. 719. There are reports of response to trastuzumab in males with metastatic HER2-positive disease,[2,4] and some consider its use justified in this instance.[3] Hormonal ablation by adrenalectomy or orchidectomy is also effective, but has become less popular since the advent of tamoxifen.

1. Giordano SH, *et al.* Breast cancer in men. *Ann Intern Med* 2002; 137: 678–87.
2. Fentiman IS, *et al.* Male breast cancer. *Lancet* 2006; 367: 595–604.
3. Czene K, *et al.* How to treat male breast cancer. *Breast* 2007; 16 (suppl 2): S147–S154.
4. Agrawal A, *et al.* Male breast cancer: a review of clinical management. *Breast Cancer Res Treat* 2007; 103: 11–21.

Malignant neoplasms of the cervix. Cancer of the uterine cervix is one of the most common cancers in women, accounting for about 12% of all female malignancies. It is associated with early sexual activity and a high number of sexual partners, and the presence of human papillomavirus (HPV); high-risk types of the virus (HPV-16 and 18) that produce proteins E6 and E7 inactivate host tumour suppressor proteins and thus encourage malignant transformation. Smoking and long-term use of oral contraceptives (p. 2235.1) may also be risk factors. Widespread screening has meant that in many women the disease has been detected in the preinvasive or early stages, when the prognosis is excellent to good. An HPV vaccine is available in some countries for the primary prevention of cervical cancer.

Preinvasive cervical lesions (cervical intraepithelial neoplasia; CIN) may resolve spontaneously if low-grade (CIN1), and may be monitored by repeat screening or HPV testing.[1,2] High-grade CIN (CIN2; cervical dysplasia) and cervical carcinoma *in situ* (CIN3) may progress to invasive carcinoma and are usually treated by ablation or excision.[1,2] Conisation of the cervix (cone biopsy) may be used to rule out the presence of invasive disease.[3,4]

Invasive cervical cancers are mostly squamous cell in origin (about 80%), with about 20% being adenocarcinoma.[3,5] Invasive cervical cancers may be divided into early-stage, locally advanced, and metastatic. The earliest stage (IA1) may be treated by conisation of the cervix (which maintains fertility) or simple hysterectomy. Other *early-stage* cancers may be treated by surgery (radical hysterectomy) or by radiotherapy (usually brachytherapy with pelvic irradiation).[3-7] For patients at this stage who wish to preserve fertility, radical trachelectomy (removal of the cervix) with pelvic lymphadenectomy may be an option.[4-8] However, those with bulky tumours, poor prognostic factors, or high-risk features after surgery should be given postoperative pelvic radiotherapy with concurrent chemotherapy (chemoradiotherapy), which has been shown to improve survival.[3-6,9,10] Most regimens use cisplatin, either alone or with fluorouracil.[3,5,6,8-10] Hydroxycarbamide has also been used by some centres, but is less effective than cisplatin.[5]

Patients with *locally advanced* cervical cancer are also usually treated with primary chemoradiotherapy using cisplatin-based regimens,[3-5,7-9] as it improves overall and progression-free survival.[11] A meta-analysis of 13 studies (including patients at various stages, from early through to metastatic) confirmed the survival benefit of chemoradiotherapy in cervical cancer; there was no significant difference between platinum- and non-platinum-based chemoradiotherapy.[12] Neoadjuvant chemotherapy has been tried and although there is some indication that its use before surgery might be of benefit in bulky early-stage or locally advanced disease, no survival advantage has been shown and this approach remains controversial; it does not appear to be beneficial before radiotherapy.[10,13]

For local recurrence of disease, treatment options include radiotherapy if it has not already been used, more extensive surgery, or cisplatin-based chemoradiotherapy.[3-5,14] Patients with recurrence who are not candidates for surgery o radiotherapy may be offered palliative chemotherapy o best supportive care; chemotherapy regimens are the sam as those used for metastatic disease.[5]

Treatment of *metastases* is palliative; radiotherapy chemotherapy, or chemoradiotherapy can be used.[3,5,7,1 Cisplatin, carboplatin, or paclitaxel may all be considered fo first-line monotherapy; if cisplatin has previously been use as a radiosensitiser a combination regimen of cisplatin wit either paclitaxel, topotecan, or gemcitabine is preferred carboplatin plus paclitaxel is also an option.[5] Drugs tha have been tried for second-line treatment include bevacizumab, docetaxel, epirubicin, fluorouracil, gemcitabine, ifosfamide, irinotecan, liposomal doxorubicin, mitomycin, pemetrexed, topotecan, and vinorelbine.[5,14] Many combination regimens have shown higher response rates and improvements in progression-free survival but not overall survival compared with monotherapy; however, the CT regimen (cisplatin plus topotecan) has shown an improvement in overall survival.[5,15] UK guidelines[6] recommend treatment with cisplatin plus topotecan (for cisplatin-naïve patients), or cisplatin plus paclitaxel, for all women with stage IVB or recurrent disease. For further information on common chemotherapy regimens, see Table 1, p. 719.

1. Miller AB, *et al.* Report on consensus conference on cervical cancer screening and management. *Int J Cancer* 2000; 86: 440–7.
2. Wright TC, *et al.* 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol* 2007; 197: 340–5. Also published in: *J Low Genit Tract Dis* 2007; 11: 223–39. Correction. *ibid.* 2008; 12: 63.
3. Waggoner SE. Cervical cancer. *Lancet* 2003; 361: 2217–25.
4. Petignat P, Roy M. Diagnosis and management of cervical cancer. *BMJ* 2007; 335: 765–8.
5. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: cervical cancer (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf (accessed 04/06/10)
6. Gray HJ. Primary management of early stage cervical cancer (IA1-IB) and appropriate selection of adjuvant therapy. *J Natl Compr Canc Netw* 2008; 6: 47–52.
7. Haie-Meder C, *et al.* ESMO Guidelines Working Group. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v37–v40. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v37.full.pdf+html (accessed 15/10/10)
8. Scottish Intercollegiate Guidelines Network. Management of cervical cancer: a national clinical guideline (issued January 2008). Available at: http://www.sign.ac.uk/pdf/sign99.pdf (accessed 21/01/09)
9. Kim RY, *et al.* Advances in the treatment of gynecologic malignancies part 1: cancers of the cervix and vulva. *Oncology (Huntingt)* 2002; 16: 1510–17, 1521.
10. Tierney JF, *et al.* Concomitant and neoadjuvant chemotherapy for cervical cancer. *Clin Oncol (R Coll Radiol)* 2008; 20: 401–16.
11. Green J, *et al.* Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 21/01/09).
12. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008; 26: 5802–12.
13. Moore DH. Neoadjuvant chemotherapy for cervical cancer. *Expert Opin Pharmacother* 2003; 4: 859–67.
14. Friedlander M. Guidelines for the treatment of recurrent and metastatic cervical cancer. *Oncologist* 2002; 7: 342–7.
15. Long HJ. Management of metastatic cervical cancer: review of the literature. *J Clin Oncol* 2007; 25: 2966–74.

Malignant neoplasms of the endometrium. Cancer of the endometrium is a disease primarily of postmenopausal women, and is more common in developed than developing countries. Based on aetiology and pathology, endometrial cancer is generally classified into 2 subtypes:

- type I are the most common, with an endometrioid histology, and are mostly low-grade, with a background of endometrial hyperplasia. They are usually oestrogen-receptor positive, and associated with increased oestrogen exposure. Factors resulting in increased endogenous exposure include obesity, anovulatory infertility, early menarche, and late menopause. Exogenous factors include use of oestrogens without progestogens for hormone replacement therapy (p. 2247.3), and tamoxifen therapy (see Carcinogenicity, p. 861.3). Other associated findings include nulliparity, diabetes mellitus, and hypertension
- poorly differentiated or non-endometrioid type II cancers appear, in contrast, to be unrelated to high oestrogen concentrations, are often associated with endometrial atrophy, and often develop in non-obese women. They include serous or clear-cell carcinomas which are highly aggressive with a poorer prognosis; endometrial intraepithelial carcinoma is believed to be a precursor

Abnormal uterine bleeding is the most common sign of endometrial cancer, and all postmenopausal women with vaginal bleeding and other risk factors should be evaluated for the disease. In menopausal or premenopausal women, diagnosis may be delayed because abnormal bleeding patterns may not be so obvious. Type I endometrioid carcinomas are surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO) system; type II are classed as high-grade by definition.

Surgery is the primary **therapy** for operable endometrial cancer;[1-7] total hysterectomy and bilateral salpingo-oophorectomy is usually performed, with lymph node dissection in selected cases. No further treatment is required in women with FIGO stage I disease who are at low risk of recurrence. In those with stage I disease and a higher risk of recurrence, adjuvant vaginal brachytherapy or pelvic irradiation are used. In all other women, adjuvant radiotherapy is given, the field being tailored depending on the disease stage.[2-6] Adjuvant hormonal therapy with a progestogen has not been shown to be effective.[8] However, progesterone therapy has been used for young women with endometrial hyperplasia who wish to preserve their fertility, as well as for women who are poor surgical candidates.[3] There are a few studies of adjuvant chemotherapy in women with early-stage disease at high risk of recurrence, but no significant survival benefit has been seen.[1,2,4,6,9,10]

For women with advanced, recurrent, or metastatic disease, adjuvant chemotherapy or hormonal therapy may be considered as treatment options,[2-6,10,11] although response rates are only up to about 30%, and evidence for a survival benefit is questionable.[12] Progestogens such as medroxyprogesterone acetate are likely to be preferred because of their better tolerability.[2,4,5,11] Tamoxifen also produces minor benefit;[3] alternation with progestogens may prolong the response to hormonal therapy.[2] Well-differentiated tumours, long disease-free interval, and positive hormone receptor status are factors that suggest increased response to progestogens.[3,7] When progestogens are ineffective, chemotherapy may be tried. Single-agent drugs of choice include cisplatin or carboplatin, doxorubicin, and paclitaxel.[2-4,6,9,11] Response rates are slightly higher with combination regimens;[9,13] these include cisplatin plus doxorubicin, sometimes with paclitaxel (the TAP regimen), or carboplatin plus paclitaxel.[2-6,10,11,13] TAP has been found to be more effective, but also more toxic than cisplatin plus doxorubicin.[3,6,10,12,13] The combination of carboplatin and paclitaxel has become standard in many centres in the management of advanced or recurrent endometrial cancer.[2,9,10] For further information on common chemotherapy regimens, see Table 1, p. 719. Drugs that are being investigated for endometrial cancer include bevacizumab, erlotinib, everolimus, sorafenib, temsirolimus, and trastuzumab.[9]

For those with medically inoperable disease, radiotherapy is well-tolerated and can provide long-term progression-free survival.[1-3]

1. Southcott BM. Carcinoma of the endometrium. *Drugs* 2001; **61**: 1395–1405.
2. Amant F, *et al.* Endometrial cancer. *Lancet* 2005; **366**: 491–505.
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: uterine neoplasms (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/uterine.pdf (accessed 04/06/10)
4. Amant F, *et al.* Treatment modalities in endometrial cancer. *Curr Opin Oncol* 2007; **19**: 479–85.
5. Bakkum-Gamez JN, *et al.* Current issues in the management of endometrial cancer. *Mayo Clin Proc* 2008; **83**: 97–112.
6. Fiorelli JL, *et al.* Current treatment strategies for endometrial cancer. *Expert Rev Anticancer Ther* 2008; **8**: 1149–57.
7. Plataniotis G, Castiglione M. ESMO Guidelines Working Group. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v41–v45. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v41.full.pdf+html (accessed 15/10/10)
8. Martin-Hirsch PL, *et al.* Progestagens for endometrial cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 26/01/09).
9. Fleming GF. Systemic chemotherapy for uterine carcinoma: metastatic and adjuvant. *J Clin Oncol* 2007; **25**: 2983–90. Correction, *ibid.*; 5048.
10. Hogberg T. Adjuvant chemotherapy in endometrial carcinoma: overview of randomised trials. *Clin Oncol (R Coll Radiol)* 2008; **20**: 463–9.
11. Kendrick JE, Huh WK. Treatment considerations in advanced endometrial cancer. *Curr Oncol Rep* 2007; **9**: 494–8.
12. Polyzos NP, *et al.* Randomized evidence on chemotherapy and hormonal therapy regimens for advanced endometrial cancer: an overview of survival data. *Eur J Cancer* 2006; **42**: 319–26.
13. Humber CE, *et al.* Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. *Ann Oncol* 2007; **18**: 409–20.

Malignant neoplasms of the eye. Tumours of the orbit of the eye in adults are most commonly metastases from primary lesions elsewhere in the body, usually in the breast or lung. Radiotherapy using external beam radiation or brachytherapy with iodine-125 is given for control of visual symptoms unresponsive to chemotherapeutic treatment of primary disease.[1]

Primary eye tumours are rare. In children, the most common intra-ocular tumour is retinoblastoma (see p. 717.2), and the most common orbital tumour is rhabdomyosarcoma (see Soft-tissue Sarcomas, p. 718.2). In adults, primary CNS lymphoma (see p. 698.1) can originate in the eye. However, the most common primary intra-ocular cancer in adults is **uveal melanoma**, which accounts for 80% of all primary ocular cancers.[2] The incidence is greater in Caucasians, and less common in brown-eyed individuals; average age at presentation is in the sixth or seventh decade.[2,3] About 40% of patients are asymptomatic, while others present with blurred or distorted vision, visual field loss, or seeing flashing lights.[3] Untreated, uveal melanomas result in loss of vision.[3] If metastasis occurs it is usually to the liver, and survival is poor;[2-4] factors associated with metastatic spread include large tumour size, ciliary body involvement, local tumour recurrence after conservative treatment, and rapid tumour regression after radiotherapy.[3]

The main objective of ***treatment*** is to prevent metastatic spread.[3] Treatment options for uveal melanomas include observation of indeterminate pigmented lesions, or eye-conserving therapies, which include brachytherapy (with iodine-125 or ruthenium-106), radiotherapy, local resection, or phototherapy such as photocoagulation or laser-induced hyperthermia (transpupillary thermotherapy).[2,3] Enucleation (removal of the eye) does not offer any survival advantage over conservative treatment, and is indicated only when eye-conserving therapy fails or for large tumours with extensive involvement of all uveal structures, diffuse growth, extensive retinal invasion or perforation, or bulky extra-ocular extension.[3]

Various treatments have been tried for patients with *metastatic* uveal melanoma. Surgical resection of isolated hepatic metastasis offers a survival advantage, but while there is continued interest in adjuvant therapy, metastatic disease is highly resistant to traditional systemic chemotherapy.[3,4] Most regimens have included dacarbazine, but these are considered to be ineffective.[4] Hepatic intra-arterial chemotherapy using fotemustine, or melphalan has been reported to be of benefit; carboplatin has also been used. Responses have been seen using hepatic artery chemoembolisation with cisplatin or carmustine; while local control was achieved with the latter drug, progression occurred at extra-hepatic sites. Embolisation with granulocyte-macrophage colony-stimulating factor (immunoembolisation) has also been reported to be effective, although data from large-scale studies are lacking. Targeted therapy is under investigation, using various drugs such as lenalidomide, sorafenib, sunitinib, and temozolomide, either alone or in combination chemotherapy regimens. Implantation of yttrium-90 microspheres is also under investigation.[4]

Ocular surface neoplasms (lesions of the conjunctival or corneal epithelium) may be benign or precancerous. They occur more commonly in sub-Saharan Africa, Australia, and regions where exposure to sunlight is more frequent. Exposure to solar UV radiation is a major aetiological factor, although human papillomavirus (HPV) and HIV infection may also have a role in the development of these tumours. Ocular surface neoplasms are usually treated with local excision. Because of a high recurrence rate, cryotherapy or brachytherapy is usually combined with surgery. Chemotherapy can be used where surgery is not feasible, or it may be used intra-operatively or as adjuvant treatment; some centres use chemotherapy initially for treating intra-epithelial ocular surface tumours. The most commonly used drugs are mitomycin C, applied topically in the form of eye drops (0.02% or 0.04%), fluorouracil (1%) eye drops, and interferon alfa-2b, which is used topically, subconjunctivally, or by intralesional injection. Patients who fail treatment with one drug may respond to another, and combination regimens have also led to tumour regression. Other drugs that have been reported to be effective when used topically include dinitrochlorobenzene, urea, tretinoin, and cidofovir.[5,6]

1. Shields CL. Plaque radiotherapy for the management of uveal metastasis. *Curr Opin Ophthalmol* 1998; **9**: 31–7.
2. Char DH. Ocular melanoma. *Surg Clin North Am* 2003; **83**: 253–74.
3. Damato B. Treatment of primary intraocular melanoma. *Expert Rev Anticancer Ther* 2006; **6**: 493–506.
4. Sato T, *et al.* The biology and management of uveal melanoma. *Curr Oncol Rep* 2008; **10**: 431–8.
5. Pe'er J. Ocular surface squamous neoplasia. *Ophthalmol Clin North Am* 2005; **18**: 1–13.
6. Poothullil AM, Colby KA. Topical medical therapies for ocular surface tumors. *Semin Ophthalmol* 2006; **21**: 161–9.

Malignant neoplasms of the gastrointestinal tract. Considered as a whole (and excluding skin cancers, which are often poorly registered) the gastrointestinal tract is the most frequent site of malignancies worldwide, although the frequencies of the various types of gastrointestinal cancer vary greatly from country to country. Genetic, environmental, and dietary factors may play a role in the aetiology of these cancers. Treatment may include surgery, radiotherapy, and chemotherapy, but the prognosis in most forms of gastrointestinal cancer is generally not encouraging.

Gastrointestinal cancers vary in their management depending on the site. Discussed in more detail below are:

- oesophageal cancer (below)
- stomach cancer (p. 706.1)
- colorectal cancer (p. 706.3) and its prophylaxis (p. 707.2)
- anal cancer (p. 708.1)

Cancers of the oral cavity are discussed under Malignant Neoplasms of the Head and Neck, p. 708.1.

Other cancers may sometimes manifest in the gastrointestinal tract, including the various endocrine neoplasms responsible for carcinoid syndrome (see Neuroendocrine Tumours, p. 716.3), and MALT lymphomas (p. 698.1). Gastrointestinal stromal tumours (GISTs) are soft-tissue sarcomas arising in the gastrointestinal tract, most commonly in the stomach and small bowel (see Soft-tissue Sarcoma, p. 718.2).

MALIGNANT NEOPLASMS OF THE OESOPHAGUS. Oesophageal cancer has perhaps the greatest variation in incidence between different geographical regions of any cancer, and is endemic in many parts of the world. The two major histological types are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is strongly associated with tobacco and alcohol use, and may occur as a second primary tumour in patients with tumours of the upper aerodigestive tract (see Malignant Neoplasms of the Head and Neck, p. 708.1). Adenocarcinoma is more common in non-endemic regions, including many developed countries, and is associated with Barrett's oesophagus (see Gastro-oesophageal Reflux Disease, p. 1810.2). Oesophageal cancer usually develops as a growth or ulcerative lesion of the oesophagus with extensive infiltration of the mucosa and invasion of neighbouring structures. Lymphatic and blood-borne metastasis occurs at a relatively early stage. Symptoms of pain and dysphagia due to obstruction occur late, and overall, more than half of all patients have unresectable or metastatic disease at initial presentation. Metastatic disease is associated with a median survival of less than 1 year.[1] The overexpression of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and human epidermal growth factor receptor-2 (HER2) has been associated with a poor prognosis in patients with oesophageal and gastric cancers.

Patients with **locoregional disease** are treated with surgery if possible, or definitive chemoradiotherapy if they are not surgical candidates.[2-8] Chemoradiotherapy regimens usually include cisplatin, with a fluoropyrimidine (fluorouracil or capecitabine), or irinotecan, or a taxane. Alternatively, a fluoropyrimidine (such as fluorouracil or capecitabine) may be combined with either oxaliplatin or a taxane.[2] However, given the high rate of failure after surgery, in an attempt to improve survival rates, there has been great interest in neoadjuvant (pre-operative) or adjuvant (postoperative) therapies, incorporating radiotherapy or chemotherapy or both.[3,4,6]

There is no evidence that ***neoadjuvant*** radiotherapy alone improves survival.[1,3,6,9,10] The evidence for use of neoadjuvant chemotherapy is more conflicting.[1,3,6,11] A systematic review[12] found that it may offer a survival advantage compared with surgery alone, although the evidence was considered to be inconclusive. Meta-analysis[13] also suggested some survival benefit in those with adenocarcinoma, but not for those with squamous cell disease. Thus, some guidelines[2,8,9] consider neoadjuvant chemotherapy as a standard treatment option for localised adenocarcinoma. The ECF regimen (epirubicin, cisplatin, and fluorouracil), or one of its variants, is commonly used.[2]

Initial studies of neoadjuvant chemoradiotherapy also conflicted or were inconclusive due to small samples or inadequate dosage.[3,4,9,13,14] A systematic review[14] found that neoadjuvant chemoradiotherapy significantly improved the 3-year mortality rate compared with surgery alone, and a later meta-analysis[13] found a significant survival benefit, versus surgery alone, in patients with local operable oesophageal carcinoma, regardless of histological tumour type. However, the risk for postoperative mortality (within 90 days of surgery) was also increased by neoadjuvant chemoradiotherapy.[14] Despite this, many centres incorporate neoadjuvant chemoradiotherapy regimens for localised, resectable disease.[1,2,4,7,11] Regimens are largely cisplatin- or fluoropyrimidine-based.[2]

Studies of ***adjuvant*** radiotherapy have failed to show a survival advantage,[2] and, aside from possible benefit in certain subgroups, may actually increase mortality compared with surgery alone.[6] Adjuvant chemotherapy is generally not recommended,[5,9] except in those patients with adenocarcinoma who also received neoadjuvant chemotherapy;[2] treatment is usually with ECF. Adjuvant chemoradiotherapy has shown improved survival rates compared with surgery alone, in patients with adenocarcinoma.[2,6] However, it is not recommended,[5] except in selected high-risk adenocarcinoma patients who have not received neoadjuvant chemoradiotherapy.[2,6] Fluoropyrimidine-based regimens are preferred.[2]

Photodynamic therapy is under investigation for early-stage disease.[15]

In half to two-thirds of patients the disease is too advanced at presentation for anything but palliation. Chemotherapy, chemoradiotherapy, or best supportive care are all options for patients with **unresectable, advanced, or metastatic disease.** Chemoradiotherapy is an option in recurrent disease in those who have not had prior chemotherapy or radiotherapy; more extensive surgery is also an option.[2] Those with poor performance status should be offered supportive care.[2] This may include brachytherapy, laser therapy, stent placement, or photodynamic therapy with photosensitisers (such as porfimer sodium) to relieve obstruction.[2,3,5,9,16] Brachytherapy may be a better

primary therapy for obstruction than a stent.[8,17] In those patients with good performance status, chemotherapy or chemoradiotherapy may also offer some palliation of the disease. Standard options include cisplatin-based, fluoropyrimidine-based, irinotecan-based, oxaliplatin-based or taxane-based combinations.[2,9] In patients with advanced disease that is HER2-positive, trastuzumab may be added to systemic chemotherapy if chemoradiotherapy is not recommended.[2] For further information on common chemotherapy regimens, see Table 1, p. 719.

1. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; 349: 2241–52.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: esophageal cancer (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf (accessed 09/06/10)
3. Jackson C, *et al.* Pharmacotherapy for oesophagogastric cancer. *Drugs* 2007; 67: 2539–56.
4. Kleinberg L, Forastiere AA. Chemoradiation in the management of esophageal cancer. *J Clin Oncol* 2007; 25: 4110–7.
5. Scottish Intercollegiate Guidelines Network. Management of oesophageal and gastric cancer: a national clinical guideline (issued June 2006). Available at: http://www.sign.ac.uk/pdf/sign87.pdf (accessed 09/06/10)
6. Ku GY, Ilson DH. Preoperative therapy in esophageal cancer. *Clin Adv Hematol Oncol* 2008; 6: 371–9.
7. Ekman S, *et al.* Esophageal cancer: current and emerging therapy modalities. *Expert Rev Anticancer Ther* 2008; 8: 1433–48.
8. Stahl M, *et al.* ESMO Guidelines Working Group. Esophageal cancer: Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v46–v49. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v46.full.pdf+html (accessed 15/10/10)
9. Allum WH, *et al.* Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology, and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2002; 50 (suppl 5): v1–v23. Also available at: http://gut.bmj.com/content/50/suppl_5/v1.full.pdf (accessed 13/07/10)
10. Arnott SJ, *et al.* Preoperative radiotherapy for esophageal carcinoma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/06/10).
11. Khushalani N. Cancer of the esophagus and stomach. *Mayo Clin Proc* 2008; 83: 712–22.
12. Vogt K, *et al.* Preoperative chemotherapy for resectable thoracic esophageal cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 09/06/10).
13. Gebski V, *et al.* Australasian Gastro-Intestinal Trials Group. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007; 8: 226–34.
14. Fiorica P, *et al.* Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. *Gut* 2004; 53: 925–30.
15. NICE. Photodynamic therapy for early-stage oesophageal cancer (issued December 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/IPG200guidance.pdf (accessed 29/01/09)
16. NICE. Palliative photodynamic therapy for advanced oesophageal cancer (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/IPG206guidance.pdf (accessed 29/01/09)
17. Homs MYV, *et al.* Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. *Lancet* 2004; 364: 1497–1504.

MALIGNANT NEOPLASMS OF THE STOMACH. Cancer of the stomach is one of the most common cancers worldwide. Geographical distribution varies greatly, with particularly high incidence in the Far East, eastern Europe, and parts of Latin America, although the incidence is declining almost everywhere. (In contrast the incidence of cancers at the gastro-oesophageal junction appears to be increasing.) Over 90% of malignant gastric neoplasms are adenocarcinomas. Less frequent gastric neoplasms include lymphomas (see MALT lymphoma, p. 698.1) and carcinoid tumours (see Neuroendocrine Tumours, p. 716.3). Histologically, tumours are divided into intestinal and diffuse forms; the latter type may have a genetic basis.

Dietary factors, such as high consumption of salted or smoked foods, are thought to play a role in the development of gastric cancer. Smoking is also considered to be an independent risk factor. *Helicobacter pylori* infection, and resultant gastritis, plays a role in gastric lymphomas, and appears to almost double the risk for the development of gastric cancer.[1-5] However, it is not yet clear if elimination of *Helicobacter pylori* infection can help prevent the development of gastric cancer.[6] It is possible that some patients will have developed irreversible mucosal changes, and that *H. pylori* eradication will be ineffective.[5,7]

Early disease is relatively asymptomatic or produces non-specific gastrointestinal symptoms such as dyspepsia. There is concern that the use of antisecretory drugs for these symptoms may delay the diagnosis of gastric cancer (see Gastric Carcinoma, under Omeprazole Precautions, p. 1873.2). Gastric epithelial dysplasia is a premalignant condition, and warrants follow-up and possible surgical intervention. Similarly, persistent gastric ulcers may be malignant. More advanced disease, which is the norm at presentation in most western countries, may produce abdominal discomfort or pain, anaemia, weight loss, and anorexia; obstruction, haemorrhage, and perforation may develop. Extension to the liver and pancreas, and lymphatic and blood-borne (portal) metastases may occur. The overexpression of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and human epidermal growth factor receptor-2 (HER2) has been associated with a poor prognosis in patients with gastric and oesophageal cancers.

Surgery is the mainstay of treatment for **locoregional disease.**[2,4,8,10] There is some uncertainty, however, about the appropriate extent of surgery and associated lymph-node dissection.[1-4,11] Typical 5-year survival rates in western patients have ranged from about 50 to 80% in those with stage I disease to 13% in those with stage III;[11,12] although much higher survival rates (over 96% in stage I disease and nearly 45% in stage III) have been reported in Japan,[11] Japanese and western patients may not be equivalent, a fact that has made comparisons difficult.[13]

Because of the poorer survival rates in patients with more advanced locoregional disease, postoperative (adjuvant) and pre-operative (neoadjuvant) treatments have been tried.[1,4,8,11,12] Postoperative radiotherapy has not been shown to produce a survival benefit, and the value of pre-operative radiotherapy is uncertain.[11,12] However, there has been considerable interest in the possible value of chemotherapy, alone or with radiotherapy (chemoradiotherapy).[1,11,12] Postoperative chemotherapy has failed to show a significant survival benefit, except for results with tegafur (plus gimeracil and oteracil potassium) in a Japanese population; it has not become standard practice in western countries.[3,8,10,12] Postoperative intraperitoneal chemotherapy (using mitomycin, cisplatin, or fluorouracil) is under investigation.[2,4,9] Preliminary studies of pre-operative chemotherapy suggested improved survival compared with historical controls, but randomised evidence is lacking.[2] However, perioperative chemotherapy, with cycles of ECF (epirubicin, cisplatin, and fluorouracil) given pre- and postoperatively, was found to improve progression-free and overall survival in patients with operable adenocarcinomas.[14] This strategy is recommended for centres with a multi-disciplinary approach, where there is an opportunity for patients to be considered for perioperative treatment.[8] Perioperative chemotherapy with ECF, or modifications thereof, has become standard practice in the UK and Europe,[4,8,10,15] and is considered an option for patients in the USA.[3] A large US study[16] found that median survival was improved from 27 to 36 months in patients given postoperative chemoradiotherapy (using a fluorouracil and folinic acid regimen). This strategy is recommended for centres where surgery is used as the primary therapy, or where referral is made postoperatively.[8] Using a regimen based on a fluoropyrimidine (such as fluorouracil or capecitabine), postoperative chemoradiotherapy has become the standard of care in the USA.[3,4,10,11] The value of pre-operative chemoradiotherapy, in contrast, remains to be determined,[3,4,11] although it may be a potential option in medically fit patients whose disease is resectable. The recommended regimen includes a taxane (paclitaxel or docetaxel) with a fluoropyrimidine (fluorouracil or capecitabine).[3] For patients with inoperable locoregional disease, radiotherapy with concurrent fluorouracil-based radiosensitisation is used. Palliative chemotherapy with any of the regimens used for metastatic disease is also an option in these patients.[3]

Treatment for **advanced disease** is purely palliative, and options include supportive care with or without chemotherapy.[3] Supportive care includes the relief of luminal obstruction with, for example, stent placement, laser surgery, or photodynamic therapy. Chemotherapy may have substantial palliative effect and modest survival gains, and may be considered in those with good performance status.[2,3] There is no gold standard regimen, although combination therapy is preferred to single-agent therapy for palliation.[17] A systematic review[18] found that combination regimens including a fluoropyrimidine, anthracyclines, and cisplatin produced significant survival benefits; ECF was considered the regimen of choice since it was best tolerated, and it is considered standard therapy in some countries.[17] Fluorouracil, doxorubicin, and mitomycin (FAM) has been widely used;[3] other combinations include the substitution of methotrexate for mitomycin, or cisplatin for doxorubicin, in the FAM regimen (FAMTX and MFC, respectively),[3,17] and the use of docetaxel instead of epirubicin in ECF (DCF).[3,15] However, ECF has shown better response and median survival than FAMTX.[3,8,15,17] In turn, the use of EOX (epirubicin, oxaliplatin, and capecitabine) was found to be as effective as ECF, but with a more favourable toxicity profile.[4,8,17] ECF, DCF, or their modifications are usually preferred as first-line therapy.[3,9,10] Other combinations used in advanced or metastatic disease include irinotecan plus cisplatin or a fluoropyrimidine (such as fluorouracil or capecitabine), oxaliplatin plus a fluoropyrimidine, and paclitaxel-based regimens.[3,10] In those patients with advanced gastric cancer or gastro-oesophageal adenocarcinoma that is HER2-positive, trastuzumab may be added to systemic chemotherapy if chemoradiotherapy is not recommended.[3] Combination therapy using newer agents such as bevacizumab, cetuximab, and gefitinib are being investigated.[4,8,10,15,17] For further information on common chemotherapy regimens, see Table 1, p. 719.

1. Hohenberger P, Gretschel S. Gastric cancer. *Lancet* 2003; 362: 305–15.
2. Allum WH, *et al.* Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology, and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2002; 50 (suppl 5): v1–v23. Also available at: http://gut.bmj.com/content/50/suppl_5/v1.full.pdf (accessed 12/07/10)
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: gastric cancer (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf (accessed 10/06/10)
4. Khushalani N. Cancer of the esophagus and stomach. *Mayo Clin Proc* 2008; 83: 712–22.
5. Lochhead P, El-Omar EM. Gastric cancer. *Br Med Bull* 2008; 85: 87–100.
6. Wong BC-Y, *et al.* Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; 291: 187–94.
7. Lee Y-C, *et al.* Is eradication of Helicobacter pylori the feasible way to prevent gastric cancer? New evidence and progress, but still a long way to go. *J Formos Med Assoc* 2008; 107: 591–9.
8. Jackson C, *et al.* Pharmacotherapy for oesophagogastric cancer. *Drugs* 2007; 67: 2539–56.
9. Scottish Intercollegiate Guidelines Network. Management of oesophageal and gastric cancer: a national clinical guideline (issued June 2006). Available at: http://www.sign.ac.uk/pdf/sign87.pdf (accessed 10/06/10)
10. Okines A, *et al.* ESMO Guidelines Working Group. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v50–v54. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v50.full.pdf+html (accessed 15/10/10)
11. Jansen EPM, *et al.* Optimal locoregional treatment in gastric cancer. *J Clin Oncol* 2005; 23: 4509–17.
12. Lim L, *et al.* Adjuvant therapy in gastric cancer. *J Clin Oncol* 2005; 23: 6220–32.
13. Sano T. Adjuvant and neoadjuvant therapy of gastric cancer a comparison of three pivotal studies. *Curr Oncol Rep* 2008; 10: 191–8.
14. Cunningham D, *et al.* MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355: 11–20.
15. Wöll E, *et al.* Chemotherapy in gastric cancer. *Anticancer Res* 2008; 28: 1213–19.
16. Macdonald JS, *et al.* Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; 345: 725–30.
17. Field K, *et al.* Locally advanced and metastatic gastric cancer: current management and new treatment developments. *Drugs* 2008; 68: 259–317.
18. Wagner AD, *et al.* Chemotherapy for advanced gastric cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 14/06/10).

MALIGNANT NEOPLASMS OF THE COLON AND RECTUM. Colorectal cancers are very common in developed areas such as the USA and western Europe, but rare among African and Asian populations. Genetic, environmental, lifestyle, and dietary factors are thought to contribute to development of the disease. Inherited predisposition syndromes include familial adenomatous polyposis and hereditary non-polyposis colorectal cancer. Most large bowel cancers arise within pre-existing intestinal polyps. Over 50% occur in the rectum and about 20% in the sigmoid colon. There may be direct invasion of neighbouring structures and metastatic spread to the lymph nodes, and to lung, bone, and in particular, liver. Over 50% of patients will develop metastases, and up to 25% present with metastatic disease. Signs and symptoms are non-specific and include blood in the stools, altered bowel habit, anaemia, abdominal pain, and weight loss; there may be local obstruction (depending on location) or perforation. Screening is effective in reducing mortality, although the ideal method to be used is controversial.

Pathological stage is an important prognostic factor. The Dukes classification and its modifications and in particular the tumour-node-metastasis (TNM) staging system have been widely used. The latter is based on depth of bowel wall invasion, extent of lymph node involvement, and presence of metastases. These are roughly grouped into stages; stages I and II have no lymph node involvement, stage III is lymph-node positive, and stage IV is metastatic.[1-3] About 40% of colorectal cancers are characterised by mutations in the KRAS gene, and about 5 to 8% show a specific mutation in the BRAF gene. KRAS mutations have been shown to predict for lack of response to cetuximab and panitumumab; mutated BRAF may be a marker of resistance to therapies that target the epidermal growth factor receptor, although data remain inconclusive.[1]

The first-line treatment for **early-stage** and **locally-advanced** disease (stages I to III; Dukes A to C) is surgery.[1-3] Survival in early-stage disease is good: published 5-year overall survival rates are 80 to 95% in patients with stage I disease, but fall to 25 to 60% (depending on prognostic factors such as nodal involvement and degree of tumour invasiveness) in those with stage III disease.[4] Adjuvant or neoadjuvant therapies have thus been widely investigated and incorporated into treatment.[1,2]

Adjuvant therapy for stage I *colon cancer* is considered to be unnecessary.[1,3] For stage III disease, fluoropyrimidine-based chemotherapy has been shown to have an overall survival benefit, and adjuvant therapy has become standard practice for these patients.[1,3,5-10] The evidence in favour of adjuvant therapy in stage II disease is weaker and its use has been controversial.[3,7,11] While it is not routinely recommended for all patients,[12] most consider that its use in high-risk patients with poor prognostic features is justified.[1,3,6,9,10,12,13] The FOLFOX regimen (infusional fluoro-

uracil, folinic acid, and oxaliplatin), compared with fluorouracil plus folinic acid, has been found to improve disease-free and overall survival in stage III patients.[1,10] The FLOX regimen (bolus fluorouracil, folinic acid, and oxaliplatin) also improves disease-free survival in patients with stage II and stage III colon cancer compared with fluorouracil and folinic acid.[1] Oral fluoropyrimidines have also been shown to improve survival after resection,[14] and oral capecitabine appears to be as effective as bolus fluorouracil plus folinic acid.[10] All the above are therefore options for adjuvant treatment.[1,10] Results with the IFL regimen (irinotecan, bolus fluorouracil, and folinic acid) have not proved satisfactory because of its toxicity,[4,7,9] and FOLFIRI (infusional fluorouracil, folinic acid, and irinotecan) has not been shown to be superior to fluorouracil plus folinic acid in the adjuvant setting.[1]

Neoadjuvant chemotherapy and adjuvant radiotherapy seem to play little role in the management of early colon cancer, and the latter is not generally recommended.[4] In contrast, in the management of early stage ***rectal cancer*** radiotherapy or chemoradiotherapy plays an important role, to decrease the size of the tumour pre-operatively, and to decrease the risk of recurrence.[4] Surgery alone may be sufficient for patients with early, favourable disease.[2,15] A meta-analysis[16] found that both neoadjuvant and adjuvant radiotherapy reduced the risk of recurrence compared with surgery alone, and that fewer patients who had neoadjuvant radiotherapy died from rectal cancer, although early deaths from other causes increased, and there was little impact on overall survival. Some still recommend neoadjuvant radiotherapy as a convenient, simple treatment with low toxicity for more locally advanced disease.[15] However, adjuvant chemoradiotherapy was shown to improve overall survival compared with surgery alone, and it was considered the standard of care for patients with stage II or stage III rectal cancer.[3,4,8,16] A large randomised study[17] subsequently found that neoadjuvant chemoradiotherapy significantly improved local control and was associated with less toxicity than adjuvant chemoradiotherapy, although there was no improvement in overall survival. As a result, neoadjuvant treatment has been advocated on the basis of better tumour control, lower morbidity,[3,4] and enhanced sphincter preservation.[4] Regimens are fluoropyrimidine-based, typically using infusional fluorouracil alone, or bolus fluorouracil plus folinic acid, or oral capecitabine. After surgery, adjuvant chemotherapy with a fluorouracil plus folinic acid regimen, FOLFOX, or capecitabine is recommended; the latter 2 options are extrapolations from results in colon cancer.[2] Adjuvant chemoradiotherapy is still used for patients if neoadjuvant radiotherapy or chemoradiotherapy has not been given.[2,15]

Palliative treatments for advanced colorectal cancer (stage IV; metastatic disease) include surgery, radiotherapy, chemotherapy, and chemoradiotherapy.[1,2,4,5,7,18] Genetic profiling may allow individualisation of therapy to improve efficacy and reduce toxicity.[19,20] Metastasis usually occurs first to the liver; for cases that are localised and resectable, surgery offers a chance of prolonged survival.[4,5] Systemic neoadjuvant chemotherapy can reduce tumour volume and render some previously unresectable metastases suitable candidates for surgery.[1,4,21] Another potential approach is the adjuvant use of hepatic arterial (intraportal) chemotherapy directed at the liver. However, it is unclear who should be offered such treatment, and what the survival benefits are; given the potential for biliary toxicity and the technical expertise required, hepatic arterial therapy is generally reserved for use at specialist centres.[1,2]

Conventional palliative chemotherapy is based on the use of fluorouracil, and has been shown to produce modest survival benefits.[22] Adding folinic acid improves the efficacy,[19,23] and the combination has long been regarded as standard. Although it has been suggested that regimens based on continuous infusion of fluorouracil are more effective than those using bolus dosage,[4,24] others consider that although response rates are improved, median survival is similar, and that differences in toxicity and convenience of administration are more significant in making the choice.[18] Oral fluorouracil prodrugs such as capecitabine, or tegafur with uracil, are considered valid alternatives to intravenous fluorouracil.[4,19,21,25]

Several newer drugs have now been shown to improve response rates and survival when used for chemotherapy in these patients. In particular, regimens including irinotecan or oxaliplatin, such as FOLFIRI or FOLFOX, are now considered options for first-line management of metastatic colorectal cancer.[1,2,6,8,18-21] There is also evidence for both improved response and survival when bevacizumab (an antagonist of vascular endothelial growth factor) is added to chemotherapy.[18,19] Similarly, cetuximab, a blocker of the epidermal growth factor receptor, appears to improve response rate and decrease the rate of progression if given with irinotecan,[8] and preliminary results suggest that it is effective when combined with a FOLFOX regimen.[20] As a result, currently recommended regimens combine bevacizumab with one of the first-line regimens—FOLFOX, FOLFIRI, a fluorouracil plus folinic acid regimen, or CapeOX (capecitabine plus oxaliplatin)—in patients with metastatic disease who are able to tolerate intensive therapy,[1,2,19-21] although the data to support some of these combinations are not yet available. Cetuximab or panitumumab may also be combined with FOLFIRI or FOLFOX (in those with the KRAS-wild type gene).[1,2,19] In those who fail to respond, an alternative first-line regimen may be tried (without bevacizumab). Other options include cetuximab plus irinotecan, or monotherapy with a drug not included in the original regimen (such as irinotecan, cetuximab, or panitumumab). In those in whom intensive therapy is not appropriate, options include capecitabine or fluorouracil plus folinic acid; either of these regimens may be combined with bevacizumab.[1,2,8,21] In those with the KRAS-wild type gene, the epidermal growth factor inhibitors cetuximab or panitumumab are alternatives.[1,2] The tyrosine kinase inhibitor regorafenib is an option when other treatments have failed.

For further information on common chemotherapy regimens, see Table 1, p. 719.

Other drugs and regimens continue to be investigated.

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: colon cancer (version 3.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf (accessed 10/06/10)
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: rectal cancer (version 3.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/rectal.pdf (accessed 10/06/10)
3. Wolpin BM, Mayer RJ. Systemic treatment of colorectal cancer. *Gastroenterology* 2008; 134: 1296–1310.
4. Weitz J, *et al.* Colorectal cancer. *Lancet* 2005; 365: 153–65.
5. NICE. Guidance on cancer services: improving outcomes in colorectal cancers (manual update, issued May 2004). Available at: http://www.nice.org.uk/nicemedia/pdf/CSGCCfullguidance.pdf (accessed 04/02/09)
6. Waters C. Colorectal cancer: an overview. *Pharm J* 2006; 276: 323–6.
7. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005; 352: 476–87.
8. Gill S, *et al.* Colorectal cancer. *Mayo Clin Proc* 2007; 82: 114–29.
9. Waterston AM, Cassidy J. Adjuvant treatment strategies for early colon cancer. *Drugs* 2005; 65: 1935–47.
10. Labianca R, *et al.* ESMO Guidelines Working Group. Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v70–v77. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v70.full.pdf+html (accessed 18/10/10)
11. Figueredo A, *et al.* Adjuvant therapy for stage II colon cancer: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group. *J Clin Oncol* 2004; 22: 3395–3407.
12. Benson AB, *et al.* American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 2004; 22: 3408–19. Also available at: http://www.jco.org/cgi/reprint/22/16/3408.pdf (accessed 04/02/09)
13. Figueredo A, *et al.* Adjuvant therapy for completely resected stage II colon cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 04/02/09).
14. Meta-Analysis Group of the Japanese Society for Cancer of the Colon and Rectum and the Meta-Analysis Group in Cancer. Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. *J Clin Oncol* 2004; 22: 484–92.
15. Glimelius B, *et al.* ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v82–v86. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v82.full.pdf+html (accessed 18/10/10)
16. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials. *Lancet* 2001; 358: 1291–1304.
17. Sauer R, *et al.* Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; 351: 1731–40.
18. Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. *J Clin Oncol* 2005; 23: 4553–60.
19. Board RE, Valle JW. Metastatic colorectal cancer: current systemic treatment options. *Drugs* 2007; 67: 1851–67.
20. Saunders M, Iveson T. Management of advanced colorectal cancer: state of the art. *Br J Cancer* 2006; 95: 131–8.
21. Van Cutsem E, *et al.* ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol* 2010; 21 (suppl 5): v93–v97. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v93.full.pdf+html (accessed 18/10/10)
22. Best L, *et al.* Palliative chemotherapy for advanced or metastatic colorectal cancer. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 04/02/09).
23. Advanced Colorectal Cancer Meta-analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; 10: 896–903.
24. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; 16: 301–308.
25. NICE. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer: Technology Appraisal 61 (issued May 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/61CapecitabineCRCfullguidance.pdf (accessed 04/02/09)

Prophylaxis of cancer of the colon and rectum. Various drugs and dietary factors have been shown in epidemiological studies to be associated with a reduced risk of colorectal cancer, and some of these have been investigated in prospective randomised studies.[1-3]

- Aspirin and NSAIDs are the most widely studied.[1-10] In short-term randomised studies, both sulindac and celecoxib have reduced the size and number of colonic polyps in patients with familial adenomatous polyposis.[4] However, prophylactic surgical removal of the colon is still considered the standard of care for these patients.[1,11] Furthermore, despite significant reductions in adenoma formation in high-risk patients, cyclo-oxygenase-2 (COX-2) inhibitors have also been associated with cardiovascular toxicity.[12] There is some evidence of a dose-response effect, since the greatest prophylactic effect of aspirin in average-risk populations appears to be associated with doses substantially greater than those required for prevention of cardiovascular disease.[5,6,8,13] The effect of aspirin may depend on COX-2 expression: it appears only to reduce the risk of colorectal cancers that overexpress COX-2.[14]
- Calcium supplementation has shown a moderate reduction in the formation of new adenomas in patients with a history of colorectal adenomas,[15] and is well tolerated, but the evidence is not strong enough to recommend general supplementation to prevent colorectal cancer.
- Despite the epidemiological evidence for dietary fibre, several large randomised studies of fibre supplements or high-fibre diets have not found any reduction in the formation of new adenomas in patients with a history of colorectal adenomas.[1,2,16]
- Antioxidant vitamins have also been investigated, but evidence for their benefit is conflicting (see Prophylaxis of Malignant Neoplasms, p. 2047.3).
- Ursodeoxycholic acid has been shown to reduce the risk of colorectal cancer in patients with ulcerative colitis and primary sclerosing cholangitis, see Inflammatory Bowel Disease, p. 1811.3.
- Epidemiological evidence[17] suggests that long-term use of statins is associated with a marked reduction in the risk of colorectal cancer. Prospective studies are required to confirm these results. A meta-analysis[18] did not support this hypothesis, although a modest reduction in risk or an effect with higher doses of statins could not be ruled out.
- Other potential chemopreventive agents on the basis of epidemiological evidence include folic acid, selenium, and menopausal HRT.[1-3] For the suggestion that folate may have dual modulatory effects on carcinogenesis, see Carcinogenicity, under Folic Acid, p. 2065.3.

An important component of the care of patients with inherited predisposition or other risk factors for colon cancer is regular screening.[2,11,19,20] Various screening methods have also been investigated for use in normal-risk individuals. US guidelines[21] recommend screening for colorectal cancer using faecal occult blood testing, sigmoidoscopy, or colonoscopy in average-risk adults, starting at 50 years of age and continuing until age 75; routine screening is not recommended for those older than this.

1. Jänne PA, Mayer RJ. Chemoprevention of colorectal cancer. *N Engl J Med* 2000; 342: 1960–8.
2. Hawk ET, Levin B. Colorectal cancer prevention. *J Clin Oncol* 2005; 23: 378–91.
3. Arber N, Levin B. Chemoprevention of colorectal neoplasia: the potential for personalized medicine. *Gastroenterology* 2008; 134: 1224–37.
4. Herendeen JM, Lindley C. Use of NSAIDs for the chemoprevention of colorectal cancer. *Ann Pharmacother* 2003; 37: 1664–74.
5. Chan AT, *et al.* A prospective study of aspirin use and the risk for colorectal adenoma. *Ann Intern Med* 2004; 140: 157–66.
6. Chan AT, *et al.* Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005; 294: 914–23.
7. Dubé C, *et al.* The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007; 146: 365–75.
8. Flossmann E, Rothwell PM. British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007; 369: 1603–13.
9. Rostom A, *et al.* Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007; 146: 376–89.
10. Stürmer T, *et al.* Colorectal cancer after start of nonsteroidal anti-inflammatory drug use. *Am J Med* 2006; 119: 494–502.
11. King JE, *et al.* Care of patients and their families with familial adenomatous polyposis. *Mayo Clin Proc* 2000; 75: 57–67.
12. Bertagnolli MM. Chemoprevention of colorectal cancer with cyclooxygenase-2 inhibitors: two steps forward, one step back. *Lancet Oncol* 2007; 8: 439–43.
13. Chan AT, *et al.* Aspirin dose and duration of use and risk of colorectal cancer in men. *Gastroenterology* 2008; 134: 21–8.
14. Chan AT, *et al.* Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med* 2007; 356: 2131–42.
15. Weingarten MA, *et al.* Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 06/02/09).
16. Park Y, *et al.* Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA* 2005; 294: 2849–57.
17. Poynter JN, *et al.* Statins and the risk of colorectal cancer. *N Engl J Med* 2005; 352: 2184–92.
18. Bonovas S, *et al.* Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. *J Clin Oncol* 2007; 25: 3462–8.
19. Cairns S, Scholefield JH, eds. The British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland. Guidelines for colorectal cancer screening in high risk groups. *Gut* 2002; 51 (suppl 5): v1–v28. Also available at: http://gut.bmjjournals.com/cgi/reprint/51/suppl_5/v1.pdf (accessed 06/02/09)
20. Rhodes JM. Colorectal cancer screening in the UK: Joint position statement by the British Society of Gastroenterology, the Royal College of Physicians, and the Association of Coloproctology of Great Britain and Ireland. *Gut* 2000; 46: 746–8. Also available at: http://gut.bmjjournals.com/cgi/reprint/46/6/746.pdf (accessed 06/02/09)
21. U. S. Preventive Services Task Force. Screening for colorectal cancer: U. S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008; 149: 627–37. Also available at: http://www.annals.org/cgi/reprint/149/9/627.pdf (accessed 12/08/09)

MALIGNANT NEOPLASMS OF THE ANUS. Anal cancer is a relatively uncommon malignancy. Tumours arising within the anal canal are most often squamous cell carcinomas.[1-5] Other types of cancer arising in the anal region include adenocarcinomas, which are managed similarly to rectal cancer (see Malignant Neoplasms of the Colon and Rectum, p. 706.3).[1,2,4] Anal intraepithelial neoplasia (AIN) is considered to be a precursor of squamous cell anal carcinoma.[5,6] Risk factors associated with anal carcinoma include immunosuppression, anal or genital human papillomavirus (HPV) infection (especially HPV-16), a history of receptive anal intercourse or sexually transmitted disease, multiple sexual partners, and a history of cervical, vulvar, or vaginal cancer. HIV infection, long-term corticosteroid use, and smoking may also be associated risk factors.[1-4,6,7] Clinical manifestations of anal carcinoma include anal bleeding, pain, or the sensation of a rectal mass; diagnosis may be delayed as bleeding is often attributed to haemorrhoids.[1,4,6]

Treatment of anal intraepithelial neoplasia includes excision for clinically definable lesions. Topical creams containing fluorouracil or imiquimod have also been used, and there is anecdotal evidence for the use of photodynamic therapy.[6] A vaccine for HPV-related AIN is under development.[5]

The primary treatment for anal canal carcinoma is combined modality treatment using chemotherapy and radiotherapy. Chemoradiotherapy with fluorouracil plus mitomycin is the regimen of choice, having been found to be superior to radiation alone.[1-8] Fluorouracil with cisplatin is also used. This regimen, when compared with fluorouracil plus mitomycin, had comparable survival and less haematological toxicity, but higher colostomy rates.[2,4,6] For persistent or locally recurrent disease, surgical resection with the formation of a colostomy is preferred.[1-6] Salvage chemoradiotherapy with a cisplatin-based regimen has also been reported to be successful in the treatment of persistent or relapsed disease.[1,4] About 12% of patients develop metastases, most commonly to the liver and lung.[6] There is no standard therapy for metastatic disease.[1,6,8] Treatment recommendations include platinum-based chemotherapy or enrolment in clinical studies.[2,4,6,8] Local chemotherapy for liver metastases using intra-arterial chemotherapy has been reported to be successful.[8]

The management of anal cancer in HIV-positive patients has improved with the advent of HAART; before this, standard chemoradiotherapy was associated with severe acute haematological toxicity.[5] HIV-positive patients should receive standard chemoradiotherapy treatment for anal squamous cell carcinoma, unless they are severely immunosuppressed (usually defined as CD4 cell count < 200 cells/mm^3), in which case monitoring and individualisation of therapy is advised.[4,6]

1. Ryan DP, *et al.* Carcinoma of the anal canal. *N Engl J Med* 2000; 342: 792–800.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: anal carcinoma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/anal.pdf (accessed 10/06/10)
3. Gervaz P, *et al.* Chemotherapeutic options in the management of anal cancer. *Expert Opin Pharmacother* 2004; 5: 2479–84.
4. Uronis HE, Bendell JC. Anal cancer: an overview. *Oncologist* 2007; 12: 524–34.
5. Gervaz P, *et al.* Diagnosis and management of anal cancer. *Curr Gastroenterol Rep* 2008; 10: 502–6.
6. Fleshner PR, *et al.* Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for anal squamous neoplasms. *Dis Colon Rectum* 2008; 51: 2–9.
7. Glynne-Jones R, *et al.* ESMO Guidelines Working Group. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v87–v92. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v87.full.pdf+html (accessed 18/10/10)
8. Sato H, *et al.* Management of anal canal cancer. *Dis Colon Rectum* 2005; 48: 1301–15.

Malignant neoplasms of the head and neck. Cancers of the head and neck are classically defined as those of the mucosal surfaces of the upper aerodigestive tract and include neoplasms of the lip, oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands. Most are squamous cell carcinomas, and the highest incidence is in men aged over 50 years. Overall, cancers of the head and neck account for about 6% of all malignant neoplasms worldwide. The major risk factor for these cancers is the use of tobacco (whether chewed, inhaled, or smoked) and alcohol. Human papillomavirus (HPV) infection appears to be a risk factor for some squamous cancers of the oropharynx. HPV-positive tumours have a better prognosis than HPV-negative disease, being more responsive to therapy. Vaccination against HPV is of potential use for primary prevention. Nasopharyngeal carcinoma is a unique type of head and neck cancer. It is endemic in Alaska, China, and North Africa and is associated with Epstein-Barr virus and the consumption of salt-cured fish. It tends to metastasise early.

Clinical manifestations of head and neck cancer vary according to the location of the primary tumour, and can be non-specific. Symptoms include mouth ulceration, tongue pain, epistaxis, hoarseness, sore throat, otalgia, dysphagia, chronic cough, haemoptysis, and stridor.

Premalignant lesions include **leucoplakia** and **erythroplakia**, and these can progress to invasive cancer. About one-third of cancers are diagnosed at early stages (I and II), and the rest are usually locally advanced (stage III and IVA). Although early-stage disease can be successfully treated, there is a high incidence of second primary cancers in the head and neck, lung, or oesophagus. Therefore, there is interest in the development of chemopreventive drugs to reduce this risk. Fewer than 30% of patients with locally advanced disease are cured. The treatment of head and neck cancer is complex, and is affected by the site and extent of disease, pathological findings, lymph node involvement, the patient's functional status, and comorbidities; the experience and skill of the team carrying out surgery and radiotherapy will also influence treatment recommendations.

Patients with early-stage **nasopharyngeal** disease are treated with radiotherapy alone. Those with locally advanced disease are treated with cisplatin-based chemotherapy given concurrently with radiotherapy (chemoradiotherapy) followed by adjuvant chemotherapy with cisplatin plus fluorouracil.[1-3] For metastatic disease, palliative chemotherapy can be considered; platinum-based combination regimens are used first-line. Other active drugs, used as monotherapy or in combination, include paclitaxel, docetaxel, gemcitabine, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin, and oxaliplatin. Treatment is based on previous treatment and toxicity.[3]

Patients with early-stage resectable **squamous cell carcinoma** of the head and neck (excluding nasopharyngeal carcinoma) are treated with surgery or radiotherapy, with curative intent.[2,4-7] The two methods have comparable efficacy, and choice depends on the specific tumour site, resectability, and functional outcome after therapy.[2,5] For those with adverse prognostic factors such as nodal involvement, positive margins, or extracapsular spread, postoperative radiotherapy or postoperative chemoradiotherapy may be used.[4,8]

Locally advanced disease needs combined modality therapy,[2,4-6] individualised according to resectability, tumour site, the need for organ preservation, and functional outcome.[2] Historically, surgery plus radiotherapy was used for resectable disease, and radiotherapy alone for unresectable disease,[9] but combined chemoradiotherapy has proved a major advance in treatment.[5] It is superior to radiotherapy alone,[2,5-10] although toxicity is increased, and to the use of chemotherapy either before or after radiotherapy.[2,5] Resectable disease is therefore usually managed with surgery followed by adjuvant treatment with radiotherapy alone or chemoradiotherapy to reduce locoregional recurrence.[2,4,5,7,8] In resectable disease where organ preservation is important, and in unresectable disease, definitive chemoradiotherapy is the standard treatment,[2,4,5,7] unless the use of chemotherapy is contra-indicated due to poor performance status or comorbidities.[4,5] Platinum-based regimens are standard.[2,4,5,8] Use of cetuximab with radiotherapy may be considered as an alternative to chemoradiotherapy in those patients unable to tolerate chemotherapy.[2,4,5,8] While chemoradiotherapy improves locoregional control, its effect on distant recurrence or metastases is inconsistent, and induction or neoadjuvant chemotherapy has been studied in the hope of reducing metastasis. Interpretation of initial studies of induction chemotherapy (used before surgery or radiotherapy) was difficult given their heterogeneity, although a survival benefit was shown in those studies using cisplatin plus fluorouracil. The addition of docetaxel further improved survival and organ preservation in studies of induction chemotherapy (used before radiotherapy or chemoradiotherapy).[2,5,6] Induction chemotherapy is not regarded as standard treatment for locally advanced disease,[5] but its use before chemoradiotherapy (compared with chemoradiotherapy alone) is under investigation.[2,5]

Palliative chemotherapy is used in *metastatic* or *recurrent* disease.[4,5,9] Salvage surgery or a repeat course of radiotherapy are other options, depending on previous treatment. Drugs used for single-agent treatment include cisplatin, carboplatin, paclitaxel, docetaxel, fluorouracil, methotrexate, ifosfamide, bleomycin, cetuximab, and gemcitabine (for nasopharyngeal cancer). Common combination regimens such as cisplatin and fluorouracil produce more responses, but no clear improvement in survival.[4,5,9] Addition of cetuximab to this standard platinum plus fluorouracil regimen has been found to improve survival.[11] Other common combinations include cisplatin or carboplatin plus a taxane.[4] Gefitinib and erlotinib have shown modest benefit when used as monotherapy, and are under investigation in combination regimens.[2,5] The choice of best supportive care or single-agent or combination chemotherapy should be dictated by the patient's performance status, as the benefits of chemotherapy are limited.[4]

A local injection of cisplatin in a gel formulation containing adrenaline has been investigated in recurrent and refractory head and neck cancer.[12] Photodynamic therapy (see under Porfimer Sodium, p. 849.1) using temoporfin is a more recent development for palliative management. Head and neck cancers have high levels of p53 gene mutations, and gene therapy is under investigation.[13] Chemoprevention by treatment of premalignant disease is also under investigation (see Leucoplakia, p. 750.3).

1. Wei WI, Sham JST. Nasopharyngeal carcinoma. *Lancet* 2005; 365: 2041–54.
2. Choong N, Vokes E. Expanding role of the medical oncologist in the management of head and neck cancer. *CA Cancer J Clin* 2008; 58: 32–53.
3. Chan ATC, *et al.* EHNS-ESMO-ESTRO Guidelines Working Group. Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v187–v189. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v187.full.pdf+html (accessed 18/10/10)
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: head and neck cancers (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf (accessed 13/07/10)
5. Argiris A, *et al.* Head and neck cancer. *Lancet* 2008; 371: 1695–1709.
6. Haddad RI, Shin DM. Recent advances in head and neck cancer. *N Engl J Med* 2008; 359: 1143–54.
7. Grégoire V, *et al.* EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v184–v186. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v184.full.pdf+html (accessed 18/10/10)
8. Scottish Intercollegiate Guidelines Network. Diagnosis and management of head and neck cancer: a national clinical guideline (issued October 2006). Available at: http://www.sign.ac.uk/pdf/sign90.pdf (accessed 10/06/10)
9. Cohen EEW, *et al.* The expanding role of systemic therapy in head and neck cancer. *J Clin Oncol* 2004; 22: 1743–52.
10. Salama JK, *et al.* Chemoradiotherapy for locally advanced head and neck cancer. *J Clin Oncol* 2007; 25: 4118–26. Correction. *ibid.* 2008; 26: 4229.
11. Vermorken JB, *et al.* Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; 359: 1116–27.
12. Wenig BL, *et al.* The role of intratumoral therapy with cisplatin/epinephrine injectable gel in the management of advanced squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 2002; 128: 880–5.
13. Al-Reefy H, *et al.* Squamous cell carcinoma in the head and neck. *Br J Hosp Med* 2007; 68: 380–3.

Malignant neoplasms of the kidney. Cancer of the kidney is relatively uncommon, accounting for about 2% of all cancers worldwide. About 90% of renal tumours are renal cell carcinoma, of which the majority are clear cell tumours. The disease is about twice as common in men as in women. Several hereditary types of renal cell carcinoma exist, the most common being von Hippel-Lindau (VHL) disease, caused by a mutation in the VHL-gene, which predisposes to clear cell carcinoma. Aside from genetic predisposition, risk factors include smoking, obesity, hypertension, use of analgesics such as phenacetin and acquired cystic kidney disease associated with end-stage renal disease. Disease is often clinically silent; there may however be haematuria, flank and back pain, and a palpable mass in the flank or abdomen. Fatigue, anaemia, and weight loss can also occur. About one quarter of patients present with advanced disease. The most common sites for metastases are the lung, liver, and bone, although unusual sites for metastases are a known feature of renal cancer.

Radical nephrectomy is the main **treatment** for *early-stage* (stages I and II) disease although nephron-sparing partial nephrectomy may be considered in some patients.[1-4] Results achieved with nephron-sparing surgery are similar to radical nephrectomy, but recurrence rates are higher.[3] Minimally invasive procedures such as radiofrequency ablation and cryotherapy are options for treatment of small tumours, although comparisons with surgery are lacking.[2] Radical nephrectomy is also used in selected patients with *locally advanced* (stage III) disease. After surgery 20 to 30% of patients with localised tumours will relapse, usually at distant sites.[2] However, adjuvant therapy has no established role.[2] Radiotherapy is not beneficial, and no systemic therapy has been shown to reduce relapse; interferon alfa or interleukin-2 are not effective.[2,3] Standard care therefore remains close observation.[2]

Patients with *invasive* or *metastatic* (stage IV) disease are also candidates for surgery.[2,5,6] Palliative nephrectomy can be considered for alleviation of symptoms.[7] Nephrectomy and surgical removal of isolated metastases may be appropriate in some patients,[2,7] and cytoreductive nephrectomy before systemic therapy is recommended for patients with potentially resectable disease and multiple metastases,[2,8] since a small survival benefit has been shown with nephrectomy before cytokine therapy compared with cytokine therapy alone.[9,10]

Renal cell carcinoma has been largely resistant to conventional antineoplastic chemotherapy,[1,3,7,11] and cytokine therapy with either interleukin-2 or interferon alfa became a standard treatment,[2,8] despite toxicity problems and generally poor overall response rates.[5] It has usually been reserved for patients with good prognostic factors and good performance status.[8] A systematic review[12] found a modest survival benefit for interferon alfa. Higher response rates were reported with high-dose interleukin-2 than low-dose therapy,[2,13] but overall survival was not improved.[12] Attempts to improve the tolerability of interleukin-2 have

included the use of continuous infusion, lower doses given subcutaneously,[1,11,14] and inhalational use.[11,14] Attempts were made to improve the response rates to interleukin-2 and interferon alfa by combining them, or by addition of antineoplastics or retinoids. However, response was still generally poor and toxicity significant.[11,15]

The majority of patients with clear-cell renal cell carcinoma have overexpression of vascular endothelial growth factor (VEGF) in tumour tissues, and newer molecular therapies aimed at VEGF or its receptors have been developed.[5,16-18] The tyrosine kinase inhibitors sunitinib and sorafenib have respectively produced better and equivalent survival to interferon alfa treatment, and are both recommended as first-line options in stage IV disease, whether of clear cell or non-clear cell histology.[2] Some consider first-line use is appropriate only in favourable- or intermediate-risk patients, but that they are suitable in any patient who has failed cytokine immunotherapy.[6] Temsirolimus has also shown a significant overall survival benefit compared with interferon alfa; combination treatment using these 2 drugs did not, however, show any benefit over interferon alfa monotherapy.[2,5] Temsirolimus is recommended as a first-line option in patients with poor prognosis.[2,4,6] Bevacizumab, a monoclonal antibody directed against VEGF, has also shown activity in metastatic disease; addition of bevacizumab to interferon alfa significantly increased progression-free survival compared with interferon alfa, and this combination is also a first-line option for patients with mainly clear-cell histology.[2,4] Pazopanib is an alternative first-line agent in those with mainly clear-cell histology, and high-dose interleukin-2 also remains an option for selected patients with good performance status.[2] Sunitinib, sorafenib, pazopanib, and temsirolimus are all options in non-clear cell disease, as is chemotherapy with gemcitabine, capecitabine, floxuridine, fluorouracil, or doxorubicin.[2]

For *progressive* clear-cell disease, an alternative first-line may be given; supportive care remains a mainstay of therapy for all patients with metastatic renal cell carcinoma.[2] Treatment with everolimus has been found to prolong progression-free survival in patients who had disease after treatment with sunitinib, sorafenib, or both.[19] Interferon alfa may be used for progressive disease in clear cell carcinoma;[2] some consider its use in metastatic renal carcinoma to be inappropriate.[6]

Evolving therapies include vaccination therapy with autologous or allogeneic dendritic cell vaccines, or peptides, and allogeneic haematopoietic stem cell transplantation.[3,13,20,21]

1. Vaishampayan U. A review of current and future treatment options in renal cancer. *Am J Cancer* 2003; **2**: 201–210.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: kidney cancer (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf (accessed 10/06/10)
3. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med* 2005; **353**: 2477–90.
4. Escudier B, Kataja V. ESMO Guidelines Working Group. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v137–v139. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v137.full.pdf+html (accessed 18/10/10)
5. Garcia JA, Rini BI. Recent progress in the management of advanced renal cell carcinoma. *CA Cancer J Clin* 2007; **57**: 112–25.
6. Halbert RJ, *et al.* Treatment of patients with metastatic renal cell cancer: a RAND Appropriateness Panel. *Cancer* 2006; **107**: 2375–83.
7. Curti BD. Renal cell carcinoma. *JAMA* 2004; **292**: 97–100.
8. Escudier B. Advanced renal cell carcinoma: current and emerging management strategies. *Drugs* 2007; **67**: 1257–64.
9. Mickisch GHJ, *et al.* Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001; **358**: 966–70.
10. Flanigan RC, *et al.* Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001; **345**: 1655–9.
11. Heinzer H, *et al.* Systemic chemotherapy and chemoimmunotherapy for metastatic renal cell cancer. *World J Urol* 2001; **19**: 111–19.
12. Coppin C, *et al.* Immunotherapy for advanced renal cell cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley: 2004 (accessed 12/02/09).
13. McDermott DF, Rini BI. Immunotherapy for metastatic renal cell carcinoma. *BJU Int* 2007; **99**: 1282–8.
14. Parton M, *et al.* Role of cytokine therapy in 2006 and beyond for metastatic renal cell cancer. *J Clin Oncol* 2006; **24**: 5584–92.
15. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. *J Urol (Baltimore)* 2000; **163**: 408–17.
16. Vogelzang NJ, Sternberg CN. Signal-transduction inhibitors in renal cell carcinoma. *BJU Int* 2007; **99**: 1289–95.
17. Motzer RJ, Bukowski RM. Targeted therapy for metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24**: 5601–8.
18. Hiles JJ, Kolesar JM. Role of sunitinib and sorafenib in the treatment of metastatic renal cell carcinoma. *Am J Health-Syst Pharm* 2008; **65**: 123–31.
19. Motzer RJ, *et al.* RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372**: 449–56.
20. Yang JC, Childs R. Immunotherapy for renal cell cancer. *J Clin Oncol* 2006; **24**: 5576–83.
21. Oosterwijk E, *et al.* Active and passive immunotherapy: vaccines and antibodies. *BJU Int* 2007; **99**: 1301–4.

WILMS' TUMOUR. In children most cases of renal tumours are due to Wilms' tumour (nephroblastoma). This is one of the most frequent solid tumours in childhood with a peak incidence between 1 and 5 years of age and accounts for about 6% of all childhood malignancies. The usual presentation is an asymptomatic abdominal mass; abdominal pain, haematuria, fever, and hypertension can occur. Metastasis in advanced disease is usually to the lungs and liver. Most primary tumours occur in one kidney, but some 5% involve both kidneys.

Unlike other forms of renal cancer, Wilms' tumour responds well to chemotherapy. The basis of **treatment** is surgery, combined with chemotherapy, and if necessary radiotherapy. Management varies with disease stage and also varies between different study groups.[1-7] The US National Wilms' Tumour Study Group (NWTSG), its successor the Children's Oncology Group (COG), and some other groups recommend initial surgery (nephrectomy) to confirm diagnosis and perform precise staging. Adjuvant chemotherapy and radiotherapy are based on stage and histology obtained at the time of surgery, which allows for accurate assessment. However, tumour spillage at the time of surgery can increase the risk of local abdominal relapse and subsequent poor outcome. In contrast, the European Société Internationale d'Oncologie Pédiatrique (SIOP) and some other groups use neoadjuvant chemotherapy to reduce the tumour size and make surgery easier. Staging is done after surgery, and adjuvant chemotherapy is given if needed. With this method, patients without a confirmed diagnosis may receive unnecessary neoadjuvant treatment, and more intensive chemotherapy regimens are needed to ensure any occult disease is treated. Although there continues to be controversy about the relative merits of the two approaches, overall survival for patients treated by either approach is very similar, being more than 90% for patients with favourable histology. The aim of the various study protocols has been to identify low-risk children who require less intensive therapy, and those with poor prognosis who require more intensive therapy or alternative investigative regimens.[1-7] It has been noted that the groups have borrowed freely from each other, with SIOP protocols advocating early surgery for infants, and COG protocols using neoadjuvant therapy for very large tumours. Neoadjuvant chemotherapy may also allow for treatment of children in developing countries in cases where surgery is not immediately feasible due to the general health status of the patient. The protocol selected should therefore be suited to the individual child and the particular patient population.[7]

SIOP *neoadjuvant* chemotherapy usually consists of dactinomycin and vincristine for clinically localised disease, with doxorubicin or epirubicin added for metastatic disease.[2,5-7] *Adjuvant* chemotherapy regimens for disease with favourable or standard histology are broadly similar between NWTS and SIOP. In early disease, chemotherapy consists of vincristine combined with dactinomycin; in more advanced disease radiotherapy, and an anthracycline (doxorubicin or epirubicin) are added.[2,5,6] The duration of adjuvant chemotherapy is dependent on the disease stage and whether or not neoadjuvant treatment was given.[2] The UK Children's Cancer Study Group found that adjuvant vincristine alone was as effective as vincristine plus dactiriomycin for patients with stage I favourable histology, although this did not apply to children aged 4 years or older.[1,4,6] Various regimens have been investigated, and the NWTSG found that pulse-intensive dactinomycin courses were as effective as standard courses, but had less haematological toxicity.[1,4,5] Adjuvant radiotherapy is given for lung metastases in both protocols, with NWTSG giving whole-lung irradiation in all cases, and SIOP not irradiating those patients whose metastases respond to chemotherapy (which may be related to the higher dose of anthracycline used in SIOP regimens).[1,2,4,7]

For patients with ***unfavourable histologies*** and a poorer prognosis such as anaplastic Wilms' tumour or clear-cell sarcoma, treatment usually consists of three-or four-agent chemotherapy with combinations of vincristine, dactinomycin, doxorubicin, and cyclophosphamide,[4,6] or vincristine, doxorubicin, cyclophosphamide, and etoposide.[1] Radiotherapy is also used.[1]

For ***relapsed disease***, the use of combination chemotherapy regimens has improved survival; drugs such as cyclophosphamide, ifosfamide, cisplatin, carboplatin, and etoposide have shown substantial activity.[1,2,4] The ICE regimen (ifosfamide, carboplatin, and etoposide) or ICED regimen (with the addition of doxorubicin) are commonly used.[2,5] For other common combination regimens used in cancer chemotherapy, see Table 1, p. 719. A small study found that a protracted schedule of topotecan was effective for recurrent disease with favourable histology.[8] Treatment with high-dose chemotherapy and autologous haematopoietic stem-cell rescue has shown promising results in relapsed disease,[1] although intensive chemotherapy alone has been shown to be equally effective.[5]

Bilateral Wilms' tumour is not usually treated with primary bilateral nephrectomy because of the need to retain renal function. It may be biopsied to assess histology and stage and then treated with neoadjuvant chemotherapy.[1,2,4-6] Surgery is then performed, preserving as much of the kidneys as is possible. Survival has been reported to be comparable with that in other patients.[2] Because of these results, some have suggested the use of partial nephrectomy in patients with small unilateral tumours. However, most tumours are too large or too centrally located for partial nephrectomy to be routinely indicated.[1]

1. Kalapurakal JA, *et al.* Management of Wilms' tumour: current practice and future goals. *Lancet Oncol* 2004; **5**: 37–46.
2. Metzger ML, Dome JS. Current therapy for Wilms' tumor. *Oncologist* 2005; **10**: 815–26.
3. Green DM. Controversies in the management of Wilms tumour - immediate nephrectomy or delayed nephrectomy? *Eur J Cancer* 2007; **43**: 2453–6.
4. Ahmed HU, *et al.* An update on the management of Wilms' tumour. *Eur J Surg Oncol* 2007; **33**: 824–31.
5. Kaste SC, *et al.* Wilms tumour: prognostic factors, staging, therapy and late effects. *Pediatr Radiol* 2008; **38**: 2–17.
6. Varan A. Wilms' tumor in children: an overview. *Nephron Clin Pract* 2008; **108**: c83–c90.
7. D'Angio GJ. Pre- or postoperative therapy for Wilms' tumor? *J Clin Oncol* 2008; **26**: 4055–7.
8. Metzger ML, *et al.* Topotecan is active against Wilms' tumor: results of a multi-institutional phase II study. *J Clin Oncol* 2007; **25**: 3130–6.

Malignant neoplasms of the liver. Hepatocellular carcinoma (hepatoma) accounts for more than 90% of primary liver cancers. It is relatively uncommon in northern Europe and America but is the most common cancer among men in large parts of sub-Saharan Africa and Asia. The incidence in men ranges from 2 to 8 times that in women. Chronic infection with hepatitis B or hepatitis C virus is by far the most important factor associated with development of liver cancer. Other risk factors include ingestion of foodstuffs contaminated with aflatoxins (see p. 2432.2), alcoholic or non-alcoholic liver disease, haemochromatosis, and the long-term use of anabolic steroids (see Effects on the Liver, under Testosterone, p. 2308.1) and, rarely, combined oral contraceptives, (see p. 2235.3). Over 70% of patients with hepatocellular carcinoma have cirrhosis of the liver.

Clinical manifestations of liver cancer include increasing obstructive jaundice, upper abdominal pain, malaise, weight loss, and the presence of an epigastric mass; there may be metastasis to the lungs, kidney, bones, brain or other sites, or invasion of local structures. Multiple staging systems are used and there is no universally accepted method although most base liver function assessment on the Child-Pugh classification of disease severity. It has been noted that since the cause of hepatocellular carcinoma may vary geographically, different scoring systems may apply to different populations.[1,2]

Screening at-risk groups for hepatocellular carcinoma is feasible, although still controversial in terms of cost-effectiveness; the recommended surveillance interval is 6 months,[2-5] although 1 year may be equally effective.[6] Screening has led to increased detection of ***early disease***, and more than half of these cases will be suitable for potentially curative treatments such as resection, liver transplantation, or ablation.[3-7] Selection of which patients are best suited to which method is based on tumour factors such as resectability, liver function, patient comorbidities, candidacy for transplantation, and organ availability.[4,6,8,9] **Liver transplantation** (p. 1940.3) may be considered in those patients with small tumours and who have advanced cirrhosis and are therefore not suitable for surgical resection.[3-5,7,9,10] **Surgical resection** is suitable for patients without cirrhosis, or in cirrhotic patients with well-preserved liver function who are not candidates for transplantation and whose tumours are considered resectable.[3-5,7,9,10] However, recurrence rates after resection are high,[2,4,5,7,11] and 5-year survival is about 40%.[3,5,12]

As a result, **adjuvant** or **neoadjuvant chemotherapy** has been investigated in early-stage disease. Neoadjuvant chemotherapy has been used to reduce tumour burden before transplantation[7,12] or to permit resection.[13] A meta-analysis[14] of 7 studies concluded that adjuvant transcatheter arterial chemotherapy (drugs injected into the hepatic artery after curative resection, usually with embolisation which temporarily occludes the artery) significantly improved survival and decreased recurrence. However, a systematic review[11] found no clear evidence that either neoadjuvant or adjuvant regimens prolonged overall or disease-free survival; some evidence for benefit on disease-free survival was seen with adjuvant immunotherapy or iodine-131 with iodised oil. In patients who have small tumours and are not candidates for surgery or transplantation, percutaneous intratumoral alcohol injection is an option. Other ablative therapies include radiofrequency ablation and cryosurgery.[3-10,12,15,16]

For disease defined as ***intermediate*** or ***advanced***,[5,6] where tumours are large or unresectable and not amenable to local ablative therapies, transcatheter arterial chemoembolisation (TACE) is also used.[2-4,6,8,17] TACE uses substances such as gelatin foam or iodised oil to temporarily occlude the artery (the sole supply of blood to the tumour). This prolongs the duration of contact between drug and tumour and also attempts to induce tumour necrosis by ischaemia.[2,4,6,12] TACE compared with arterial embolisation

without chemotherapy was found to improve survival in one study.[18] Systematic review[19] confirmed a survival benefit with chemoembolisation, using doxorubicin or cisplatin, and suggested this method as standard therapy for selected patients with small unresectable tumours, and well-preserved liver function. Patients with severe hepatic impairment and portal vein thrombosis should not be treated with TACE as there is a risk of precipitating acute liver failure.[4,5,8,17] Other strategies to improve tumour response include the use of drug-eluting beads containing doxorubicin,[5,16] or transarterial radioembolisation (TARE), which injects radioactive isotopes such as iodine-131 or yttrium-90 into the hepatic artery, using the same principles as TACE.[2,4-6,17]

Systemic chemotherapy has been tried for the treatment of ***advanced or metastatic*** hepatocellular carcinoma, but has had no impact on survival.[1,3,8,10] The most active drug is doxorubicin, which has been associated with partial responses in about 10% of cases,[1,4,5] and has been widely used as the standard of care in disease not amenable or refractory to TACE.[17] Combination chemotherapy using a regimen of cisplatin, interferon, doxorubicin, and fluorouracil (PIAF) doubled the response rates compared with doxorubicin monotherapy, but toxicity was higher, and overall survival unaffected.[1,4,5,17] More recently, however, a survival benefit has been shown with the use of sorafenib when compared with placebo,[5,6,16] and some now consider it to be the new standard of care for patients with advanced disease,[5,10] although others consider it standard only in those who are not candidates for curative or locoregional therapies such as TACE, and have noted that it has only been studied in those with good liver function.[17] Other drugs under investigation for hepatocellular carcinoma include bevacizumab, sunitinib, and erlotinib.[1,3,5,6,10,16]

In contrast to the poor response of hepatocellular carcinoma to therapy, better progress has been made in strategies for its **prevention**. Neonatal vaccination against hepatitis B has dramatically decreased the incidence of chronic infection in children in Taiwan, and reduced the incidence of hepatocellular carcinoma[20] although some have noted that more time is needed to show the real impact of this measure.[2] Treatment of chronic hepatitis (p. 952.1) can prevent progression to liver cirrhosis and subsequent hepatocellular carcinoma.[20] There is also some suggestion of a possible inverse relation between coffee consumption and liver cancer risk.[16] Chemoprevention may also be a useful approach after surgical resection: use of a synthetic retinoid, peretinoin, was found to reduce the development of second primary tumours after resection.[21,22]

The liver is the most common site of ***metastatic disease.***[23] For most malignancies the presence of liver metastases is indicative of generalised dissemination, but isolated metastatic liver disease is common in colorectal cancer (p. 706.3) and rarer cancers such as some neuroendocrine tumours (p. 716.3).

1. Abou-Alfa GK. Hepatocellular carcinoma: molecular biology and therapy. *Semin Oncol* 2006; 33 (suppl 11): S79–S83.
2. Lau W-Y, Lai ECH. Hepatocellular carcinoma: current management and recent advances. *Hepatobiliary Pancreat Dis Int* 2008; 7: 237–57.
3. Schwartz M, *et al.* Strategies for the management of hepatocellular carcinoma. *Nat Clin Pract Oncol* 2007; 4: 424–32.
4. Alberts SR, *et al.* Treatment options for hepatobiliary and pancreatic cancer. *Mayo Clin Proc* 2007; 82: 628–37.
5. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol* 2008; 48 (suppl 1): S20–S37.
6. El-Serag HB, *et al.* Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 2008; 134: 1752–63.
7. Lopez PM, *et al.* Neoadjuvant therapies for hepatocellular carcinoma before liver transplantation: a critical appraisal. *Liver Transpl* 2006; 12: 1747–54.
8. Parikh S, Hyman D. Hepatocellular cancer: a guide for the internist. *Am J Med* 2007; 120: 194–202.
9. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: hepatobiliary cancers (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf (accessed 10/06/10)
10. Jelic S, Sotiropoulos GC. ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v59–v64. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v59.full.pdf+html (accessed 21/10/10)
11. Samuel M, *et al.* Neoadjuvant and adjuvant therapy for surgical resection of hepatocellular carcinoma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 17/02/09).
12. Yu AS, Keeffe EB. Management of hepatocellular carcinoma. *Rev Gastroenterol Disord* 2003; 3: 8–24.
13. Johnson PJ. Hepatocellular carcinoma: is current therapy really altering outcome? *Gut* 2002; 51: 459–62.
14. Mathurin P, *et al.* Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2003; 17: 1247–61.
15. Guan Y-S, Liu Y. Interventional treatments for hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2006; 5: 495–500.
16. Walzer N, Kulik LM. Hepatocellular carcinoma: latest developments. *Curr Opin Gastroenterol* 2008; 24: 312–19.
17. O'Neil BH, Venook AP. Hepatocellular carcinoma: the role of the North American GI Steering Committee Hepatobiliary Task Force and the advent of effective drug therapy. *Oncologist* 2007; 12: 1425–32.
18. Llovet JM, *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359: 1734–9.
19. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003; 37: 429–42.
20. Blum HE. Hepatocellular carcinoma: therapy and prevention. *World J Gastroenterol* 2005; 11: 7391–7400.
21. Muto Y, *et al.* Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. *N Engl J Med* 1996; 334: 1561–7.
22. Muto Y, *et al.* Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. *N Engl J Med* 1999; 340: 1046–7.
23. Choti MA, Bulkley GB. Management of hepatic metastases. *Liver Transpl Surg* 1999; 5: 65–80.

Malignant neoplasms of the lung. Lung cancer is the most common non-skin cancer in the developed countries and the second most common overall worldwide. About 20 to 25% of all lung cancers are small cell lung cancers (SCLC) derived from endocrine cells in the bronchial mucosa; the remainder, comprising chiefly squamous cell carcinomas (40 to 45% of cases), adenocarcinoma (25 to 30%), and large-cell carcinoma (about 10%), are known collectively as non-small cell lung cancer (NSCLC). More than 80% of all lung cancers are associated with tobacco smoking, and there is also evidence that exposure to the cigarette smoke of others can increase the risk in non-smokers. Other risk factors may include occupational exposure to substances such as asbestos, and the effects of environmental toxins such as air pollutants.

Symptoms due to a lesion in a main bronchus (the most common site) include persistent cough, dyspnoea, haemoptysis, weight loss and sometimes chest pain. Metastatic spread is common, and may affect sites such as brain, liver, and bone. It occurs early with adenocarcinoma and SCLC, but late with squamous cell carcinoma.

Disease staging plays an important role in determining treatment. The management of SCLC differs significantly from that of NSCLC (see below and p. 711.1, respectively).

Given the poor prognosis of lung cancers, and the high incidence of second primaries in patients curatively treated for early-stage disease, there has been great interest in **prophylaxis.** The most important factor in primary and secondary prevention is cessation of tobacco smoking, for which a number of interventions may be tried (see Smoking Cessation, p. 2570.2). Diets rich in fruit and vegetables have been associated with a lower incidence of malignant disease, and have prompted the investigation of antoxidant vitamins. However, primary prevention studies in those at risk of lung cancer have failed to show any benefit for vitamin supplements, and in the case of betacarotene, an increase in lung cancer was seen in those most at risk (see Prophylaxis of Malignant Neoplasms, p. 2047.3). Other drugs under investigation are retinoids and NSAIDs.[1]

While a meta-analysis[2] concluded that screening of patients with chest radiography or sputum cytology was ineffective, the Early Lung Cancer Action Project found that computed tomography improves the likelihood of detection of nodules suggestive of lung cancer in high-risk patients.[3] Since most of those cancers detected were at an early stage, resection was possible, and it is theorised that this technique may reduce mortality,[4] although it remains investigational.

Metastatic lung disease. The lung is the second most frequent site for metastatic disease, occurring in about 30% of cancer patients. Surgical resection may be used to treat pulmonary metastases when there are no effective systemic therapies, no extrapulmonary metastases, the pulmonary metastasis is completely resectable, and the patient is able to undergo surgery.[5] Specific cancers for which surgical resection of pulmonary metastases is considered include soft-tissue sarcoma, osteosarcoma, and sometimes breast cancer.

1. Goodman GE. Lung cancer 1: prevention of lung cancer. *Thorax* 2002; 57: 994–9.
2. Manser RL, *et al.* Screening for lung cancer. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 20/02/09).
3. Henschke CI, *et al.* Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999; 354: 99–105.
4. Carney DN. Lung cancer—time to move on from chemotherapy. *N Engl J Med* 2002; 346: 126–8.
5. Downey RJ. Surgical treatment of pulmonary metastases. *Surg Oncol Clin N Am* 1999; 8: 341–54.

SMALL CELL LUNG CANCER. The mainstay of treatment for small cell lung cancer (SCLC) is chemotherapy.[1-5] In ***limited disease*** (disease limited to one hemithorax with hilar and mediastinal lymph node involvement that can be encompassed within one tolerable radiotherapy field) the combination of chemotherapy and chest radiotherapy has been shown to improve survival[6,7] and is recommended therapy.[2-5] The most common chemotherapy regimen is 4 to 6 cycles of etoposide and cisplatin (EP or PE),[1,3-5,7,8] which offers a survival advantage over the previously used regimen of cyclophosphamide, doxorubicin, and vincristine (CAV). The optimum scheduling of chemotherapy and radiotherapy has been investigated and concurrent therapy found to be superior to sequential radiotherapy.[3] In comparing early and late concurrent therapy, a meta-analysis[9] of 7 studies found that a small improvement in overall survival at 2 years was associated with early radiotherapy (begun within 9 weeks of starting chemotherapy, or before the third cycle of chemotherapy) compared with late radiotherapy. There was also evidence that the use of hyperfractionated radiotherapy (given twice daily) and platinum-based regimens contributed to this benefit. In general, for limited disease it is recommended[2,3,5,7] that concurrent chest radiotherapy should be started with the first or second chemotherapy cycle. Response rates of 70 to 90% are reported, but median survival rates are only 14 to 20 months and the 2-year survival rate is about 40%.[5]

Only a few patients present with resectable early stage disease. Careful pre-operative staging is essential to rule out nodal involvement, and all patients should receive adjuvant chemotherapy. If nodal metastases are found, the addition of postoperative chest radiotherapy should be considered. Patients with later disease stages do not benefit from surgery.[3,5]

In ***extensive*** SCLC (spread beyond one hemithorax and thus beyond the boundaries of a single radiotherapy field; may include malignant pleural or pericardial effusion or haematogenous spread) chemotherapy alone is used to palliate symptoms and prolong survival. The combination of etoposide and cisplatin (or carboplatin) is also used in these patients[3-5,7] but response is poorer than that for limited disease, with response rates of 60 to 70% and a 2 year survival rate of less than 5%.[5] Alternative first-line regimens include irinotecan with cisplatin (or carboplatin), or the CAV regimen.[5] Other strategies that have been tried, but with little consistent evidence of improved results, include the addition of further drugs to EP (such as ifosfamide, paclitaxel, or cyclophosphamide plus an anthracycline), and the use of dose-intense or dose-dense regimens.[1,5,8]

The use of **consolidation or maintenance** chemotherapy has been studied in both limited and extensive disease. Most studies have found no improvement in progression-free or overall survival, and the general recommendation is that such extra therapy, with its associated toxicity, should not be used.[1-5,8] This view has been challenged by a meta-analysis[10] of 14 studies suggesting that there is evidence for benefit from maintenance therapy, although it is unclear which patients might benefit and which regimen would be most effective.

Patients who have responded to initial treatment still have a more than 50% risk of developing brain ***metastases.*** Prophylactic cranial irradiation reduces this risk and improves survival in patients in complete remission.[4,5,11] It is generally recommended for all patients with limited disease who achieve remission, and for those with extensive disease who achieve remission and have good prognostic factors and performance status.[2-5,7,8]

The value of chemotherapy in ***relapsed*** SCLC depends in part on the duration of remission before relapse, with greater responses the longer the remission.[3,5,7,8] In the UK, NICE guidelines recommend second-line chemotherapy only in patients whose disease responded to first-line treatment.[2] Patients who relapse within 3 months of achieving remission are considered to have refractory disease; second-line drugs include ifosfamide, paclitaxel, docetaxel, irinotecan, topotecan, and gemcitabine, although response is likely to be poor. Response rates are better if relapse occurs between 3 and 6 months after remission, and topotecan has been suggested as the best option. Other drugs that may be considered include irinotecan, gemcitabine, a taxane, oral etoposide, vinorelbine, or the CAV regimen.[5,7,8] Drugs under investigation for SCLC include amrubicin, pemetrexed, and picoplatin.[7,8] Patients may be given a repeat of initial therapy if they have relapsed after more than 6 months. Second-line chemotherapy should be given until the patient receives maximal benefit, becomes refractory, or develops unacceptable toxicity. Radiotherapy may also be given for localised symptomatic palliation.[5]

1. Sandler AB. Chemotherapy for small cell lung cancer. *Semin Oncol* 2003; 30: 9–25.
2. NICE. The diagnosis and treatment of lung cancer (clinical guideline 24, issued February 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/cg024fullguideline.pdf (accessed 18/02/09)
3. Jackman DM, Johnson BE. Small-cell lung cancer. *Lancet* 2005; 366: 1385–96.
4. Sørensen M, *et al.* ESMO Guidelines Working Group. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v120–v125. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v120.full.pdf+html (accessed 21/10/10)
5. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: small cell lung cancer (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/sclc.pdf (accessed 10/06/10)
6. Pignon JP, *et al.* A meta-analysis of thoracic radiotherapy for small cell lung cancer. *N Engl J Med* 1992; 327: 1618–24.
7. Sher T, *et al.* Small cell lung cancer. *Mayo Clin Proc* 2008; 83: 355–67.
8. Ferraldeschi R, *et al.* Modern management of small-cell lung cancer. *Drugs* 2007; 67: 2135–52.
9. Fried DB, *et al.* Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol* 2004; 22: 4837–45. Correction. *ibid.* 2005; 23: 248.
10. Bozcuk H, *et al.* Does maintenance/consolidation chemotherapy have a role in the management of small cell lung cancer (SCLC)? A

metaanalysis of the published controlled trials. *Cancer* 2005; 104: 2650–7.
11. The Prophylactic Cranial Irradiation Overview Collaborative Group. Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 18/02/09).

NON-SMALL CELL LUNG CANCER. Non-small cell lung cancer (NSCLC), like many malignancies, is treated according to the stage of the disease, for more information see p. 691.1.

For resectable NSCLC and locally-advanced unresectable disease, chemotherapy can be used with surgery or radiotherapy but, for advanced or metastatic disease, chemotherapy is the main treatment.[1-8] Platinum-based regimens prolong survival; cisplatin or carboplatin are effective when combined with docetaxel, etoposide, gemcitabine, irinotecan, conventional or albumin-bound paclitaxel, pemetrexed, vinblastine, or vinorelbine. Two-drug regimens are preferred although single-agent treatment is an option for those with poor performance status and the elderly; a third cytotoxic increases response but not survival. Targeted therapy may be added to chemotherapy for those whose tumours are a particular histology or have a specific genetic abnormality.

First-line options for advanced or metastatic NSCLC include:
- chemotherapy preferably with platinum-based regimens ± bevacizumab
- afatinib, erlotinib, or gefitinib in those with epidermal growth factor receptor (EGFR) mutations
- cetuximab plus cisplatin and vinorelbine in those with EGFR mutations
- crizotinib in those who are anaplastic lymphoma kinase (ALK) positive
- cisplatin plus pemetrexed for those with non-squamous histology
- cisplatin plus gemcitabine for those with squamous histology

First-line, platinum-based chemotherapy regimens are usually given for 4 to 6 cycles. For those who respond, or those with stable disease, the following options may be considered, although their relative benefits are still uncertain:
- continue first-line regimen
- continue treatment with a drug that was included in the first-line regimen (continuation maintenance). Often, targeted drug treatment or gemcitabine is continued after the initial 4 to 6 cycles of platinum-based chemotherapy
- change to a different drug that was not included first-line (switch maintenance). Second-line options (see below) are often used
- drug holiday

When disease progresses, a different regimen is started. Second-line options include:
- single-agent docetaxel
- single-agent afatinib, erlotinib, or gefitinib
- single-agent pemetrexed in those with non-squamous histology
- single-agent crizotinib in those who are ALK positive

Erlotinib may also be considered as a third-line option.

Emerging treatment options and alternative approaches for NSCLC include:[9,10]
- individualising treatment based on genetics or tumour characteristics
- drugs targeting the EGFR pathway
- vascular endothelial growth factor (VEGF) receptor kinase inhibitors
- cancer vaccines and immunotherapies
- histone deacetylase inhibitors

1. Azzoli CG, *et al.* American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009; 27: 6251–66. Also available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2793036/pdf/zlj6251.pdf (accessed 08/01/13)
2. Crinò L, *et al.* Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v103–v115. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v103.full.pdf+html (accessed 08/01/13)
3. Azzoli CG, *et al.* 2011 focused update of 2009 American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2011; 29: 3825–31. Correction. *ibid.*; 4725. Also available at: http://jco.ascopubs.org/content/early/2011/09/06/JCO.2010.34.2774.full.pdf+html (accessed 08/01/13)
4. NICE. The diagnosis and treatment of lung cancer (clinical guideline 121, issued April 2011). Available at: http://www.nice.org.uk/nicemedia/live/13465/54202/54202.pdf (accessed 08/01/13)
5. Peters S, *et al.* Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; 23 (suppl 7): vii56–vii64. Also available at: http://annonc.oxfordjournals.org/content/23/suppl_7/vii56.full.pdf+html (accessed 08/01/13)
6. Ganti AK, *et al.* Treatment of non-small cell lung cancer in the older patient. *J Natl Compr Canc Netw* 2012; 10: 230–9.
7. Grossi F. Management of non-small cell lung in cancer patients with stable disease. *Drugs* 2012; 72 (suppl 1): 20–7.
8. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-small cell lung cancer (version 1.2013). Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 08/01/13)
9. Triano LR, *et al.* Management of patients with advanced non-small cell lung cancer: current and emerging options. *Drugs* 2010; 70: 167–79.
10. Goldstraw P, *et al.* Non-small-cell lung cancer. *Lancet* 2011; 378: 1727–40.

MALIGNANT PLEURAL MESOTHELIOMA. Malignant pleural mesothelioma is a relatively rare tumour of the lining of the lung, yet its incidence is increasing. Occupational exposure to asbestos is the causative factor in most cases, with a mean latent interval of about 40 years between first exposure and death. Typical clinical manifestations include chest pain or dyspnoea or both. Neurological entrapment and pericardial involvement may occur. The disease is progressive, and median survival is poor. Histologically, disease may be epithelioid, sarcomatoid, or a mixture of the two. The epithelioid type is the most common, and may be confused with adenocarcinoma (see Malignant Neoplasms of the Lung, p. 710.2).

In patients with potentially resectable disease, surgery may be considered. Radical surgery (extrapleural pneumonectomy, EPP) is suitable only for a few patients, such as those with epithelioid tumours, and mortality and morbidity are high, despite the use of adjuvant chemotherapy and radiotherapy.[1-5] If EPP is planned, platinum-based neoadjuvant or adjuvant chemotherapy should be considered.[6] Pleurectomy is a cytoreductive procedure used for limited disease, or as palliation. Talc pleurodesis is usually the treatment of choice in the management of pleural effusions associated with mesothelioma. Palliative radiotherapy may be effective for pain relief,[1,6,7] but is generally of limited value.[2,8]

Numerous drugs have been tried in mesothelioma, but responses to monotherapy have been in the region of 10 to 20%, with cisplatin, carboplatin and doxorubicin being the most active agents.[3,9,10] Combination chemotherapy regimens, mostly cisplatin- or doxorubicin-based, have shown higher response,[5] but with little effect on overall survival.[9,10] However, the combination of pemetrexed and cisplatin was shown to improve survival,[1-4,6,8] and it is generally considered to be standard first-line therapy in patients with good performance status and unresectable disease.[2,3,5,7] The regimen is associated with high toxicity, however, and prophylactic use of vitamin B_{12} and folate is recommended.[2,4,10] Carboplatin has been substituted for cisplatin in attempts to reduce toxicity; comparable survival has been reported[4] and some recommend carboplatin with pemetrexed as an alternative first-line treatment.[6,7] The use of raltitrexed with cisplatin has also improved response rates and overall survival, with comparatively little toxicity, and this combination is considered to be an alternative first-line regimen.[4,6,10] Gemcitabine plus cisplatin is also active;[2,4,5] some consider it suitable first-line,[7] while others recommend it for second-line use.[3] Other combinations have been investigated; early use of the MVP regimen (mitomycin, vinblastine, and cisplatin) has shown a trend towards improved survival compared with delayed use.[4] No standard second-line therapy has been defined.[10] Vinorelbine, alone or with gemcitabine, has also been tried as a salvage regimen.[5] Multimodality approaches are increasingly used; neoadjuvant therapy has shown promising results.[4,10] Gene therapy, immunomodulation, angiogenesis inhibitors, ribonuclease inhibitors, and proteasome inhibitors are also being tried.[1,2,4,5,8,10]

1. British Thoracic Society Standards of Care Committee. BTS statement on malignant mesothelioma in the UK, 2007. *Thorax* 2007; 62 (suppl 2): ii1–ii19. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Malignant%20Mesothelioma/Guidelines/statement%20on%20malignant%20mesothelioma2007.pdf (accessed 23/02/09)
2. Robinson BWS, *et al.* Malignant mesothelioma. *Lancet* 2005; 366: 397–408.
3. Goudar RK. Management options for malignant pleural mesothelioma: clinical and cost considerations. *Drugs* 2007; 67: 1149–65.
4. Ceresoli GL, *et al.* Multidisciplinary treatment of malignant pleural mesothelioma. *Oncologist* 2007; 12: 850–63.
5. Tsao AS, *et al.* Malignant pleural mesothelioma. *J Clin Oncol* 2009; 27: 2081–90.
6. Stahel RA, *et al.* ESMO Guidelines Working Group. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v126–v128. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v126.full.pdf+html (accessed 22/10/10)
7. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: malignant pleural mesothelioma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/mpm.pdf (accessed 10/06/10)
8. Robinson BWS, Lake RA. Advances in malignant mesothelioma. *N Engl J Med* 2005; 353: 1591–1603.
9. Tomek S, *et al.* Chemotherapy for malignant pleural mesothelioma: past results and recent developments. *Br J Cancer* 2003; 88: 167–74.
10. Fennell DA, *et al.* Advances in the systemic therapy of malignant pleural mesothelioma. *Nat Clin Pract Oncol* 2008; 5: 136–47.

Malignant neoplasms of the ovary. Ovarian cancers account for about 5% of all malignancies in women. The most common form (90% of cases) is **epithelial ovarian cancer**, which ranks as fourth in the leading causes of cancer deaths in women. The lethality of this disease is related to the absence of symptoms in most women during its early stages: in about three-quarters of all patients disease is advanced at diagnosis and has spread to the peritoneum or beyond. It is mainly a disease of older women, the median age at diagnosis being 63 years. The risk of epithelial ovarian cancer appears to be related to the number of ovulatory cycles a women has in her lifetime, thus nulliparity increases the risk, whereas multiparity, breast feeding, and combined oral contraceptives (p. 2236.1) decrease the risk. Other risk factors are a family history (particularly when associated with the BRCA1 and BRCA2 genes), and possibly fertility drugs (see Clomifene, p. 2259.2), perineal talc use (p. 1722.3), and menopausal HRT (p. 2248.1).

The main *treatment* for epithelial ovarian cancer in most patients is surgical removal of womb, ovaries and fallopian tubes, and omentum, with debulking of any remaining gross disease.[1,2] For younger patients with favourable histology and disease confined to one ovary, and who wish to conserve fertility, unilateral salpingo-oophorectomy is possible.[1-4] The use of adjuvant chemotherapy depends on disease stage. Optimal surgical staging of early disease identifies those who have little or nothing to gain from adjuvant chemotherapy.[5]

For patients with *early stage* (stages IA/IB), well-differentiated (grade 1) disease, surgery alone is adequate;[1,2] more than 90% of women will have long-term (> 10 years) disease-free survival without further treatment.[4] In patients with poorly differentiated (high-grade) disease, or more extensive disease (stages IC and IIA), adjuvant chemotherapy should be considered.[1,2] Generally, 3 to 6 cycles of intravenous chemotherapy with carboplatin plus a taxane are recommended;[2,4] some recommend 6 cycles of carboplatin monotherapy.[1]

For patients with *advanced* disease (stages IIB to IV), intravenous adjuvant chemotherapy is also recommended, usually with a platinum and a taxane[1,2,4] for 6 to 8 cycles.[1,2] No difference in efficacy has been shown between cisplatin or carboplatin,[6] although carboplatin is usually preferred.[7] The amount of residual disease is an important prognostic factor[8,9] and secondary surgery (interval debulking surgery) can be considered for patients with suboptimal debulking at primary surgery who respond to chemotherapy.[1,3,8] However, a systematic review[9] found similar survival rates in patients who did and did not receive interval debulking surgery. Some recommend that this interval debulking surgery be performed after 3 cycles of chemotherapy, followed by a further 3 cycles of chemotherapy.[1] For patients who are considered initially not optimally resectable (for patient- or tumour-related factors), neoadjuvant chemotherapy followed by debulking surgery may be an option.[4,8-10] Some recommend this approach as standard for stage IV patients.[10]

Intraperitoneal chemotherapy is an option for those with *minimal residual disease* after surgery,[2,11,12] and may improve progression-free and overall survival compared with intravenous use.[4,7,13] However, it is not universally advocated,[3,4] because of adverse effects and complications, and the need for technical expertise;[4,11] some recommend it for stage III, optimally debulked patients.[1] The recommended regimen consists of intraperitoneal cisplatin and intraperitoneal paclitaxel, after an initial intravenous paclitaxel infusion.[2]

In patients with *recurrent* disease, the choice of therapy depends on the time since initial therapy and the drugs used.[1,2,14] Patients with long treatment-free intervals (more than 2 years) may be considered for secondary surgical resection of recurrent disease.[1] Relapse occurring more than 6 months after initial therapy is potentially platinum-sensitive and may be re-treated with platinum-based combination therapy.[1,2,4,15] Carboplatin or cisplatin monotherapy is used if combination therapy cannot be tolerated; oxaliplatin is also an option.[2] Those whose disease recurs in less than 6 months are considered to be platinum-resistant or platinum-refractory.[1,2,15] While re-treatment with a platinum compound is not generally recommended, some data suggest that altering the paclitaxel schedule may produce a secondary response.[2] Other drugs with activity include topotecan, liposomal doxorubicin, altretamine, capecitabine, cyclophosphamide, docetaxel, epirubicin, oral etoposide, gemcitabine, ifosfamide, irinotecan, pemetrexed, and vinorelbine.[1,2,7,8,12,14,15] Hormonal therapy is also an option; drugs include tamoxifen, anastrozole, letrozole, leuprorelin acetate, or megestrol acetate.[2] However, response rates are relatively low, and enrollment in clinical studies should be encouraged.[1,8] There has been considerable interest in the potential use of targeted therapy, but results in ovarian cancer with these drugs have generally not been favourable, except for bevacizumab.[4,12,15,16] Bevacizumab is active in both platinum-sensitive and platinum-resistant disease, and may be used in combination therapy in relapsed disease.[2] The monoclonal antibody oregovomab and ovarian cancer vaccines are under investigation.[16,17] Some success has been reported using high-dose chemotherapy followed by autologous stem cell transplantation,[18] although an improvement in survival has not been shown.[2,8]

Prophylaxis. The identification of genes conferring an inherited predisposition to ovarian cancer, and the difficulty

in identifying the disease and its poor prognosis has led to increased interest in prevention. Oral contraceptives are known to be protective in the general population, and there is growing evidence that women with mutation of the BRCA1 or BRCA2 gene might benefit similarly (see Ovary, under Carcinogenicity in Hormonal Contraceptives, p. 2236.1). Prophylactic oophorectomy may be considered in women with BRCA1 mutations after child-bearing or at age 35 years.[19,20] The risk/benefit ratio of this procedure is unknown, and a few women who undergo this procedure subsequently develop a primary peritoneal cancer.

Ovarian germ-cell cancers account for less than 3% of ovarian cancers and typically occur in women aged 20 to 30 years. Unlike epithelial ovarian cancer, most patients present with early disease, and have an excellent prognosis. Surgery is the main therapy (fertility-sparing if appropriate). Adjuvant chemotherapy is used except in those with stage I disease able to undergo frequent follow-up. Common regimens are similar to those used in male germ-cell tumours, such as bleomycin, etoposide, and cisplatin (BEP) or vinblastine, bleomycin, and cisplatin (VBP).[2,21-24]

Ovarian stromal tumours account for about 7% of ovarian cancers[25] and are mainly treated with surgery (fertility-sparing if appropriate).[2] For those with high-risk stage I tumours, recommendations include observation, radiotherapy, or platinum-based chemotherapy. For those with tumour stages II to IV, options include radiotherapy for limited disease, or platinum-based regimens such as BEP or paclitaxel plus carboplatin.[2,21,24]

1. Colombo N, *et al.* ESMO Guidelines Working Group. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v23–v30. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v23.full.pdf+html (accessed 29/10/10)
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: ovarian cancer including fallopian tube cancer and primary peritoneal cancer (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf (accessed 13/07/10)
3. SIGN. Epithelial ovarian cancer: a national clinical guideline (issued October 2003). Available at: http://www.sign.ac.uk/pdf/sign75.pdf (accessed 05/02/10)
4. Hennessy BT, *et al.* Ovarian cancer. *Lancet* 2009; 374: 1371–82.
5. Winter-Roach BA, *et al.* Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley: 2009 (accessed 05/02/10).
6. Stewart L. Advanced Ovarian Cancer Trialists Group. Chemotherapy for advanced ovarian cancer. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 05/02/10).
7. Markman M. Pharmaceutical management of ovarian cancer: current status. *Drugs* 2008; 68: 771–89.
8. Aletti GD, *et al.* Current management strategies for ovarian cancer. *Mayo Clin Proc* 2007; 82: 751–70.
9. Tangjitgamol S, *et al.* Interval debulking surgery for advanced epithelial ovarian cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 05/02/10).
10. Schwartz PE. What is the role of neoadjuvant chemotherapy in the management of ovarian cancer? *Oncology (Williston Park)* 2008; 22: 1118–25.
11. Markman M, Walker JL. Intraperitoneal chemotherapy of ovarian cancer: a review, with a focus on practical aspects of treatment. *J Clin Oncol* 2006; 24: 988–94.
12. Markman M. Antineoplastic agents in the management of ovarian cancer: current status and emerging therapeutic strategies. *Trends Pharmacol Sci* 2008; 29: 515–19.
13. Rao G, *et al.* Intraperitoneal chemotherapy for ovarian cancer: overview and perspective. *J Clin Oncol* 2007; 25: 2867–72.
14. Markman M, Bookman MA. Second-line treatment of ovarian cancer. *Oncologist* 2000; 5: 26–35.
15. Martin LP, Schilder RJ. Management of recurrent ovarian carcinoma: current status and future directions. *Semin Oncol* 2009; 36: 112–25.
16. Oei ALM, *et al.* The use of monoclonal antibodies for the treatment of epithelial ovarian cancer (review). *Int J Oncol* 2008; 32: 1145–57.
17. Sabbatini P, Odunsi K. Immunologic approaches to ovarian cancer treatment. *J Clin Oncol* 2007; 25: 2884–93.
18. Stiff PJ, *et al.* High-dose chemotherapy and autologous stem-cell transplantation for ovarian cancer: an autologous blood and marrow transplant registry report. *Ann Intern Med* 2000; 133: 504–15.
19. Burke W, *et al.* Recommendations for follow-up care of individuals with an inherited predisposition to cancer: BRCA1 and BRCA2. *JAMA* 1997; 277: 997–1003.
20. Eisinger F, *et al.* Recommendations for medical management of hereditary breast and ovarian cancer: the French National Ad Hoc Committee. *Ann Oncol* 1998; 9: 939–50. Also available at: http://annonc.oxfordjournals.org/cgi/reprint/9/9/939.pdf (accessed 15/05/06)
21. Reed N, *et al.* ESMO Guidelines Working Group. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v31–v36. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v31.full.pdf+html (accessed 29/10/10)
22. Bridgewater JA, Rustin GJS. Management of non-epithelial ovarian tumours. *Oncology* 1999; 57: 89–98.
23. Gershenson DM. Management of ovarian germ cell tumors. *J Clin Oncol* 2007; 25: 2938–43.
24. Koulouris CR, Penson RT. Ovarian stromal and germ cell tumors. *Semin Oncol* 2009; 36: 126–36.
25. Colombo N, *et al.* Management of ovarian stromal cell tumors. *J Clin Oncol* 2007; 25: 2944–51.

Malignant neoplasms of the pancreas. Pancreatic adenocarcinoma (cancer of the exocrine pancreas) accounts for about 95% of pancreatic tumours. A very small percentage of pancreatic tumours arise in the endocrine pancreas, and have different clinical features and treatment (see under Neuroendocrine Tumours, p. 716.3). Worldwide, pancreatic adenocarcinoma accounts for about 2% of all cancers, but is the eighth leading cause of cancer deaths. Its incidence is higher in developed countries. The risk for pancreatic carcinoma increases with age, and mean onset is in the seventh or eighth decade. Pancreatic adenocarcinoma is ductal in origin and metastasises early to the lymph nodes, and about 40% of patients present with metastatic disease. The 5-year survival rate is about 5%, and most patients die within the first 2 years. The most frequent symptom at presentation in patients with cancer of the pancreatic head is jaundice, often with other symptoms indicative of obstruction of the bile duct. In lesions of the body and tail of the pancreas severe and relentless pain may develop. Other symptoms include weight loss, steatorrhoea, dyspepsia, nausea, and depression. Diabetes mellitus is a manifestation of the disease, but there is also some evidence that it may be a predisposing factor. About 30% of pancreatic cancers are probably due to tobacco smoking.

Pancreatic adenocarcinoma has a very poor prognosis because of its usually advanced stage at diagnosis and lack of effective therapies.[1,2] The only curative therapy is resection of the tumour and the surrounding pancreatic tissue.[3] In the few patients who present with ***early-stage*** disease (tumour confined to the pancreas), radical surgery results in a 5-year survival of about 20% in optimally staged patients.[1] *Adjuvant treatment* has been shown to increase disease-free and overall survival and should be offered to all curatively resected patients.[4] The choice of the most effective adjuvant regimen has been the subject of much controversy and no definitive standard exists. Adjuvant chemotherapy with either fluorouracil or gemcitabine improves survival[5] and European guidelines[6] recommend 6 cycles of either drug; US guidelines state that where chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over fluorouracil or capecitabine for most patients.[3] Results with adjuvant chemoradiotherapy have been conflicting.[4,5] Early evidence showed that adjuvant fluorouracil-based chemoradiotherapy improved survival.[4] However, the results of a large European randomised study[7,8] suggested that there was no benefit from adjuvant fluorouracil-based chemoradiotherapy. A subsequent review[9] that included this study concluded that chemoradiotherapy should not yet be dismissed from further study because studies to date had used radiotherapy regimens that were now considered to be suboptimal, and the possibility of benefit could not be ruled out. European guidelines[6] state that fluorouracil-based chemoradiotherapy may be suitable for some patients after resection and gemcitabine chemotherapy, and US guidelines[3] state that, where chemoradiotherapy is the adjuvant treatment of choice, systemic gemcitabine followed by fluorouracil-based chemoradiotherapy should be used. However, with the emergence of newer drugs, patient enrolment into adjuvant clinical studies is encouraged in the USA.[3] Pre-operative (*neoadjuvant*) chemoradiotherapy is also under investigation, but a survival benefit has not been proven, and toxicity can be severe.[1,10,11] However, US guidelines state that, while data are lacking, it has not been shown to be clearly disadvantageous, and that some patients may benefit: prolonged recovery after resection may delay the use of adjuvant therapy; neoadjuvant treatment may also allow for selection of patients responsive to therapy, and could convert unresectable disease to resectable status.[3] For these reasons, patients with borderline resectable disease should be considered for neoadjuvant chemoradiotherapy; regimens are usually fluorouracil-based, and patients are still candidates for adjuvant therapy after surgery.[3,6]

In patients with symptomatic localised ***unresectable disease***, chemoradiotherapy may be used.[3] Most studies have reported a modest survival benefit from the combination of radiotherapy and fluorouracil.[1-3,11] Evidence suggests that radiotherapy with gemcitabine can yield similar outcomes.[3] A period of chemotherapy followed by chemoradiotherapy may be preferable to first-line chemoradiotherapy. Chemotherapy alone is also an option in these patients;[3,6] European regimens are similar to those for resectable disease, whereas gemcitabine monotherapy or gemcitabine-based combination therapy is advocated in the USA. Studies of neoadjuvant chemoradiotherapy to improve resectability rates in locally advanced disease should be encouraged.[6]

For patients with ***advanced*** (metastatic) disease, gemcitabine is recommended as the standard of care.[3,6,11,12] There is also some evidence that its effectiveness may be improved if it is given at a fixed dose rate of 10 mg/m^2 per minute, rather than by conventional infusion.[3,13] Other options in metastatic disease include gemcitabine-based combination therapy for those with good performance status, or best supportive care.[3] A meta-analysis[14] found a survival benefit for gemcitabine-based combination therapy compared with gemcitabine alone. Combinations showing benefit in terms of progression-free survival or overall survival include gemcitabine with capecitabine (GEMCAP), cisplatin (GEMCIS), oxaliplatin (GEMOX), erlotinib, or albumin-bound paclitaxel.[3,5,13,15-17] The combination of cisplatin, epirubicin, fluorouracil, and gemcitabine (PEFG) has also shown impressive results.[13]

There is no consensus on second-line therapy for patients with *refractory* disease. Gemcitabine may offer palliation if patients have not previously been treated with this drug; there is some suggestion that fixed-dose gemcitabine plus oxaliplatin may be useful in those patients refractory to standard gemcitabine therapy. For those patients who have had gemcitabine, enrolment in clinical studies is encouraged. If investigational therapy is not possible, treatment options include capecitabine or fluorouracil, both with or without oxaliplatin.[3]

Pancreatic cancer vaccines are under investigation for pancreatic cancer.[5,18]

1. Li D, *et al.* Pancreatic cancer. *Lancet* 2004; 363: 1049–57.
2. Willett CG, *et al.* Locally advanced pancreatic cancer. *J Clin Oncol* 2005; 23: 4538–44.
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: pancreatic adenocarcinoma (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf (accessed 13/07/10)
4. Oettle H, Neuhaus P. Adjuvant therapy in pancreatic cancer: a critical appraisal. *Drugs* 2007; 67: 2293–2310.
5. Ghaneh P, *et al.* Biology and management of pancreatic cancer. *Gut* 2007; 56: 1134–52.
6. Cascinu S, *et al.* ESMO Guidelines Working Group. Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v55–v58. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v55.full.pdf+html (accessed 22/10/10)
7. Neoptolemos JP, *et al.* Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001; 358: 1576–85.
8. Neoptolemos JP, *et al.* A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; 350: 1200–10. Correction. *ibid.*; 351: 726. [dose]
9. Chua YJ, Cunningham D. Adjuvant treatment for resectable pancreatic cancer. *J Clin Oncol* 2005; 23: 4532–7.
10. Anonymous. Management of pancreatic cancer. *Drug Ther Bull* 2003; 41: 36–40.
11. Pancreatic Section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, and the Special Interest Group for Gastro-Intestinal Radiology. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. *Gut* 2005; 54 (suppl 5): v1–v16. Also available at: http://gut.bmj.com/cgi/reprint/54/suppl_5/v1.pdf (accessed 09/02/10)
12. Spalding DRC. Pancreatic and periampullary cancers: treatment and outcome. *Br J Hosp Med* 2006; 67: 14–20.
13. Xiong HQ, *et al.* Cytotoxic chemotherapy for pancreatic cancer: advances to date and future directions. *Drugs* 2006; 66: 1059–72.
14. Sultana A, *et al.* Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007; 25: 2607–15.
15. Van Cutsem E, *et al.* Lessons learned in the management of advanced pancreatic cancer. *J Clin Oncol* 2007; 25: 1949–52.
16. Cunningham D, *et al.* Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; 27: 5513–18.
17. Von Hoff DD, *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; 369: 1691–1703.
18. Saad ED, Hoff PM. Molecular-targeted agents in pancreatic cancer. *Cancer Control* 2004; 11: 32–8.

Malignant neoplasms of the prostate. Prostatic cancer is the most commonly diagnosed non-skin malignancy in men in the western world, and the second most common cause of cancer deaths in men in the UK and USA: about one in 6 white men can be expected to develop clinically evident carcinoma of the prostate during his lifetime. Black men are at higher risk for the disease. The incidence rises steadily with age. There is also a familial component to the disease. More than 95% of all prostate cancer is adenocarcinoma, which begins as a hard mass in the peripheral portion of the gland and infiltrates surrounding tissues slowly. Metastasis may occur in advanced disease, notably to bone. Presenting symptoms of advanced disease are usually those of urinary outflow obstruction, or pelvic or back pain due to bone metastases. However, most men are asymptomatic, and may be diagnosed as a result of screening.

Controversy exists regarding all aspects of the management of prostate cancer, from screening to the best treatment for each stage of the disease. Much of this is because of the lack of clear data to guide treatment decisions. Factors that guide treatment decisions include the extent (stage) of the tumour, tumour grade (Gleason score), baseline prostate specific antigen (PSA) levels, the patient's life expectancy (based on age and comorbid conditions), treatment morbidity, and patient preference.[1-3]

There is great controversy over the value of screening for early disease by detection of PSA. Screening increases the incidence, but may not decrease mortality, and can result in unnecessary treatment. PSA screening in the USA did not result in significant differences in mortality compared with the UK, where PSA screening was not widely adopted.[4] A large European study found that PSA screening reduced the rate of mortality from prostate cancer by 20% but was associated with a high risk of overdiagnosis.[5] European guidelines state that decisions on population screening await longer follow-up.[3] US expert groups vary in their recommendations. A large US study found that screening provided no reduction in death rates after 7 to 10 years of follow-up.[6] The US Preventive Services Task Force deemed the evidence insufficient to assess the balance of benefit and harm of screening in men younger than 75 years; men aged 75 years or older should not be

screened.[7] Others favour screening, subject to patient preference after discussing risks and benefits; the time at which they consider screening should start is based on the patient's perceived risk, and has varied from 40 to 50 years of age.[2,8,9]

In patients with **localised disease**, detected incidentally or by screening, the choices are radical prostatectomy, radical external beam radiotherapy, brachytherapy, or deferred treatment (active surveillance or watchful waiting).[1-3,10,11] There is no general consensus as to what constitutes best treatment.[3] Men may be stratified as low-, intermediate-, or high-risk, depending on stage, grade, and PSA level.[2,3] Treatment morbidity and patient preferences are particularly important. Adverse effects of surgery include impotence and incontinence, and for radiotherapy, radiation proctitis, impotence, urinary retention, or incontinence.[2,10,11] In medically fit patients with a life expectancy of 10 years or more or those with poorly differentiated tumours, many clinicians would consider radical prostatectomy or radiotherapy with curative intent.[1,2,12] In men with a life expectancy of less than 10 years and with low-grade tumours, there is a definite role for deferring treatment.[2,10,12] Use of continuous or intermittent androgen deprivation therapy (ADT) as primary treatment has increased,[11] although it does not improve survival, and some guidelines do not recommend it.[2] However, its use with other therapies may be considered. (For further discussion of ADT, see below.) A systematic review[13] concluded that neoadjuvant (given for 3 to 6 months before the primary curative therapy) or adjuvant hormonal therapies, used with prostatectomy or radiotherapy, were associated with clinical benefit in terms of local control. Use of either with prostatectomy did not affect survival, but neoadjuvant hormonal therapy before radiotherapy significantly improved disease-free survival, and adjuvant hormonal therapy after radiotherapy significantly improved disease-free and overall survival. Some US guidelines[2] recommend that where radiotherapy is used for intermediate-risk localised disease, short-term (4 to 6 months) of neoadjuvant, concomitant, or adjuvant ADT can be considered; for high-risk disease, long-term use (2 to 3 years) is recommended.

For patients with **locally advanced disease**, options include radiotherapy with neoadjuvant, concomitant, or adjuvant ADT, ADT alone, or radical prostatectomy.[2,3] There is evidence that the use of hormonal therapy before or after radiotherapy improves disease-free and overall survival.[13-15] Studies of ADT have found that treatment for 3 years[16] and 5 years[17] after radiotherapy have improved survival when compared with treatment of shorter duration. US guidelines recommend 2 to 3 years of ADT when radiotherapy is used for locally advanced disease.[2]

PSA may be used to monitor the efficacy of therapy and detect biochemical relapse.[1,2] For those thought at low risk of metastases, salvage options after surgery include radiotherapy with or without ADT, while after primary radiotherapy options include observation, salvage prostatectomy in selected cases, cryotherapy, or brachytherapy.[2]

For patients with **metastatic disease** cure is not possible and therapy is aimed at prolonging survival and palliating symptoms. The basis of therapy is hormonal manipulation: about 80% of patients will respond to such therapy, but resistance eventually develops.[1,18] Historically, oestrogens such as diethylstilbestrol were used, but these are no longer recommended due to cardiotoxicity.[1,19] Standard first-line therapy is now ADT, using a gonadorelin analogue (such as goserelin, leuprorelin, or triptorelin) to produce medical castration, or opting for surgical castration (orchidectomy);[1-3,18,19] these have been shown to be equally effective.[2] However, medical castration with a gonadorelin analogue causes an immediate increase in testosterone (flare reaction), and a short course of an anti-androgen (such as bicalutamide, flutamide, or nilutamide) is given (either before or with the LHRH agonist) to prevent this surge.[2,3,18]

Some consider that anti-androgen monotherapy (with nonsteroidal drugs) may be discussed as an alternative to medical or surgical castration,[19] but others[2] do not recommend it. There is some evidence that survival rates may be lower, and treatment withdrawals (due to gastrointestinal adverse effects) higher.[20] Steroidal anti-androgen monotherapy should not be offered.[19] The gonadorelin antagonist abarelix can also be used for ADT. It has a more rapid onset of effect than the gonadorelin analogue leuprorelin and does not stimulate tumour flare.[21,22] Abarelix may be an alternative for men who are not suitable candidates for orchidectomy or gonadorelin analogue therapy.

Combined androgen blockade (longer use of an anti-androgen with medical or surgical castration) is also an acceptable first-line option;[2,19] this blocks the action of adrenal androgens as well (total androgen blockade).[1] Early studies suggested a small survival advantage with this approach, but adverse effects are increased,[1,19] and some guidelines[2] state that combined androgen blockade provides no proven benefit over castration alone.

The timing of ADT is controversial; there is some suggestion that early ADT may be better than delayed ADT, but data are limited,[18,19] and treatment should be individualised.[2] However, in the presence of symptomatic or overt metastases, treatment should be started immediately.[2] Intermittent ADT may potentially offer improved disease control and quality of life; however, data are limited and this approach, while feasible, remains investigational.[1,18,19]

In patients who relapse after or during hormonal therapy, second-line hormonal therapy may be tried, although responses are variable. Anti-androgens may be used sequentially, particularly in men who wish to defer more aggressive approaches such as chemotherapy;[18] drugs used include bicalutamide, flutamide, ketoconazole, oestrogens, and corticosteroids.[2,3,18,23]

Patients with **hormone-refractory (castration-refractory)** disease should be offered chemotherapy as an option.[2,3,18,24] Personalised immunotherapy with sipuleucel-T is also an option in some countries; it is recommended for patients with good performance status, life expectancy of more than 6 months, and no visceral disease.[2] In those given chemotherapy, docetaxel-based regimens are considered the standard of care.[25] A schedule in which docetaxel is given every 3 weeks is advocated first-line.[2,3,24] since this has shown a survival benefit.[2] Docetaxel is used with prednisone or estramustine, although use with the latter increases adverse effects and is generally not recommended. Alternative regimens include weekly docetaxel plus prednisone, or mitoxantrone every 3 weeks plus prednisone.[2] No consensus exists for second-line chemotherapy after failure of docetaxel and enrolment into clinical studies is encouraged.[2] Combinations of docetaxel are under investigation, including with vinorelbine, capecitabine, or high-dose calcitriol.[25] Estramustine with etoposide, vinblastine, or vinorelbine has also shown favourable results.[26] Other drugs that might be used after treatment with docetaxel-based therapy include oral cyclophosphamide, alone or with vincristine and dexamethasone;[23,25] intravenous cabazitaxel with a corticosteroid or oral enzalutamide may be options in those with metastatic disease. Abiraterone acetate, an inhibitor of androgen synthesis, may be given to patients with disease progression after docetaxel-based therapy,[27] or where ADT has failed but chemotherapy is not yet indicated.[28] Drugs under investigation include satraplatin and ixabepilone.[23,25]

A herbal combination preparation, PC-SPES, had some beneficial results in androgen-dependent and androgen-independent disease and has been used widely as a complementary medicine, but there have been reports of adverse cardiovascular effects and contamination with diethylstilbestrol and warfarin, resulting in the withdrawal of this product from most markets.[29,30] Bone metastases are usually treated with palliative radiotherapy (see p. 700.3). Bone-targeted therapy with strontium-89 or samarium-153 may be beneficial;[2,3] radium-223 is also used. Combinations of radiopharmaceuticals with docetaxel are under investigation.[31] Intravenous bisphosphonates such as zoledronic acid are recommended for bone pain and to prevent skeletal complications.[2,3] Prostate cancer growth is thought to be stimulated by endothelin-1, a small peptide that acts at endothelin-A receptors; atrasentan is an endothelin-A receptor antagonist under investigation, and early studies have shown improvements in time to disease progression and markers of bone metastases.[25,26]

Prophylaxis.

Because of the difficulties involved in managing prostate cancer there has been interest in the concept of disease prophylaxis. In healthy men, a large controlled study[32] found that seven years of finasteride prophylaxis reduced the incidence of prostate cancer by about 25% compared with placebo, but this benefit was offset by an increased risk of high-grade tumours associated with finasteride. However, later studies found that finasteride increased the accuracy of PSA testing,[33] and decreased prostate gland volume,[34] which could have contributed to the greater detection of all grades of cancer with finasteride. Guidelines issued by the American Society of Clinical Oncology and the American Urological Association[35] concluded that while the higher incidence of high-grade cancer seen in the finasteride group was likely due to these confounding factors, an increased incidence of high-grade cancer could not be excluded with certainty. However, some men may benefit from 5-α-reductase inhibitor therapy. A systematic review[36] concluded that reduction of prostate cancer with 5-α-reductase inhibitors was limited to men who had a baseline PSA value of less than 4 nanograms/mL. Dutasteride is also under investigation.[35,37]

Results from a case-control study have suggested an association between warfarin use and a decreased risk of prostate cancer.[38] Suggestions that selenium (see p. 2087.2) or vitamin E (see p. 2047.3) supplementation, alone or in combination, might reduce the risk of prostate cancer have not been borne out.[39] However, interest in compounds such as vitamin D (see p. 2116.1) and soya isoflavones[40] continues.

1. Damber J-E, Aus G. Prostate cancer. *Lancet* 2008; 371: 1710–21.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: prostate cancer (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf (accessed 25/06/10)
3. Horwich A, *et al.* ESMO Guidelines Working Group. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v129–v133. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v129.full.pdf+html (accessed 25/10/10)
4. Esserman L, *et al.* Rethinking screening for breast cancer and prostate cancer. *JAMA* 2009; 302: 1685–92.
5. Schröder FH, *et al.* ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009; 360: 1320–8.
6. Andriole GL, *et al.* PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009; 360: 1310–19.
7. U. S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008; 149: 185–91.
8. American Urological Association. Prostate-specific antigen best practice statement: 2009 update. Available at: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/psa09.pdf (accessed 12/02/10)
9. American Cancer Society. Guidelines for the early detection of cancer. Available at: http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp (accessed 12/02/10)
10. Walsh PC, *et al.* Localized prostate cancer. *N Engl J Med* 2007; 357: 2696–2705.
11. Wilt TJ, Thompson IM. Clinically localised prostate cancer. *BMJ* 2006; 333: 1102–6.
12. Jani AB, Hellman S. Early prostate cancer: clinical decision-making. *Lancet* 2003; 361: 1045–53.
13. Kumar S, *et al.* Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 12/02/10).
14. Payne H, Lim P. Optimizing decisions about treatment in locally advanced prostate cancer. *Br J Hosp Med* 2007; 68: 252–6.
15. Widmark A, *et al.* Scandinavian Prostate Cancer Group Study 7. Swedish Association for Urological Oncology 3. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009; 373: 301–8.
16. Bolla M, *et al.* EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009; 360: 2516–27.
17. Souhami L, *et al.* Impact of the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy: a secondary analysis of RTOG 85-31. *J Clin Oncol* 2009; 27: 2137–43.
18. Walczak JR, Carducci MA. Prostate cancer: a practical approach to current management of recurrent disease. *Mayo Clin Proc* 2007; 82: 243–9.
19. Loblaw DA, *et al.* Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2007 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2007; 25: 1596–1605. Correction, *ibid.*; 4512. Also available at: http://jco.ascopubs.org/cgi/reprint/25/12/1596.pdf (accessed 15/02/10)
20. Seidenfeld J, *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; 132: 566–77.
21. McLeod D, *et al.* A phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. *Urology* 2001; 58: 756–61.
22. Trachtenberg J, *et al.* A phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. *J Urol (Baltimore)* 2002; 167: 1670–4.
23. Berthold DR, *et al.* Management of advanced prostate cancer after first-line chemotherapy. *J Clin Oncol* 2005; 23: 8247–52.
24. Shelley M, *et al.* Chemotherapy for hormone-refractory prostate cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 15/02/10).
25. Di Lorenzo G, *et al.* Hormone-refractory prostate cancer: where are we going? *Drugs* 2007; 67: 1109–24.
26. Rosenbaum E, Carducci MA. Pharmacotherapy of hormone refractory prostate cancer: new developments and challenges. *Expert Opin Pharmacother* 2003; 4: 875–87.
27. de Bono JS, *et al.* COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; 364: 1995–2005.
28. Ryan CJ, *et al.* COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; 368: 138–48. Correction, *ibid.*; 584.
29. de Lemos ML. Herbal supplement PC-Spes for prostate cancer. *Ann Pharmacother* 2002; 36: 921–6.
30. Kosty MP. PC-SPES: hope or hype? *J Clin Oncol* 2004; 22: 3657–9.
31. Sartor O. Radiopharmaceutical and chemotherapy combinations in metastatic castrate-resistant prostate cancer: a new beginning? *J Clin Oncol* 2009; 27: 2417–18.
32. Thompson IM, *et al.* The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; 349: 215–24.
33. Thompson IM, *et al.* Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 2006; 98: 1128–33.
34. Lucia MS, *et al.* Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2007; 99: 1375–83.
35. Kramer BS, *et al.* American Society of Clinical Oncology Health Services Committee. American Urological Association Practice Guidelines Committee. Use of 5-α-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Clin Oncol* 2009; 27: 1502–16. Also available at: http://jco.ascopubs.org/cgi/reprint/27/9/1502.pdf (accessed 04/05/10)
36. Wilt TJ, *et al.* 5-Alpha-reductase Inhibitors for prostate cancer prevention. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 15/02/10).
37. Parnes HL, *et al.* Prevention of hormone-related cancers: prostate cancer. *J Clin Oncol* 2005; 23: 368–77.
38. Tagalakis V, *et al.* Use of warfarin and risk of urogenital cancer: a population-based, nested case-control study. *Lancet Oncol* 2007; 8: 395–402.
39. Lippman SM, *et al.* Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2009; 301: 39–51.

40. Kurahashi N, *et al.* Plasma isoflavones and subsequent risk of prostate cancer in a nested case-control study: the Japan Public Health Center. *J Clin Oncol* 2008; 26: 5923–9.

Malignant neoplasms of the skin. Basal cell carcinoma is the most common form of skin cancer, accounting for about 80% of cases. The second most common skin cancer is squamous cell carcinoma. These 2 types of carcinoma (collectively referred to as nonmelanoma skin cancers) are the most common malignancies among white populations, but because many are not recorded the exact incidence is uncertain and they are often omitted from calculations of the relative frequency of malignancy. A small but increasing proportion of all skin cancers are melanomas, arising from melanocytes (pigment cells). Other cancers that manifest in the skin include cutaneous T-cell lymphomas (see Mycosis Fungoides, p. 698.3) and Kaposi's sarcoma (see p. 718.1).

Nonmelanoma and melanoma skin cancers are related to solar radiation, and the incidence is greatest in those regions where light-skinned populations live closest to the equator. Individuals at particular risk include those with fair skin, blue eyes, red hair, a tendency to freckle, and to burn rather than tan. Use of methoxsalen with ultraviolet light (PUVA) has also been associated with an increased incidence of skin cancers (see Effects on the Skin, under Methoxsalen, p. 1713.1). Other risk factors for nonmelanoma skin cancers include various inherited disorders such as xeroderma pigmentosum (see Photosensitivity Disorders, p. 1686.2) and albinism (see Pigmentation Disorders, p. 1687.2). Immunosuppressive therapy, as used after solid organ transplantation (see p. 1936.2 *et seq.*), is associated with a very large increase in risk of squamous cell carcinoma.

Prophylaxis. Although nonmelanoma and melanoma skin cancers are related to solar radiation, and measures to reduce sun exposure are therefore advocated for prophylaxis, the relationship appears to differ between the types.

- Squamous cell carcinoma and its precursor lesions are clearly linked to cumulative chronic sun exposure.[1,2] These lesions are more common on frequently exposed skin (head, neck, and back of hands), and are more common in individuals with outdoor occupations. In addition, there is evidence that regular sunscreen use can reduce the incidence of new actinic keratoses and increase remission of existing lesions,[3] and reduce incident squamous cell carcinomas.[4,5]
- Although basal cell carcinomas are also common on sun-exposed skin (head and neck), it appears that they may be more related to a history of severe sunburns, particularly in childhood and adolescence, rather than to cumulative sun exposure.[1] In one study,[4] there was no difference in incidence of basal cell carcinomas between sunscreen users and non-users. Long-term follow-up of another study[5] found no clear benefit of regular sunscreen use in reducing basal cell carcinomas.
- Cutaneous melanoma is more common on skin exposed to the sun occasionally (particularly the legs in women, and the back in men), and appears to be more common in indoor than outdoor workers.[1,2] Cumulative occupational exposure seems to be protective in some white populations.[6] This suggests that intermittent sun exposure may be more risky than regular exposure for this cancer.[1,2] Short, sharp bursts of acute exposure in childhood and severe sunburn are also strongly associated with melanoma risk.[6] Although the use of sunscreens is advocated for protection against melanoma, some reports have suggested that sunscreen use may actually increase the risk.[7] However, systematic reviews[8,9] have found no good evidence for an association between sunscreens and the increasing incidence of melanoma, but did find that studies varied in accounting for confounding factors such as patient complexion and recall bias. Also, people at higher risk of sunburn and melanoma may also be more likely to use sunscreens, and some people may use sunscreens to allow for prolonged sun exposure, thus receiving a higher cumulative amount of UV radiation. Sunscreen formulation (see p. 1681.3), sun protection factor (SPF) rating, and protection against UVA (see Light-induced Skin Reactions, p. 1685.3), have also changed considerably over the last few decades, making it difficult to compare study results. Sunscreens are therefore recommended as an adjunct to other measures (such as protective clothing) to prevent over exposure, especially in young children.[7]

Chemoprevention has also been investigated as a means of reducing the incidence of squamous and basal cell cancers, particularly in those most at risk. Retinoids such as acitretin, etretinate, and isotretinoin have been shown to reduce the incidence of new squamous cell carcinomas in individuals with xeroderma pigmentosum, and in renal transplant recipients.[10] Conversely, neither betacarotene (p. 2047.3) nor selenium (p. 2087.2) has reduced the incidence of squamous or basal cell carcinomas in patients previously treated for these disorders. There is some evidence that a low-fat diet may reduce the incidence of actinic keratosis in patients with a history of nonmelanoma skin cancer.[11] Certain substances such as flavonoids, curcumin, grape seeds, resveratrol, silymarin, and green tea have been proposed as having antiphotocarcinogenic properties.[12]

1. Anonymous. Do sunscreens prevent skin cancer? *Drug Ther Bull* 1998; 36: 49–51.
2. Bruce AJ, Brodland DG. Overview of skin cancer detection and prevention for the primary care physician. *Mayo Clin Proc* 2000; 75: 491–500.
3. Thompson SC, *et al.* Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993; 329: 1147–51.
4. Green A, *et al.* Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 1999; 354: 723–9.
5. van der Pols JC, *et al.* Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2546–8.
6. Bataille V, de Vries E. Melanoma—Part 1: epidemiology, risk factors, and prevention. *BMJ* 2008; 337: a2249.
7. Gallagher RP. Sunscreens in melanoma and skin cancer prevention. *CMAJ* 2005; 173: 244–5.
8. Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case–control studies. *Am J Public Health* 2002; 92: 1173–7.
9. Dennis LK, *et al.* Sunscreen use and the risk for melanoma: a quantitative review. *Ann Intern Med* 2003; 139: 966–78.
10. DiGiovanna JJ. Retinoid chemoprevention in patients at high risk for skin cancer. *Med Pediatr Oncol* 2001; 36: 564–7.
11. Black HS, *et al.* Effect of a low-fat diet on the incidence of actinic keratosis. *N Engl J Med* 1994; 330: 1272–5.
12. Baliga MS, Katiyar SK. Chemoprevention of photocarcinogenesis by selected dietary botanicals. *Photochem Photobiol Sci* 2006; 5: 243–53.

BASAL CELL AND SQUAMOUS CELL CARCINOMA. The great majority of skin cancers are basal cell carcinomas, which are completely curable if diagnosed early and treated appropriately. Although they rarely metastasise, they have a tendency to be locally destructive. The remainder are mainly squamous cell carcinomas, which, although curable when treated early, have a greater risk of metastatic spread. Common precursor lesions for squamous cell carcinoma are actinic keratosis (solar keratosis) and Bowen's disease (squamous cell carcinoma in situ).

- Treatments for **actinic keratosis** and **Bowen's disease** include cryosurgery, curettage, excision, radiotherapy, laser treatment, photodynamic therapy (see Porfimer Sodium, p. 849.1) using 5-aminolevulinic acid or methyl aminolevulinate, and topical fluorouracil or topical imiquimod.[1-3] Topical diclofenac or topical salicylic acid may be used for actinic keratosis.[2-4] The choice of treatment depends on the site and size of the lesion, evidence for efficacy, ease of application, and availability.[1]
- Treatment options for superficial low-risk **basal cell carcinomas** include curettage and electrodesiccation or cryosurgery.[6-9] Topical fluorouracil may be used for superficial lesions in some instances, as are topical imiquimod or photodynamic therapy using 5-aminolevulinic acid, methyl aminolevulinate, or porfimer.
- For superficial tumours at high-risk sites, and for most **squamous cell carcinomas**, excision with postoperatively determined margins or Mohs' micrographic surgery (tumour margins examined during the procedure) is more appropriate.[6-11] Radiotherapy is an alternative in patients at risk of surgical complications or where surgery would be difficult or extensive.

The prognosis with appropriate treatment is good, with 5-year disease free survival of over 90%. However, about 50% of patients will subsequently develop another skin cancer, and regular monitoring to detect this as early as possible is desirable.[7] In addition, patients should be educated about sun protection measures, and chemoprevention with retinoids may be appropriate for some high-risk patients (see Prophylaxis, in Malignant Neoplasms of the Skin, above).

1. Cox NH, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for management of Bowen's disease: 2006 update. *Br J Dermatol* 2007; 156: 11–21. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Bowens%20Disease%20update%20January%202007.pdf (accessed 18/02/10)
2. Anonymous. New treatments for actinic keratoses. *Med Lett Drugs Ther* 2002; 44: 57–8.
3. Anonymous. Managing solar keratoses. *Drug Ther Bull* 2002; 40: 33–5.
4. de Berker D, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of actinic keratoses. *Br J Dermatol* 2007; 156: 222–30. Correction. *ibid.* 2008; 158: 873. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Actinic%20Keratoses.pdf (accessed 18/02/10)
5. Lee S, *et al.* Pharmacological treatments for basal cell carcinoma. *Drugs* 2007; 67: 915–34.
6. Telfer NR, *et al.* British Association of Dermatologists. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008; 159: 35–48. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/BCC%20Guidelines%20BJDJul08.pdf (accessed 18/02/10)
7. Martinez J-C, Otley CC. The management of melanoma and nonmelanoma skin cancer: a review for the primary care physician. *Mayo Clin Proc* 2001; 76: 1253–65.
8. Rubin AI, *et al.* Basal-cell carcinoma. *N Engl J Med* 2005; 353: 2262–9.
9. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: basal cell and squamous cell skin cancers (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/nmsc.pdf (accessed 18/02/10)
10. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med* 2001; 344: 975–83.
11. Motley RJ, *et al.* British Association of Dermatologists' British Association of Plastic Surgeons; Royal College of Radiologists', Faculty of Clinical Oncology. Multi-professional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/SCC%20Guidelines%20Final%20Aug%2009.pdf (accessed 18/02/10)

MELANOMA. Although cutaneous melanoma is rare it is the most aggressive skin cancer, accounting for the majority of all skin cancer deaths. Melanoma may arise in apparently normal skin or from an existing naevus. Early signs of a naevus that may indicate development of a melanoma are change in size, shape, or colour. Other signs include itching, ulceration, and bleeding. The most common site in women is the legs, and in men the back. For a discussion of sun protection measures in the prevention of melanoma, see Prophylaxis, in Malignant Neoplasms of the Skin, above.

Surgical resection is the mainstay of **curative treatment** for primary melanomas, and the margins of excision are determined by tumour depth (Breslow thickness).[1-7] Patients with thin tumours (less than 1 mm) can be treated with wide local excision only; patients with intermediate (1 to 4 mm) or thick (more than 4 mm) melanoma are at high risk for nodal disease, and lymph node dissection may also be performed if node biopsy is positive.[1,3,8] Because of the high risk of recurrence after surgery in the latter group, there is great interest in adjuvant therapies. There is no accepted standard adjuvant therapy in the UK,[2,7] and it is not recommended for stage II and III disease other than in the context of a clinical study.[8] In the USA, the FDA has approved high-dose interferon alfa, which has shown benefit in terms of relapse-free survival, although the effects on overall survival are less apparent.[1,5,6] As toxicity is a significant problem with high-dose therapy, both low-dose and intermediate dosage regimens have been studied, but neither have shown a clear benefit in terms of overall survival.[1,5,6] Some recommend pegylated interferon, if tolerated, in patients with low tumour burden.[9] Isolated limb perfusion (ILP) with melphalan has been used as adjuvant therapy, but a review of four randomised studies failed to show any survival benefit for this compared with surgery alone[10] and it is considered to have no role in the adjuvant setting.[8] Similarly, systemic chemotherapy has not proved useful in the adjuvant setting.[11] Various melanoma vaccines (e.g. GM2 ganglioside, autologous melanoma-associated antigens) have been investigated for adjuvant use, but high-dose interferon alfa was shown to produce greater clinical benefit than vaccination with GM2.[3,4,8,12,13] Other drugs such as bevacizumab,[7] cytokines such as interleukin-2,[5,6] and newer immunotherapeutic approaches[13] are under investigation in the adjuvant setting.

Local **recurrences** and in-transit metastases are treated by surgical excision where possible.[1-3,6,7] Other options include cryotherapy, carbon dioxide laser ablation, intralesional injection with BCG or interferon alfa, or topical imiquimod.[1-3,8] Radiotherapy is also included as a treatment option in some centres,[3] although others do not recommend its use in the first instance.[2] Adjuvant radiotherapy may be considered for positive margins unsuitable for re-excision.[1] ILP with melphalan is considered the standard treatment option for patients with limb involvement,[1,2,8] and those with disease that progresses despite surgery or laser therapy,[2] and as an option for those with unresectable in-transit metastases or recurrence.[3] ILP with melphalan plus tissue necrosis factor-α may also be used[2,8] although this does not significantly improve response rate. However, there is some evidence that a second ILP using this combination may be of value after an initial ILP with a poor response.[1] The ILP procedure is complex[1,6] and should only be performed in specialist centres.[8] Isolated limb infusion (ILI) is a simpler alternative that may produce equivalent results.[1,3,6] ILI usually uses melphalan with or without dactinomycin. However, it may be less effective than ILP, and some consider it more suitable for patients with low volume disease or for those with comorbidities that prevent ILP.[2]

For patients who present with **metastatic melanoma** the 5-year survival rate is poor.[11] Median survival in disseminated disease is only 6 to 9 months.[1,7,8] There is no evidence to show that any systemic treatments are better than best supportive care in these patients.[14] Chemotherapy has been tried in disseminated disease,[4-6,13] and dacarbazine, with response rates of about 5 to 20%, is the most commonly used single agent. However, the response duration is short, and complete responses are rare.[1] The orally active analogue temozolomide produces similar responses,[1] and is an alternative first-line agent.[3] Ipilimumab may also be considered for initial therapy, although extreme caution is advised in those with serious underlying auto-immune disorders because of the possibility of immune-mediated reactions.[3] Nitrosoureas (such as carmustine and lomustine) have response rates of

around 15% as single agents.[15] Fotemustine appears to be more active, particularly in the treatment of brain metastases.[15] It has been reported to have a higher response rate compared with dacarbazine, but with only a trend towards increased overall survival.[1,16] Other drugs with a response rate of about 15% include cisplatin, vinblastine, vindesine, docetaxel, and paclitaxel;[15] response duration has generally been poor. Vemurafenib has improved overall and progression-free survival compared with dacarbazine in those with metastatic melanoma with the $BRAF^{V600E}$ mutation,[17] although its place in therapy is not yet established. Dabrafenib and trametinib are other options for those with BRAF mutations.

Combination regimens have been used, such as CVD (cisplatin, a vinca alkaloid, and dacarbazine),[15] but they do not improve survival compared with monotherapy.[1] Tamoxifen has also been added to regimens, on the hypothesis that melanoma is oestrogen-dependent; an example was the CDBT or Dartmouth regimen (cisplatin, dacarbazine, carmustine, and tamoxifen; see Table 1, p. 719).[15] However, this regimen was no more effective than dacarbazine alone,[1] and the addition of tamoxifen to chemotherapy is ineffective.[1,8]

Cytokines such as interferon alfa and interleukin-2 have similar activity to chemotherapy in metastatic melanoma;[15] high-dose intravenous interleukin-2 is used in the USA,[6] but not for patients with untreated or active brain metastases.[3] Cytotoxic chemotherapy has been given with these cytokines and there have been some reports of improved response rates, but overall survival has not been improved.[1,2,5-7] Second-line therapy may be offered to patients (with good performance status) who progress or are unresponsive to, or intolerant of, first-line therapy. Options include clinical studies, or treatment with a different first-line agent.[3] Surgical resection or radiotherapy may be used palliatively or for symptomatic control.[1-3,6,9] Melanoma vaccines are also being used or investigated in metastatic or recurrent disease,[12,13] as are gene therapy,[5] antiangiogenic agents such as thalidomide,[15,16] and the antisense oligonucleotide oblimersen.[6,16] Sorafenib monotherapy is minimally active, but results of its use with carboplatin plus paclitaxel were encouraging and combination studies continue.[6,7,16]

1. Australian Cancer Network Melanoma Guidelines Revision Working Party/National Health and Medical Research Council/ Cancer Council Australia/New Zealand Guidelines Group. Clinical practice guidelines for the management of melanoma in Australia and New Zealand (issued 2008). Available at: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp111.pdf (accessed 21/07/11)
2. Marsden JR, *et al.* British Association of Dermatologists Clinical Standards Unit. Revised U.K. guidelines for the management of cutaneous melanoma 2010. *Br J Dermatol* 2010; 163: 238–56. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Melanoma%20guidelines%202010.pdf (accessed 21/07/11)
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: melanoma (version 4.2011). Available at: http://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf (accessed 21/07/11)
4. NICE. Guidance on cancer services: improving outcomes for people with skin tumours including melanoma (issued February 2006). Available at: http://www.nice.org.uk/nicemedia/live/10901/28906/28906.pdf (accessed 21/07/11)
5. Tsao H, *et al.* Management of cutaneous melanoma. *N Engl J Med* 2004; 351: 998–1012. Correction. *ibid.*; 2461.
6. Thompson JF, *et al.* Cutaneous melanoma. *Lancet* 2005; 365: 687–701.
7. Thirlwell C, Nathan P. Melanoma—part 2: management. *BMJ* 2008; 337: a2488.
8. SIGN. Cutaneous melanoma: a national clinical guideline (issued July 2003). Available at: http://www.sign.ac.uk/pdf/sign72.pdf (accessed 21/07/11)
9. Dummer R, *et al.* ESMO Guidelines Working Group. Melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v194–v197. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v194.full.pdf+html (accessed 21/07/11)
10. Lens MB, Dawes M. Isolated limb perfusion with melphalan in the treatment of malignant melanoma of the extremities: a systematic review of randomised controlled trials. *Lancet Oncol* 2003; 4: 359–64.
11. Jackson DP, Patel PM. The current place of systemic therapy in the treatment of malignant melanoma. *CME Oncology* 1998; 1: 4–8.
12. Brinckerhoff LH, *et al.* Melanoma vaccines. *Curr Opin Oncol* 2000; 12: 163–73.
13. Kirkwood JM, *et al.* Next generation of immunotherapy for melanoma. *J Clin Oncol* 2008; 26: 3445–55.
14. Crosby T, *et al.* Systemic treatments for metastatic cutaneous melanoma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 21/07/11).
15. Bajetta E, *et al.* Metastatic melanoma: chemotherapy. *Semin Oncol* 2002; 29: 427–45.
16. Danson S, Lorigan P. Improving outcomes in advanced malignant melanoma: update on systemic therapy. *Drugs* 2005; 65: 733–43.
17. Chapman PB, *et al.* BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364: 2507–16.

Malignant neoplasms of the testis. Testicular cancer only accounts for about 1% of all male malignancies but it is the most common cancer in young men. Patients with a history of cryptorchidism are at increased risk. Other risk factors include family history, infertility, and white race. About 95% of testicular tumours arise in germ cells, and 40% or so of these are pure seminomas. The remainder are collectively known as nonseminomatous germ cell tumours (NSGCT) in the WHO classification, and are commonly of mixed cell types with or without a seminoma component. Nonseminomatous tumours have been referred to as teratomas in the British classification system, but this term has a more specific meaning in the WHO classification.

Metastasis first occurs to the lymph nodes, then, in advanced disease, to distant sites such as lung, liver, brain, and bones. The leading symptom is a hard, painless swelling of the testis, but once metastasis occurs the patient may present with back pain (due to enlargement of retroperitoneal lymph nodes), cough, dyspnoea, gynaecomastia due to chorionic gonadotrophin production, or weight loss.

Surgical removal of the testis (orchidectomy) when diagnosis is confirmed is fundamental to the treatment of all types of testicular cancer, but further therapy depends upon the disease type and stage.[1-4]

In patients with **nonseminomatous** disease with the ***tumour confined to the testis*** (stage I), options after orchidectomy include surveillance, adjuvant chemotherapy, or retroperitoneal lymph-node dissection (RPLND). Overall survival rates are good, with a cure rate close to 100%.[4-6] With surveillance, about 20 to 30% of patients will relapse and it is not appropriate for patients who are unable to undergo regular follow-up.[1,4] Treatment options vary slightly between countries. In the USA, RPLND may be carried out to further stage the disease before making a decision regarding surveillance or adjuvant chemotherapy.[1] If resected nodes are clear, patients undergo surveillance, but if they involve tumour the decision to give adjuvant chemotherapy is based on the degree of nodal involvement and the ability of the patient to undergo regular follow-up.[1] In the UK and Europe, stage I patients are classified as low-risk or high-risk, based on the absence or presence, respectively, of vascular (venous or lymphatic) invasion.[3-6] The standard option for low-risk patients is surveillance, with treatment on relapse.[3,5,6] High-risk patients can also be surveyed, but relapse rates are higher, and about 50% of patients will require chemotherapy.[3,5] The usual regimen used for stage I patients is 2 cycles of BEP (bleomycin, etoposide, and cisplatin).[1,3] However, there is some suggestion that one cycle of BEP may be sufficient.[3] RPLND is considered only if surveillance or chemotherapy is declined by the patient for specific or personal reasons, as it has the highest treatment burden.[3,5]

Where ***metastasis to the lymph nodes*** (stage IIA/B) has occurred, options for management are 3 cycles of BEP, 4 cycles of EP (etoposide and cisplatin), or primary RPLND (followed by either surveillance or chemotherapy).[1,3,4] Patients with ***advanced*** nonseminoma (stage IIC and III) are treated with primary chemotherapy regimens based on risk status; extent of disease and serum tumour markers are prognostic, and patients are accordingly classified into good-, intermediate-, and poor-risk groups.[1,3] For patients with good prognosis, standard treatment regimens are 3 cycles of BEP or 4 cycles of EP.[1,3,4] Standard management for patients with intermediate- or poor-risk disease is 4 cycles of BEP.[1,3,4] For patients who may not tolerate bleomycin, ifosfamide can be substituted (VIP regimen).[1,3,4] Less than 50% of poor-prognosis patients achieve a durable response, and enrolment into clinical studies is encouraged.[1] Any residual tumour is resected after chemotherapy; further management depends on the results of the primary treatment and secondary surgery; consolidation chemotherapy with 2 cycles of EP, VIP, VeIP (vinblastine, ifosfamide, and cisplatin) or TIP (paclitaxel, ifosfamide, and cisplatin) may be given.[1,3]

Patients who fail, or who relapse after, standard chemotherapy, or who have unresectable disease, are treated with *salvage therapy*.[1] Common salvage regimens include cisplatin and ifosfamide with either vinblastine (VeIP regimen), paclitaxel (TIP regimen), or etoposide (VIP regimen).[1,3,5,7] High-dose chemotherapy with stem cell support may also be considered.[1,5,6,8,9] Drugs with activity as single agents in relapsed disease include paclitaxel, oxaliplatin, and gemcitabine.[5-7] Combinations of these have been tried as second-line salvage chemotherapy regimens for patients with cisplatin-resistant or refractory disease;[7,9,10] gemcitabine with either oxaliplatin (GEMOX regimen)[1] or paclitaxel[3] may be tried.

About 75% of patients with **seminoma** have stage I disease at diagnosis, with a cure rate close to 100%.[2,5,6] Treatment options after orchidectomy include surveillance (with treatment only in the case of relapse), adjuvant radiotherapy or adjuvant carboplatin monotherapy.[1,2,4-6] Surveillance offers the lowest burden of treatment,[2] and is an option for selected patients who are committed to long-term follow-up.[1,6] The optimum surveillance schedule is still uncertain,[4] but should include measurement of serum tumour markers, clinical examination, and imaging of the abdomen, pelvis, and thorax.[1,4] Seminomas are extremely sensitive to radiation,[4] and adjuvant radiotherapy is the treatment of choice after orchidectomy in stages IIA and IIB.[1,5,6] For those with relative contra-indications to radiotherapy, chemotherapy is recommended;[1,5] 3 cycles of BEP, or 4 cycles of EP are used. There is an increasing role for chemotherapy in stage IIB[3] and some[2] distinguish slightly between stages in terms of treatment, and advocate radiotherapy and chemotherapy as standard for stages IIA and IIB, respectively; non-candidates for either therapy may be offered the alternative. Patients with stages IIC to III seminoma have a relapse rate of 20 to 30% after adjuvant radiotherapy, and adjuvant chemotherapy is preferred.[5] Standard regimens are 3 cycles of BEP or 4 cycles of EP for good-risk patients, and 4 cycles of BEP for intermediate-risk patients;[1,2] using ifosfamide instead of bleomycin can also be an option in those at intermediate-risk.[2] About 90% of patients with advanced seminoma are cured with cisplatin-containing chemotherapy.[1] Salvage regimens for relapsed or unresponsive seminoma are similar to those used for nonseminomatous disease.[1,2]

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: testicular cancer (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/testicular.pdf (accessed 13/07/10)
2. Schmoll H-J, *et al.* ESMO Guidelines Working Group. Testicular seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v140–v146. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v140.full.pdf+html (accessed 25/10/10)
3. Schmoll H-J, *et al.* ESMO Guidelines Working Group. Testicular non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v147–v154. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v147.full.pdf+html (accessed 25/10/10)
4. Rustin G, Rehman F. State-of-the-art approach in selective curable tumors: germ cell tumors. *Ann Oncol* 2008; 19 (suppl 7): vii161–vii165.
5. Kopp H-G, *et al.* Advances in the treatment of testicular cancer. *Drugs* 2006; 66: 641–59.
6. Horwich A, *et al.* Testicular germ-cell cancer. *Lancet* 2006; 367: 754–65. Correction. *ibid.*; 1398.
7. Sonpavde G, *et al.* Management of recurrent testicular germ cell tumors. *Oncologist* 2007; 12: 51–61.
8. Einhorn LH, *et al.* High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med* 2007; 357: 340–8.
9. Feldman DR, *et al.* Medical treatment of advanced testicular cancer. *JAMA* 2008; 299: 672–84.
10. Kollmannsberger C, *et al.* Recent advances in management of patients with platinum-refractory testicular germ cell tumors. *Cancer* 2006; 106: 1217–26.

Malignant neoplasms of the thymus. Thymomas are tumours of the mediastinum, arising from thymic tissue. They are rare, and most commonly present in patients between 40 and 60 years of age. Thymoma originates from the epithelium of the thymus but may also contain a lymphocyte component, which is probably not neoplastic. Up to 50% of patients are asymptomatic, and others have local symptoms such as cough, chest pain, dyspnoea, and obstruction of the vena cava; associated systemic disorders include myasthenia gravis, red cell aplasia, and hypogammaglobulinaemia.

Thymomas may be classified based on cell type; they are also staged as non-invasive (encapsulated, stage I), invasive (localised, stage II; extensive, stage III; and disseminated, IVa), and metastatic (IVb).

The treatment of thymoma may involve surgery, radiation, and chemotherapy; these may be combined, with the combination determined by the stage of the tumour.[1] Non-invasive stage I disease can be treated solely by surgical resection[1-4] with low recurrence rates and long-term survival approaching 100%.[3] Use of adjuvant radiation therapy for stage II thymoma has been controversial,[2] with studies showing conflicting results.[3] Generally, however, routine adjuvant radiotherapy is not recommended for stage II disease;[1,4] it may be considered in those patients at high risk for local recurrence,[1] or in patients with incomplete resection;[4] late complications of radiation therapy may occur.[1,2] Patients with stage I or II disease who are medically unfit for surgery may be offered chemoradiotherapy or radiotherapy alone.[1]

For patients with potentially resectable invasive disease (stages III and IVa), surgery is considered either initially or after neoadjuvant therapy. Chemoradiotherapy is often used before surgery, although the optimal regimen or sequencing has not yet been established.[1] Cisplatin-based combination regimens are recommended.[1,4] Concurrent chemoradiotherapy is recommended, but if the tumour is bulky, sequential therapy, with chemotherapy given before radiation, is an option.[1] Adjuvant radiotherapy is also often used in stage III,[1] and is recommended to maximise local control.[4] Adjuvant chemotherapy may be considered, but is not routinely recommended.[1] For stage IVa, adjuvant chemoradiotherapy is an option.[1] Patients with unresectable invasive disease may be treated with chemotherapy alone,[1] radiotherapy alone,[4] or concurrent or sequential chemoradiotherapy.[1,4] Cisplatin plus anthracycline-containing regimens similar to those in metastatic disease (below) are used first-line, and single agents second-line.[1]

Therapy for recurrent or metastatic disease is not well established because of the rarity of the condition.[1,5] Radiotherapy may be appropriate in stage IVB, especially for life-threatening situations,[1] but chemotherapy is often used.[1,4] Cisplatin and anthracycline-containing regimens are used first-line.[1,4] These include cisplatin, doxorubicin, and cyclophosphamide (CAP or PAC regimen), and the same drugs with vincristine (ADOC regimen). Cisplatin plus

etoposide (PE regimen) or these 2 drugs with ifosfamide (VIP regimen) are also options.[2,4,5] For these and other commonly used chemotherapy regimens, see Table 1, p. 719. Carboplatin and paclitaxel can also be used first-line.[4] Second-line single agents with activity include etoposide, ifosfamide, pemetrexed, fluorouracil, gemcitabine, and paclitaxel.[4] There is some evidence that thymomas possess somatostatin receptors, and octreotide, alone or with a corticosteroid, is also a second-line option.[1,4]

Surgery is considered for localised recurrence after apparently successful initial therapy. For some patients with stage IV disease, resection of isolated pleural metastases is appropriate. Radiotherapy, alone or with cisplatin-based chemotherapy, may be used. Octreotide with or without a corticosteroid is also a reasonable option for recurrent disease.[1]

1. Falkson CB, *et al.* Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. The management of thymoma: a systematic review and practice guideline. *J Thorac Oncol* 2009; **4**: 911–19.
2. Kondo K. Optimal therapy for thymoma. *J Med Invest* 2008; **55**: 17–28.
3. Duwe BV, *et al.* Tumors of the mediastinum. *Chest* 2005; **128**: 2893–2909.
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: thymic malignancies (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/thymic.pdf (accessed 08/03/10)
5. Schmidt-Wolf IGH, *et al.* Malignant thymoma: current status of classification and multimodality treatment. *Ann Hematol* 2003; **82**: 69–76.

Malignant neoplasms of the thyroid. Thyroid cancer accounts for only about 1% of all malignancies. The incidence is reportedly higher in women than men, in patients who received irradiation of the thyroid during childhood, and in populations where goitre is endemic. The natural history varies with the cell type and degree of differentiation. Well-differentiated papillary or follicular tumours (which constitute over 80% and about 10% of cases, respectively) are very slow to grow and metastasise, sometimes persisting for years with little change in size and extent, although they may prove more aggressive in children. In contrast medullary carcinomas (5 to 10% of cases), which develop from the cells responsible for calcitonin secretion, and undifferentiated (anaplastic) tumours (1%) metastasise early and follow a much more rapid and aggressive course. About 25% of medullary cancers are hereditary, including those due to multiple endocrine neoplasia type 2.

The well-differentiated types usually present as a thyroid nodule, although most nodules are not malignant, while with anaplastic tumours there is usually invasion into the trachea, larynx, or recurrent laryngeal nerve which leads to obstructive symptoms, haemoptysis, dysphagia, and hoarseness.

In patients with **well-differentiated tumours** total or partial thyroidectomy is the treatment of choice.[1-7] This may be followed by a course of iodine-131 to destroy any residual tumour (thyroid ablation), although in patients who have small tumours with no other high-risk features (such as extension beyond the thyroid capsule or lymph node metastases) there are no benefits to such ablation and iodine-131 is not usually recommended.[1-7] External radiation therapy may be considered in patients with evidence of extrathyroid extension at the time of surgery.[3,4] There is no role for routine adjunctive chemotherapy in the management of differentiated thyroid cancer.[4] Levothyroxine treatment is given to all patients to prevent hypothyroidism and to minimise stimulation of tumour growth by thyroid stimulating hormone (TSH).[2,5,6] Measurement of serum thyroglobulin concentrations aids the detection of residual, recurrent, or metastatic disease. After surgery and thyroid ablation, this should be undetectable after about 3 months, although occasionally it may take up to 2 years; raised concentrations imply the presence of functional thyroid tissue or tumour. Sensitivity of thyroglobulin measurements is enhanced by an increase in TSH. TSH stimulation can be achieved either by levothyroxine withdrawal or by injections of human recombinant thyrotropin alfa.[1-4,6]

Disease recurrence or metastases are commonly treated with further surgery, ablative iodine-131 therapy or external radiation therapy.[1-4] Chemotherapy for metastatic disease has been inadequately studied.[2,5] It may have a role in refractory disease.[1,3,6] Doxorubicin is often used,[5] with a response rate of up to 40%;[2] cisplatin is also used.[1] Durable responses are rare.[1,2] Combination chemotherapy is not clearly superior to doxorubicin monotherapy.[3] Some[7] recommend against chemotherapy due to a lack of efficacy and recommend enrolment into clinical studies. Novel agents are under investigation;[1,3,5,7,8] preliminary results with tyrosine kinase inhibitors have been promising.[7]

In patients with **medullary cancers** total thyroidectomy and central neck compartment dissection are indicated,[1-3,7] with levothyroxine treatment if needed.[2,3] Serum calcitonin should be measured to detect residual disease.[2,3] Adjuvant external beam radiotherapy may be used in patients at high risk of regional recurrence[2,3] but routine use has not shown any survival benefit.[1] There is no role for radioactive iodine in medullary disease,[2,3] and chemotherapy is generally ineffective.[1,3] Further surgery with or without adjuvant radiotherapy is recommended for recurrent disease. Palliative resection or radiofrequency ablation can be tried for distant metastases; chemotherapy is usually dacarbazine-based.[3] Novel agents such as tyrosine kinase inhibitors have been investigated, with promising initial results;[7] cabozantinib is used for metastatic disease, and vandetanib for unresectable locally advanced or metastatic disease. Prophylactic thyroidectomy may be considered in patients with a hereditary predisposition to medullary cancer.[1,2] In patients with **anaplastic tumours**, cure is impossible and treatment is purely palliative, with survival measured in months.[2,3,7] Treatment options include surgery, radiotherapy, and chemotherapy. *Multimodality* therapy should be considered.[2,3,9] Use of hyperfractionated radiotherapy with doxorubicin can increase response, with median survival of 1 year. Paclitaxel has also been tried.[2,3,7] Novel agents are under investigation,[7,8,10] including the vascular targeting agent fosbretabulin.[3]

1. British Thyroid Association and Royal College of Physicians. Guidelines for the management of thyroid cancer (2007). Available at: http://www.british-thyroid-association.org/news/Docs/Thyroid_cancer_guidelines_2007.pdf (accessed 13/07/10)
2. Sherman SI. Thyroid carcinoma. *Lancet* 2003; **361**: 501–11.
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: thyroid carcinoma (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/thyroid.pdf (accessed 10/03/10)
4. Cooper DS, *et al.* American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; **19**: 1167–1214. Also available at: http://www.liebertonline.com/doi/abs/10.1089/thy.2009.0110 (accessed 10/03/10)
5. Baudin E, Schlumberger M. New therapeutic approaches for metastatic thyroid carcinoma. *Lancet Oncol* 2007; **8**: 148–56.
6. Pacini F, *et al.* European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* 2006; **154**: 787–803. Correction. *ibid.*; **155**: 385. Also available at: http://eje-online.org/cgi/reprint/154/6/787 (accessed 10/03/10)
7. Pacini F, *et al.* ESMO Guidelines Working Group. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v214–v219. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v214.full.pdf+html (accessed 25/10/10)
8. Woyach JA, Shah MH. New therapeutic advances in the management of progressive thyroid cancer. *Endocr Relat Cancer* 2009; **16**: 715–31.
9. Patel KN, Shaha AR. Poorly differentiated and anaplastic thyroid cancer. *Cancer Control* 2006; **13**: 119–28.
10. Smallridge RC, *et al.* Anaplastic thyroid cancer: molecular pathogenesis and emerging therapies. *Endocr Relat Cancer* 2009; **16**: 17–44.

Neuroblastoma. Neuroblastoma accounts for about 7% of all childhood malignancies overall but is the most common extra-cranial solid tumour in children. The majority of cases present before the age of 5 years. The tumour is derived from cells of the neural crest, and may occur anywhere within the sympathetic nervous system, notably the sympathetic ganglia and the adrenal medulla. Clinical behaviour ranges from spontaneous remission to rapid metastatic progression and death. Sites of metastasis include lymph nodes, bone marrow, liver, and skin. Symptoms depend on the site of the primary tumour and extent of disease. About 50% of children present with metastatic disease. Adverse prognostic factors include age over 1 year at diagnosis, advanced or metastatic disease, and amplification of the oncogene MYCN. The International Neuroblastoma Staging System (INSS) divides localised tumours into stages 1 and 2, based on regional lymph node status; unresectable tumours are classified as stage 3, and stage 4 refers to all patients aged 1 year or older with distant disease. Stage 4S (4 special) refers to infants less than 1 year of age with small localised primary tumour and limited dissemination (confined to liver, skin, or bone marrow).[1,2] However, the INSS is based on the extent of surgical excision, and a new staging system has also been developed by the International Neuroblastoma Risk Group, which is based on tumour imaging and risk factors. Locoregional tumours are staged as L1 or L2 based on the absence or presence of one or more image-defined risk factors, respectively. Metastatic tumours are classified as stage M, except for stage MS, in which metastases are confined to the liver, skin, and/or bone marrow in children younger than 18 months of age.[3,4]

Treatment protocols are designed according to the risk stratification:[1,5,6]

- the *low-risk* group consists of stage 1, stage 2, and stage 4S non-amplified hyperploid tumours with favourable histology
- the *intermediate-risk* group includes stage 3, 4, and 4S MYCN non-amplified tumours
- the *high-risk* group consists of stage 2 to 4 MYCN amplified tumours, including stage 3 tumours with unfavourable histology in children older than 18 months

Surgical resection alone is appropriate for those with **low-risk** tumours; these patients have a good prognosis.[1,2,6] Patients with local recurrence after surgery can be salvaged with chemotherapy and local radiotherapy. Neoadjuvant chemotherapy is also an option for those with paraspinal tumours and spinal cord compression, in order to avoid the morbidity of laminectomy and radiation. Patients with symptomatic stage 4S disease may also require chemotherapy.[2]

In those classified as **intermediate-risk**, surgery is usually followed by a short course of standard-dose combination chemotherapy.[1,2,6] Regimens used include cisplatin (or carboplatin), etoposide, cyclophosphamide, and doxorubicin.[2]

High-risk tumours can be treated with surgery, combination chemotherapy, myeloablative chemotherapy with haematopoietic stem cell transplantation, and local radiation.[1,2,6] Most remission induction regimens incorporate some or all of the most active drugs available for neuroblastoma, including the platinum derivatives, cyclophosphamide, ifosfamide, doxorubicin, etoposide, and topotecan.[1,2] One such dose-intensive regimen that was reported to have good response rates in a small study consisted of cyclophosphamide, vincristine, plus doxorubicin, alternating with cisplatin and etoposide.

Consolidation with myeloablative chemotherapy is used to eradicate any residual cancer cells. The addition of isotretinoin improved event-free survival and some consider high-dose myeloablation followed by isotretinoin to be the standard of care for children with high-risk disease who are older than 1 year at diagnosis.[2] Stem cell transplantation may be autologous or allogeneic,[2] although autologous peripheral blood stem cells appear to be the preferred source; tandem transplants are under investigation.[2,7]

Neuroblastoma is radiosensitive and if complete surgical resection is not possible, adjuvant radiation is indicated. It may also be used after chemotherapy, and occasionally as palliation for metastases.[1] However, the role of total body irradiation (TBI) in the treatment of high-risk neuroblastoma has not been established, and most protocols do not include TBI.[2]

Metaiodobenzylguanidine (*m*-iodobenzylguanidine; iobenguane; MIBG) is a guanethidine derivative and norepinephrine analogue that concentrates in neural crest tissues. When radiolabelled with isotopes of iodine, MIBG has been shown to be useful for both imaging and treatment of neuroblastoma. MIBG uptake can be seen at the site of primary disease as well as metastatic tumour sites.[6] Iodine-123-labelled MIBG is the radioisotope of choice for imaging, whereas Iodine-131-labelled MIBG is used for therapeutic purposes.[5,6] It has been used as monotherapy or with combination chemotherapy in advanced, relapsed, or refractory disease, and has been investigated for use in newly diagnosed patients.[6,8] MIBG with radiosensitisers is also under investigation.[6] Multiple infusions of MIBG have also been used.[6,8]

1. Papaioannou G, McHugh K. Neuroblastoma in childhood: review and radiological findings. *Cancer Imaging* 2005; **5**: 116–27.
2. Goldsby RE, Matthay KK. Neuroblastoma: evolving therapies for a disease with many faces. *Paediatr Drugs* 2004; **6**: 107–22.
3. Cohn SL, *et al.* INRG Task Force. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *J Clin Oncol* 2009; **27**: 289–97.
4. Monclair T, *et al.* INRG Task Force. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. *J Clin Oncol* 2009; **27**: 298–303.
5. Boubaker A, Bischof Delaloye A. MIBG scintigraphy for the diagnosis and follow-up of children with neuroblastoma. *Q J Nucl Med Mol Imaging* 2008; **52**: 388–402.
6. Taggart D, *et al.* Radiolabeled metalodobenzylguanidine for imaging and therapy of neuroblastoma. *Q J Nucl Med Mol Imaging* 2008; **52**: 403–18.
7. Fish JD, Grupp SA. Stem cell transplantation for neuroblastoma. *Bone Marrow Transplant* 2008; **41**: 159–65.
8. DuBois SG, Matthay KK. Radiolabeled metaiodobenzylguanidine for the treatment of neuroblastoma. *Nucl Med Biol* 2008; **35** (suppl 1): S35–S48.

Neuroendocrine tumours. Neuroendocrine tumours are rare and constitute a heterogeneous group of neoplasms that share certain biological features. They originate from cells that produce and secrete regulatory hormones, and frequently present as hypersecretory syndromes. Common sites of origin include the endocrine pancreas, gastroenteric tissue in the gut, and neuroendocrine cells in the respiratory epithelium, as well as the thyroid, parathyroid, adrenal, or pituitary glands. Examples of syndromes associated with such secretory neoplasms include acromegaly (p. 1921.1), Cushing's syndrome (p. 2559.1), hyperprolactinaemia (p. 2252.2), and phaeochromocytoma (p. 1278.1). Multiple endocrine neoplasia type 1 (MEN1) and type 2 (MEN2) are inherited conditions in which many tumours occur in often more than one endocrine organ; tumours in this disorder are often secretory.

Gastroenteropancreatic neuroendocrine tumours include carcinoid tumours and pancreatic endocrine tumours.

Carcinoid syndrome. Carcinoid tumours have traditionally been classified according to their embryological origin, namely fore-gut (bronchi, stomach, duodenum), mid-gut (jejunum, ileum, appendix, proximal colon), and hind-gut (distal colon and rectum).[1-4] Carcinoid tumours can secrete various hormones. The carcinoid syndrome describes symptoms related to the secretion of serotonin, histamine, or tachykinins. However, symptomatic carcinoid syndrome

is rare, both because the tumours vary in their behaviour depending on their embryological origin and because the liver is capable of metabolising those tumour products which are secreted into the portal circulation; only if the carcinoid tumour secretes into the systemic circulation, notably after metastasis to the liver, do symptoms occur. Carcinoid syndrome is therefore most often associated with tumours of the mid-gut, since they are commonest, and frequently metastasise.[2,5]

The characteristic **symptoms** of carcinoid syndrome include episodic flushing of the face and upper trunk (which may be provoked by alcohol, food, or stress), secretory diarrhoea, wheezing and dyspnoea, weight loss, pellagra, painful hepatomegaly, and right-sided valvular heart disease, which sometimes progresses to right heart failure and death.[2,4,5]

The **management** of carcinoid tumours usually involves surgical resection.[2-5] For localised disease, surgery may be curative.[1,6] Although many patients present with metastatic disease,[1] cytoreductive surgery is a mainstay of management.[4,6] Other cytoreductive procedures can also be used, such as radiofrequency ablation, laser therapy, and hepatic regional therapy (arterial embolisation, or trans-arterial chemoembolisation).[1,2,4-6] Drugs used for chemoembolisation include doxorubicin, streptozocin,[5] or a combination regimen of cisplatin, doxorubicin, and mitomycin.[4] Systemic antineoplastic chemotherapy has been used, but is considered to be of limited benefit for carcinoid tumours.[5-7] However, combination regimens may be used first-line for malignant, highly proliferative carcinoid tumours.[4] A common combination includes streptozocin, fluorouracil, plus doxorubicin;[4] cisplatin plus etoposide has also been used.[7] Despite some initial reports of response to interferon alfa, its value has not been borne out in practice.[5] It has, however, been considered to be of value for symptomatic control.[7]

For **symptomatic relief** of carcinoid syndrome somatostatin analogues such as octreotide or lanreotide are highly effective[4,5,8] and are the treatment of choice.[1,2] The availability of depot intramuscular preparations has simplified treatment, removing the need for multiple daily subcutaneous injections.[1,7,9] However, with prolonged use a few patients develop resistance even to the highest doses; the mechanism behind this tachyphylaxis is not yet known, although down-regulation of receptors has been suggested.[3,4,7] Octreotide is also used in the perioperative management of these patients to treat or prevent carcinoid crisis, when it may be given intravenously.[1] Use of somatostatin analogues with interferon alfa does not appear to be superior to monotherapy with either drug, and most do not recommend combination therapy as a standard treatment option.[7,9,10] While some consider the sequential use of these drugs, or the use of the combination after progression on monotherapy, to be justified,[10] others rarely add interferon when somatostatin analogues are no longer effective.[3] There is growing interest in the use of radiolabelled somatostatin analogues for the management of tumours that express high levels of somatostatin receptors;[2,4,5,9] promising results have been reported with palliative use in inoperable or metastatic disease.[1,11] Newer therapies such as gefitinib, everolimus, sunitinib, and bevacizumab are also being tried.[2,5,6] Other drugs that reduce the effects of serotonin have been tried, including cyproheptadine.[5] Patients with histamine-producing tumours should avoid histaminic drugs; treatment is with somatostatin analogues, blockade of histamine receptors, and possibly corticosteroids.[3]

Apart from such specific pharmacological therapies, antidiarrhoeals such as loperamide are sometimes helpful in controlling diarrhoea. Supplementation with vitamin B substances is advisable to prevent pellagra. It is also important to avoid provocative factors such as stress, alcohol, and particular foods.[3]

Pancreatic endocrine tumours. Neoplasms of the pancreatic islet cells (pancreatic endocrine tumours) are uncommon compared with those of the exocrine pancreas (see Malignant Neoplasms of the Pancreas, p. 712.1). Pancreatic endocrine tumours, whether benign or malignant, often secrete clinically significant amounts of hormone; the hormone secreted, and hence the resultant clinical syndrome, depends on which of the several types of hormone-secreting islet cells is the origin of the tumour.[2] Primary **therapy** for solitary pancreatic endocrine tumours is surgical resection;[2] metastatic tumours may require a combination of symptomatic drug therapy, chemotherapy, radiotherapy, and surgical debulking. As for carcinoid tumours, somatostatin analogues such as octreotide or lanreotide are used to control symptomatic disease.[1,2] For those who present with significant tumour burden, or with disease progression, options include everolimus or sunitinib, which have been found to improve progression-free survival, or cytotoxic chemotherapy.[2] The most frequently used regimens involve combinations of streptozocin, doxorubicin, fluorouracil, and dacarbazine.[1,2,7] Capecitabine and temozolomide have also been used.[2] Hepatic regional therapy, including arterial embolisation or chemoembolisation, is used for patients who are not surgical candidates.[2]

Symptoms of hormonal excess should be treated, before surgery and/or after resection if needed; therapies depend on the tumour type,[2] and are used in cases refractory to somatostatin analogues, or in combination with them.[3]

- Up to 90% of **insulinomas** are benign[2,6] and do not metastasise. Only about half of these tumours have somatostatin type II receptors and are thus less sensitive to treatment with somatostatin analogues.[1,3] Excessive insulin secretion results in hypoglycaemia; glucose concentrations can be stabilised by diet and/or diazoxide.[1-3] Glucose infusions may be needed.[1]
- Most **glucagonomas**, which secrete glucagon, are malignant, and over 80% have metastases at presentation.[2,3] Common symptoms include a characteristic rash (necrolytic migratory erythema), diabetes mellitus, weight loss, and diarrhoea. Patients should be stabilised with intravenous fluids, octreotide, and zinc.[2,3]
- Another well-characterised syndrome results from tumours which release vasoactive intestinal polypeptide (VIP). Such **VIPomas** result in profound secretory diarrhoea, with consequent hypokalaemia and acidosis;[2,3] the syndrome is sometimes known as pancreatic cholera. Metabolic imbalances should be corrected by fluid and electrolyte supplementation.[1,2] Somatostatin analogues such as octreotide are used for chronic control of the diarrhoea;[1-3] other antidiarrhoeals are seldom effective, although glucocorticosteroids can be used for acute exacerbations.[3]
- Of the other pancreatic endocrine tumours **gastrinoma** is the commonest: it results in Zollinger-Ellison syndrome, for which proton pump inhibitors are the treatment of choice. For further information on the treatment of Zollinger-Ellison syndrome see p. 1817.3. Rarer malignant tumours include **somatostatinoma** (which secretes somatostatin) and **PPoma** (which secretes pancreatic polypeptide).[2,3]

1. Ramage JK, *et al.* UK and Ireland Neuroendocrine Tumour Society. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 2012; 61: 6–32.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: neuroendocrine tumors (version 1.2012). Available at: http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf (accessed 03/05/12)
3. Kaltsas GA, *et al.* The diagnosis and medical management of advanced neuroendocrine tumors. *Endocr Rev* 2004; 25: 458–511.
4. Pinchot SN, *et al.* Carcinoid tumors. *Oncologist* 2008; 13: 1255–69.
5. Bendelow J, *et al.* Carcinoid syndrome. *Eur J Surg Oncol* 2008; 34: 289–96.
6. Öberg K, *et al.* ESMO Guidelines Working Group. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v223–v227. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v223.full.pdf+html (accessed 04/08/11)
7. Plöckinger U, Wiedenmann B. Treatment of gastroenteropancreatic neuroendocrine tumors. *Virchows Arch* 2007; 451 (suppl 1): S71–S80.
8. Öberg K, *et al.* Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol* 2004; 15: 966–73.
9. Delaunoit T, *et al.* Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumors. *Mayo Clin Proc* 2005; 80: 502–6.
10. Fazio N, *et al.* Interferon-alpha and somatostatin analog in patients with gastroenteropancreatic neuroendocrine carcinoma: single agent or combination? *Ann Oncol* 2007; 18: 13–19.
11. Kaltsas GA, *et al.* Treatment of advanced neuroendocrine tumours with radiolabelled somatostatin analogues. *Endocr Relat Cancer* 2005; 12: 683–99.

Retinoblastoma. Retinoblastoma is the most common eye tumour in children and accounts for about 3% of all childhood malignancies in the UK (for other malignant neoplasms of the eye, see p. 705.1). In about 60% of cases the tumour is sporadic and non-hereditary, producing a unilateral, unifocal lesion. In other cases there is an inherited abnormal tumour suppressor gene (RB1 gene mutation): these tumours are typically bilateral and are sometimes associated with an intracranial neuroblastic tumour or pinealoblastoma (trilateral retinoblastoma). In addition, patients with the hereditary form are at very high risk of secondary primary malignancies, particularly osteosarcoma and soft tissue sarcomas. Onset after age 5 is rare, but retinoblastomas are occasionally reported in adults. The most common manifestations of retinoblastoma are leukocoria (white pupil) and strabismus (squint). In intra-ocular disease, the tumour is confined to the eye; the majority of patients with unilateral disease present with advanced intra-ocular disease. Nevertheless, 5-year disease-free survival after treatment in these patients is over 90% in developed countries. Extra-ocular retinoblastoma is an advanced stage of the disease where the tumour has spread into the tissues around the eye (orbital invasion) or beyond the optic nerve with metastatic spread to the CNS and beyond. Extra-ocular disease is more prevalent in developing countries due to delayed diagnosis. The 5-year survival rate is less than 10% despite treatment. Management of retinoblastoma is individualised with consideration of the size and location of the tumour, laterality of the disease, age, risk of metastases, and stage.

The aim of treatment for **intra-ocular** retinoblastoma is to cure the disease, and to preserve as much vision as possible.[1,2] In patients with unilateral tumours, enucleation (removal of the eye) is the standard primary treatment when there is no expectation of useful vision (e.g. extensive disease within the eye).[3] The role of *adjuvant* treatment is controversial; adjuvant chemotherapy regimens include carboplatin plus etoposide, or vincristine, cyclophosphamide, and doxorubicin. Radiotherapy has also been used in cases of incomplete resection.[4] In bilateral retinoblastoma, standard treatment was enucleation of the advanced eye and external beam radiation therapy in the less advanced eye. However, there is increasing use of therapies to preserve the eye and to reduce the use of external beam radiotherapy which further increases the risk of secondary malignancies.[1,4,5] These include local treatments such as laser therapy, cryotherapy, thermotherapy, and plaque radiotherapy (brachytherapy).[1,3,4] Intravenous *neoadjuvant* chemotherapy may be given before local treatment to reduce tumour size (chemoreduction); regimens usually include carboplatin, etoposide (or teniposide), and vincristine.[1,3-5] Ciclosporin has also been included to overcome multidrug resistance due to P-glycoprotein.[3,5]

Chemothermotherapy (chemotherapy and thermotherapy used within hours of each other) may be useful for larger tumours, or for small tumours adjacent to the fovea or optic nerve.[3] *Local delivery* of chemotherapy directly into the periorbital tissues (focal chemotherapy) has also been investigated;[1,4,5] subconjunctival carboplatin may be useful in cases of vitreous seeding,[4] but local toxicity may be a problem and some reserve periocular injection for advanced intra-ocular disease that has not responded to multiple cycles of systemic chemotherapy.[5]

There is no standard treatment for **extra-ocular** retinoblastoma.[1,6] Patients with regional disease without overt metastases (micrometastatic retinoblastoma) may benefit from conventional systemic chemotherapy and external beam radiotherapy.[3,6] Patients with orbital extension may be treated with enucleation, radiotherapy, and intensive chemotherapy.[1] Regimens typically include cyclophosphamide, doxorubicin, and vincristine, and may include carboplatin and etoposide.[3,6] Intrathecal methotrexate and cranial irradiation may be added for CNS involvement or trilateral retinoblastoma.[6] Metastatic disease may be treated similarly,[6] but although conventional combination chemotherapy may produce a response it is rarely curative in such advanced disease.[1,3] High-dose chemotherapy with autologous stem cell rescue may be beneficial in metastatic disease, but it has not been effective for disease involving the CNS.[1,3]

1. De Potter P. Current treatment of retinoblastoma. *Curr Opin Ophthalmol* 2002; 13: 331–6.
2. Deegan WF. Emerging strategies for the treatment of rednoblastoma. *Curr Opin Ophthalmol* 2003; 14: 291–5.
3. Chintagumpala M, *et al.* Retinoblastoma: review of current management. *Oncologist* 2007; 12: 1237–46.
4. Aerts I, *et al.* Retinoblastoma. *Orphanet J Rare Dis* 2006; 1: 31.
5. Kim JW, *et al.* Current management strategies for intraocular retinoblastoma. *Drugs* 2007; 67: 2173–85.
6. Finger PT, *et al.* Chemotherapy for retinoblastoma: a current topic. *Drugs* 1999; 58: 983–96.

Sarcomas. The sarcomas are tumours arising from mesodermal cells, which form the bone and connective tissue (as opposed to carcinomas, which arise from ectodermal and endodermal cells, and leukaemias and lymphomas, which arise from the bone marrow and immune system).

Sarcomas are uncommon, and vary considerably in their sites, presentation, and prognosis. The primary malignancies of bone include osteosarcoma and Ewing's sarcoma, which most often occur in older children and adolescents, and chondrosarcoma which is most common in later life. Soft tissue sarcomas include those of fibrous tissue (fibrosarcoma), skeletal muscle (rhabdomyosarcoma), smooth muscle (leiomyosarcoma), adipose tissue (liposarcoma), and blood vessels (a group which includes Kaposi's sarcoma).

BONE SARCOMA. The commonest primary malignant tumour of bone is **osteosarcoma** (osteogenic sarcoma). It is composed of malignant osteoblasts, which form an osteoid matrix within which new bone formation may occur. Most osteosarcomas are aggressive high-grade malignancies that destroy overlying cortical bone and invade adjacent soft tissue, as well as spreading along the medulla. Metastasis, almost exclusively via the vascular system to the lungs and other distant sites, is usual and occurs early. Most patients present between 15 and 25 years of age.

Therapy is multimodal. Complete surgical resection is primarily used, with an increasing trend to more conservative, limb-sparing operations rather than amputation. Adjuvant chemotherapy is an important component of therapy, as metastasis of the tumour is common.[1-3] Neoadjuvant chemotherapy is also often given before surgery to attack micrometastases, shrink the primary tumour and enable evaluation of the tumour response.[2,4,5] Combinations of cisplatin, doxorubicin (or epirubicin),

ifosfamide, and high-dose methotrexate are recommended.[1-6] Aggressive treatment regimens can result in long-term relapse-free survival rates of 70%, although patients with overt metastatic disease at presentation have a poorer prognosis.[1,7] Osteosarcomas are relatively resistant to radiation therapy;[1,3] however, for unresectable high-grade osteosarcoma, radiotherapy followed by adjuvant chemotherapy is recommended.[4] Recurrent disease is treated surgically where possible. The role of second-line chemotherapy remains to be defined.[3,6,8] Regimens may include combinations of cyclophosphamide or ifosfamide, carboplatin, and etoposide. Gemcitabine, alone or with docetaxel, may also be tried. Progressive disease after second-line therapy can be treated with resection, palliative radiotherapy, or best supportive care.[4] Osteoclast-targeted therapy (such as bisphosphonates)[9] and the addition of mifamurtide to conventional chemotherapy[2,4] are under investigation.

Like osteosarcoma, **Ewing's sarcoma** is seen mainly in adolescents and older children. It is a round cell tumour that most often arises in the pelvis or the long bones of the limbs. There may be diffuse erosion of the bone and marked periosteal reaction. It spreads through the medullary cavity, and metastases to lung and other bones are common. Treatment is also multimodal.[9,10]

Initial treatment is neoadjuvant chemotherapy for several months.[1,4,6] Combinations of cyclophosphamide, ifosfamide, etoposide, doxorubicin, dactinomycin, and vincristine are recommended,[1,2,4,6,9] although the use of dactinomycin for localised disease is controversial.[1] Typically, patients are then given local therapy (surgery, radiation, or both), with additional adjuvant chemotherapy.[1,4,9,10] Ewing's sarcoma is relatively radiosensitive,[1] and unresponsive or progressive disease is best managed with radiation therapy with or without surgery, followed by chemotherapy or best supportive care.[4] The prognosis of recurrent Ewing's sarcoma is poor.[4,6,9] Salvage chemotherapy regimens are not standardised.[6,9] Combinations include ifosfamide plus etoposide with or without carboplatin, cyclophosphamide plus topotecan, temozolomide plus irinotecan, and gemcitabine plus docetaxel.[4] High-dose chemotherapy with stem cell rescue has been investigated[2,5,6] but its role has yet to be determined.[4] Targeted therapy with anti-angiogenic agents may represent a future therapeutic approach.[9]

Chemotherapy appears to have little place in the treatment of other bone sarcomas such as **chondrosarcoma**[1,4] (despite some reports of efficacy[4]) or **osteoclastoma** (giant cell tumours of bone);[1] it has been used in high-grade **fibrosarcomas** and in **histiocytoma** but its value is uncertain.

1. Skubitz KM, D'Adamo DR. Sarcoma. *Mayo Clin Proc* 2007; 82: 1409–32.
2. Bielack SS, Carrle D. State-of-the-art approach in selective curable tumors: bone sarcoma. *Ann Oncol* 2008; 19 (suppl 7): vii155–vii160.
3. Picci P. Osteosarcoma (osteogenic sarcoma). *Orphanet J Rare Dis* 2007; 2: 6.
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: bone cancer (version 3.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/bone.pdf (accessed 31/03/10)
5. Sakamoto A, Iwamoto Y. Current status and perspectives regarding the treatment of osteo-sarcoma: chemotherapy. *Rev Recent Clin Trials* 2008; 3: 228–31.
6. Hogendoorn PCW, *et al.* ESMO/EUROBONET Working Group. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 (suppl 5): v204–v213. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v204.full.pdf+html (accessed 26/10/10)
7. Akiyama T, *et al.* Novel therapeutic strategy for osteosarcoma targeting osteoclast differentiation, bone-resorbing activity, and apoptosis pathway. *Mol Cancer Ther* 2008; 7: 3461–9.
8. Bielack SS, *et al.* Second and subsequent recurrences of osteosarcoma: presentation, treatment, and outcomes of 249 consecutive cooperative osteosarcoma study group patients. *J Clin Oncol* 2009; 27: 557–65.
9. Bernstein M, *et al.* Ewing's sarcoma family of tumors: current management. *Oncologist* 2006; 11: 503–19.
10. Iwamoto Y. Diagnosis and treatment of Ewing's sarcoma. *Jpn J Clin Oncol* 2007; 37: 79–89.

KAPOSI'S SARCOMA. Kaposi's sarcoma is a tumour of endothelial or spindle cell origin. In its classical form it manifests as red or violet cutaneous lesions of the limbs in elderly men, usually of Jewish or Mediterranean ancestry. An endemic form is also seen in certain areas of Africa.[1,2] Lesions may eventually affect the whole of the skin, upper airways, gastrointestinal tract, lungs, and lymph nodes, but in general disease is only very slowly progressive, and may require no treatment. Patients given immunosuppressive therapy may be at greater risk of developing Kaposi's sarcoma, particularly if they are from ethnic groups that are susceptible to the classic or endemic forms of the disease.[1] In recent years an epidemic form of the disease has appeared in patients with disease due to HIV infection (p. 957.2).[2] HIV-associated Kaposi's sarcoma is more aggressive, with a greater tendency to disseminated and metastatic disease.

A novel herpesvirus (human herpesvirus 8, HHV8) has been implicated in the pathogenesis of Kaposi's sarcoma. HHV8 induces changes in endothelial cells that make them more susceptible to inflammatory cytokines and angiogenesis.[3] Some antivirals, such as cidofovir and to a lesser extent foscarnet and ganciclovir, have shown activity against HHV8 *in vitro*, but they have not been equally successful in treating Kaposi's sarcoma *in vivo*. Treatment with HAART has greatly reduced the occurrence of Kaposi's sarcoma in AIDS patients, and may cause regression of milder forms of the disease, but this is thought to be due to improvements in immune function rather than a direct effect on Kaposi's sarcoma.[4] The development of Kaposi's sarcoma is likely to be multifactorial, and as infection with HHV8 alone does not produce disease, and the replication of HHV8 in sarcoma cells is low, antiviral therapy alone is unlikely to be sufficient to control symptoms.[4]

Patients with classic or **endemic** Kaposi's sarcoma are often treated with surgery or radiotherapy of individual lesions.[1] Extensive or recurrent disease may be treated with vinca alkaloids, bleomycin, doxorubicin, and dacarbazine, alone or in combination.[1] Etoposide and interferon alfa have also been tried.[1] Patients with immunosuppression-associated Kaposi's sarcoma may be treated similarly to those with the classic form, or preferably by alteration of the immunosuppressive regimen if this can be done without graft loss.[1] Clinical and histological regression of cutaneous Kaposi's sarcoma has been described in a small number of renal transplant recipients when ciclosporin and mycophenolate mofetil were replaced with sirolimus.[5]

The **epidemic** form of Kaposi's sarcoma is associated with HIV infection, and seen particularly in homosexual patients. HAART may control Kaposi's sarcoma, and is considered first-line therapy,[6-8] but the response is unpredictable, so specific therapy is often needed.[1] ***Localised*** disease may be managed with cryotherapy or radiotherapy, but intralesional vinblastine, interferon alfa, and topical alitretinoin are also used.[2,3,6-9] Photodynamic therapy is also used.[2,7,8]

Systemic chemotherapy is generally reserved for patients with more *extensive* disease or mucosal or visceral involvement.[6,8] In patients with a CD4 cell count of 200 cells/mm^3 or above, treatment with interferon alfa plus zidovudine, has been advocated by some, but systemic chemotherapy is the treatment of choice.[1,3,4,6,7] The main combination regimens use a vinca alkaloid and bleomycin, with or without doxorubicin.[3,4] Liposomal formulations of doxorubicin and daunorubicin have produced response rates of 40 to 85%, and may be less toxic than conventional chemotherapy;[3,4,9] it has been suggested that a liposomal anthracycline is the drug of choice in extensive disease.[1,3,6-8] Paclitaxel is also used as a single agent in advanced disease.[3,4,8,9] However, although highly effective, doses may need to be reduced if given to patients taking HAART because of the risk of drug interactions.[6,8] Although data are limited, docetaxel may be a reasonable alternative.[8] Some response has also been reported for oral etoposide.[1]

Control of Kaposi's sarcoma has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but tumour regression ceased and regrowth occurred when dosage was reduced or withdrawn.[10] Further reports of intralesional or systemic use have included partial remissions and disease stabilisation, as well as no effect or disease progression. The reasons for these contradictory results are unclear, but they may be due to variability in chorionic gonadotrophin preparations, which contain a mixture of biological contaminants. A cytotoxic ribonuclease and the degradation product of the β-hCG subunit have been proposed as active contaminants against Kaposi's sarcoma, but other contaminants may stimulate the tumour.[11] Other lines of investigation include the use of sulfated polysaccharide peptidoglycans, imatinib, the tyrosine kinase inhibitors sorafenib and sunitinib, other inhibitors of angiogenesis including thalidomide, and the retinoids.[1,2,6-9]

1. Antman K, Chang Y. Kaposi's sarcoma. *N Engl J Med* 2000; 342: 1027–38.
2. Sullivan RJ, *et al.* Epidemiology, pathophysiology, and treatment of Kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. *Clin Infect Dis* 2008; 47: 1209–15.
3. Mitsuyasu RT. Update on the pathogenesis and treatment of Kaposi sarcoma. *Curr Opin Oncol* 2000; 12: 174–80.
4. Hermans P. Opportunistic AIDS-associated malignancies in HIV-infected patients. *Biomed Pharmacother* 2000; 54: 32–40.
5. Stallone G, *et al.* Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; 352: 1317–23.
6. Cheung MC, *et al.* AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy. *Oncologist* 2005; 10: 412–26.
7. Wilkins K, *et al.* Cutaneous malignancy and human immunodeficiency virus disease. *J Am Acad Dermatol* 2006; 54: 189–206.
8. Di Lorenzo G, *et al.* Management of AIDS-related Kaposi sarcoma. *Lancet Oncol* 2007; 8: 167–76.
9. Dezube BJ, *et al.* Management of AIDS-related Kaposi sarcoma: advances in target discovery and treatment. *AIDS Read* 2004; 14: 236–8, 243–4, 251–3.
10. Harris PJ. Treatment of Kaposi's sarcoma and other manifestations of AIDS with human chorionic gonadotropin. *Lancet* 1995; 346: 118–19.
11. Simonart T, *et al.* Treatment of Kaposi's sarcoma with human chorionic gonadotropin. *Dermatology* 2002; 204: 330–3.

SOFT-TISSUE SARCOMA. Soft-tissue sarcomas are a varied group of malignant tumours that originate from mesenchymal stem cells residing in muscle, fat, or connective tissue,[1,2] and whose subtypes vary in terms of prognosis and response to different treatments.[3] The majority of soft-tissue sarcomas occur in the limb or limb girdle; some occur within the abdomen (retroperitoneal), in the head or neck, or in the gastrointestinal tract.[4,5] Patients have a 5-year survival rate of about 50 to 60%;[4] survival in those with extremity sarcomas is better than that in patients with retroperitoneal sarcomas.[2] Tumours often metastasise to the lung; those arising in the abdomen metastasise to the liver and peritoneum.[4]

Rhabdomyosarcoma is the commonest soft-tissue sarcoma in childhood, and is thought to arise from progenitor cells for skeletal muscle. The most frequent sites are the head and neck, genito-urinary tract, and extremities. Some genetic disorders are associated with rhabdomyosarcoma.[6,7] All patients are presumed to have micrometastatic disease at diagnosis; histologically the most common types are embryonal, which occurs at an earlier age, and alveolar, which is more common in adolescents.[7]

Surgery is the primary *therapy* for soft-tissue sarcomas,[1,2,4,8,9] and may be curative for *localised disease*.[5,10,11] Radiotherapy, as external-beam therapy or brachytherapy, may be given with surgery, or alone if surgery is inappropriate or declined by the patient.[5] Radiation may be given pre-operatively, during surgery, or postoperatively;[1,9] optimal timing is unclear.[5,8] Similar rates of local control and progression-free survival have been reported for pre- and postoperative radiotherapy, although preoperative treatment has been associated with a greater incidence of wound complications, especially in lower extremity tumours.[4] Postoperative radiation can cause acute and delayed bowel toxicity in those with retroperitoneal tumours, and significant toxicity has occurred with the use of brachytherapy, especially when used in the upper abdomen.[2]

Surgery and/or radiotherapy may be combined with chemotherapy. Pre-operative chemotherapy may allow for more efficient resection of the tumour.[1,8] The use of postoperative chemotherapy is controversial,[5,8,9] except for some tumours such as extraosseous Ewing's sarcoma or rhabdomyosarcoma. For these tumours, combinations of vincristine, dactinomycin, doxorubicin, cyclophosphamide, ifosfamide, or etoposide form the basis of most regimens.[5-8,11]

For those with *unresectable* or *metastatic* disease, chemotherapy may be used: ifosfamide and doxorubicin are routinely used in this setting.[5,9] These may be used as single agents or in combination; other acceptable single agent choices are dacarbazine, epirubicin, gemcitabine, temozolomide, or liposomal doxorubicin.[4] Data support the use of adjuvant doxorubicin-based chemotherapy to improve disease-free survival;[12] however, overall survival is not improved. For palliative treatment in advanced soft-tissue sarcoma, a systematic review[13] concluded that combination chemotherapy did not significantly increase survival rates compared with single-agent doxorubicin. A retrospective analysis[14] found that, in patients with high-risk disease, clinical benefits of doxorubicin-based chemotherapy were not sustained beyond 1 year. There is no consensus on the best second-line chemotherapy regimen for patients with metastatic disease refractory to doxorubicin-or ifosfamide-based regimens.[2,3] Dose-intensified combination regimens, with colony-stimulating factor support, have been investigated as adjuvant therapy[15] and in advanced disease;[16] although both these studies found a delay in disease progression, a beneficial effect on overall survival was only found in the former. Intensive combination chemotherapy benefited a subgroup of children with metastatic rhabdomyosarcoma and fewer than 2 unfavourable risk factors, in terms of event-free survival and overall survival. However, most patients have more than 2 risk factors; these patients should be considered for novel first-line therapies. No evidence was found for improved outcome after consolidation therapy with high-dose melphalan and autologous bone marrow or peripheral-blood stem cell rescue.[17] Response to topotecan has been reported in a study of metastatic rhabdomyosarcoma,[18] and trabectedin has shown some activity in advanced soft-tissue sarcomas.[3,5] Tasonermin and melphalan can be used together for isolated limb perfusion of unresectable soft-tissue sarcomas, but severe toxicity may limit use of this regimen. Potential salvage therapy options after failure of first-line therapy include paclitaxel, docetaxel, gemcitabine, trofosfamide, temozolomide, and various combinations thereof.[3]

The gastrointestinal stromal tumours (GISTs) are soft-tissue sarcomas arising in the gastrointestinal tract, most commonly in the stomach and small bowel.[4,8,19] Symptoms may include abdominal pain, anorexia, weight loss, haemorrhage, changes in bowel movements, bowel obstruction, or perforation. Patients with liver metastases may have oedema of the lower extremity, ascites, or jaundice.[20] Spread to the lungs and other locations is seen only in advanced cases.[4]

Continued on p. 726.

Table 1. Common chemotherapy regimens for malignant disease.

Regimen	Drugs and Administration	Cycle	Typically used for	References
ABCM	Doxorubicin 30 mg/m^2 iv day 1; carmustine 30 mg/m^2 iv day 1; cyclophosphamide 100 mg/m^2 oral days 22–25; and melphalan 6 mg/m^2 oral days 22–25.	42 days	Multiple myeloma	1
ABVD	Doxorubicin 25 mg/m^2 iv days 1, 15; bleomycin 10 000 IU/m^2 iv[(b)] days 1, 15; vinblastine 6 mg/m^2 iv days 1, 15; and dacarbazine 375 mg/m^2 iv days 1, 15.	28 days	Lymphomas	2, 3
AC	Doxorubicin 60 mg/m^2 iv day 1 and cyclophosphamide 600 mg/m^2 iv day 1.	21 days (for 4 cycles; some studies used up to 8 cycles)	Breast cancer	4–6
AC + paclitaxel	As above, then followed by paclitaxel 175 mg/m^2 iv day 1.	21 days (further 4 cycles)	Breast cancer	7
AC + trastuzumab	Doxorubicin 60 mg/m^2 iv day 1; cyclophosphamide 600 mg/m^2 iv day 1; and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	21 days (for 6 cycles)	Breast cancer (HER2 overexpressing)	8
ACE	Doxorubicin 45 mg/m^2 iv day 1; cyclophosphamide 1 g/m^2 iv day 1; and etoposide 50 mg/m^2 iv days 1–5.	21 days	Small cell lung cancer	9
AT	Doxorubicin 60 mg/m^2 iv day 1 and paclitaxel 200 mg/m^2 iv day 1.	21 days (for 4 cycles)	Breast cancer	4
AT	Doxorubicin 50 mg/m^2 iv day 1 and docetaxel 75 mg/m^2 iv day 1.	21 days (for up to 8 cycles)	Breast cancer (metastatic)	5
BEAM (Mini-BEAM)	Carmustine 60 mg/m^2 iv day 1; etoposide 75 mg/m^2 iv days 2–5; cytarabine 100 mg/m^2 twice daily iv days 2–5; and melphalan 30 mg/m^2 iv day 6.	usually 28 to 42 days	Lymphomas (salvage)	10
BEP	Bleomycin 30 000 IU iv[(b)] days 2, 9, 16; etoposide 100 mg/m^2 iv days 1–5; and cisplatin 20 mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Testicular cancer	11
CAF	Cyclophosphamide 500 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and fluorouracil 500 mg/m^2 iv day 1.	21 days	Breast cancer	12
CAP	Cyclophosphamide 750 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and prednisone 40 mg/m^2 oral days 1–5.	28 days	Chronic lymphocytic leukaemia	13
CAP	Cyclophosphamide 500 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and cisplatin 50 mg/m^2 iv day 1 (these doses are optimised from the original 600 mg/m^2, 45 mg/m^2, and 50 mg/m^2 respectively).	21 days (for 6 cycles)	Ovarian cancer	14, 15
CAV	Cyclophosphamide 900 mg/m^2 iv day 1; doxorubicin 45 mg/m^2 iv day 1; and vincristine 2 mg iv day 1.	21 days (for 6 cycles)	Small cell lung cancer	16
CHOP	Cyclophosphamide 750 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; vincristine 1.4 mg/m^2 (max. 2 mg) iv day 1; and prednisone 100 mg oral days 1–5.	21 days (for 6 to 8 cycles)	Lymphomas, chronic lymphocytic leukaemia	17, 18
CMF	Cyclophosphamide 100 mg/m^2 oral days 1–14; methotrexate 40 mg/m^2 iv days 1, 8; and fluorouracil 600 mg/m^2 iv days 1, 8.	28 days	Breast cancer	6, 19

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
CMF	Cyclophosphamide 600 mg/m^2 iv day 1; methotrexate 40 mg/m^2 iv day 1; and fluorouracil 600 mg/m^2 iv day 1.	21 days	Breast cancer	20
CMF	Cyclophosphamide 750 mg/m^2 iv day 1; methotrexate 40 mg/m^2 iv days 1, 8; and fluorouracil 600 mg/m^2 iv days 1, 8.	28 days	Breast cancer	6
CMV	Cisplatin 100 mg/m^2 iv day 2; methotrexate 30 mg/m^2 iv days 1, 8; and vinblastine 4 mg/m^2 iv days 1, 8.	21 days	Bladder cancer	21
COP (CVP)	Cyclophosphamide 800 mg/m^2 iv day 1; vincristine 2 mg iv day 1; and prednisone 60 mg/m^2 oral days 1–5, then tapered over days 6–8.	21 days (for 6 cycles)	Lymphomas (the original report of this regimen used a 14-day cycle)	22
CP	Cisplatin 100 mg/m^2 iv day 1 and cyclophosphamide 600 mg/m^2 iv day 1 *or* carboplatin 300 mg/m^2 iv day1 and cyclophosphamide 600 mg/m^2 iv day 1.	28 days (for 6 cycles)	Ovarian cancer	23
CT	Cisplatin 50 mg/m^2 iv day 1; topotecan 750 micrograms/m^2 iv days 1–3.	21 days	Cervical cancer	72
CYVADIC	Cyclophosphamide 500 mg/m^2 iv day 1; vincristine 1.5 mg/m^2 iv[a] days 1, 5; doxorubicin 50 mg/m^2 iv day 1; and dacarbazine 250 mg/m^2 iv days 1–5.	21 days	Sarcoma (alternative versions of this regimen using vincristine on day 1 only have also been reported)	24
Dartmouth regimen	Dacarbazine 220 mg/m^2 iv days 1–3, 22–24; cisplatin 25 mg/m^2 iv days 1–3, 22–24; carmustine 150 mg/m^2 iv day 1; and tamoxifen 10 mg oral twice daily.	42 days	Melanoma (metastatic)	25, 26
DCF	Docetaxel 75 mg/m^2 iv day 1; cisplatin 75 mg/m^2 iv day 1; fluorouracil 750 mg/m^2 continuous iv days 1–5.	21 days	Gastric cancer	75
DHAP	Dexamethasone 40 mg oral or iv days 1–4; cytarabine 2 g/m^2 iv over 3 hrs, repeated after 12 hrs, day 2; and cisplatin 100 mg/m^2 iv over 24 hrs, day 1.	21–28 days	Lymphomas (salvage)	27
EAP	Etoposide 120 mg/m^2 iv days 4–6; doxorubicin 20 mg/m^2 iv days 1, 7; and cisplatin 40 mg/m^2 iv days 2, 8.	21–28 days	Stomach cancer	28, 29
EC	Etoposide 100 mg/m^2 iv days 1–3 and carboplatin 450 mg/m^2 iv day 1.	28 days	Small cell lung cancer	30
EC	Etoposide 100 mg/m^2 iv days 1–3 and carboplatin 325 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	31
ECF	Epirubicin 50 mg/m^2 iv day 1; cisplatin 60 mg/m^2 iv day 1; and fluorouracil 200 mg/m^2 daily continuous iv.	21 days (for up to 8 cycles)	Stomach cancer	32
EDAP	Etoposide 100–200 mg/m^2 continuous iv, days 1–4; dexamethasone 40 mg oral or iv days 1–5; cytarabine 1 g/m^2 iv day 5; and cisplatin 20 mg/m^2 continuous iv, days 1–4.	21–28 days	Multiple myeloma (salvage), lymphomas	33

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
EMA-CO (or EMA-EP)	Etoposide 100 mg/m^2 iv days 1, 2; methotrexate 300 mg/m^2 iv over 12 hrs, day 1; folinic acid 15 mg oral or im, twice daily for 4 doses, starting day 2; and dactinomycin 500 micrograms iv days 1, 2. *with* cyclophosphamide 600 mg/m^2 iv day 8 and vincristine 1 mg/m^2 iv[a] day 8. *or* etoposide 150 mg/m^2 iv day 8 and cisplatin 75 mg/m^2 iv day 8.	14 days	Gestational trophoblastic tumours	34
EOX	Epirubicin 50 mg/m^2 iv day 1; oxaliplatin 130 mg/m^2 iv day 1; capecitabine 1.25 g/m^2 oral days 1–21.	21 days	Oesophagogastric cancer	74
EP (PE)	Etoposide 80 mg/m^2 iv days 1–3 and cisplatin 80 mg/m^2 iv day 1.	21 days	Small cell lung cancer (standard dose – other versions exist)	35
EP (PE)	Etoposide 80 mg/m^2 iv days 1–5 and cisplatin 27 mg/m^2 iv days 1–5.	21 days	Small cell lung cancer (high dose)	35
EP (PE)	Etoposide 100 mg/m^2 iv day 1, *then* 200 mg/m^2 oral days 2–4 and cisplatin 75 mg/m^2 iv day 1.	21 days	Small cell lung cancer	36
EPOCH	Etoposide 50 mg/m^2 continuous iv days 1–4; vincristine 400 micrograms/m^2 continuous iv[a] days 1–4; doxorubicin 10 mg/m^2 continuous iv days 1–4; cyclophosphamide 750 mg/m^2 iv day 5; and prednisone 60 mg/m^2 oral days 1–5.	21 days	Lymphomas (salvage)	37
ESHAP	Etoposide 40 mg/m^2 iv days 1–4; methylprednisolone 250–500 mg iv days 1–5; cisplatin 25 mg/m^2 continuous iv days 1–4; and cytarabine 2 g/m^2 iv day 5.	21–28 days (for up to 8 cycles)	Lymphomas (salvage)	38
FAM	Fluorouracil 600 mg/m^2 iv days 1, 8, 29, 36; doxorubicin 30 mg/m^2 iv days 1, 29; and mitomycin 10 mg/m^2 iv day 1.	56 days	Stomach cancer, pancreatic cancer	39–41
FAMTX	Fluorouracil 1.5 g/m^2 iv day 1; doxorubicin 30 mg/m^2 iv day 15; methotrexate 1.5 g/m^2 iv day 1, 1 hour before fluorouracil; and folinic acid 15 mg/m^2 oral every 6 hrs for 3 days, starting 24 hrs after methotrexate.	28 days	Stomach cancer	29, 32
FOLFIRI	Irinotecan 180 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv day 1; fluorouracil 400 mg/m^2 iv bolus day 1, then 2.4 g/m^2 continuous iv infusion (increased to 3 g/m^2 from cycle 3 if tolerated) over 46 hours.	14 days	Colorectal cancer	69
FOLFOX4	Oxaliplatin 85 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv days 1, 2; fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2.	14 days	Colorectal cancer (in addition to FOLFOX6, below, other variants of the FOLFOX regimen exist; combination with bevacizumab or cetuximab is also being tried)	70
FOLFOX6	Oxaliplatin 100 mg/m^2 iv day 1; folinic acid 200 mg/m^2 iv day 1; fluorouracil 400 mg/m^2 iv bolus day 1, then 2.4 g/m^2 continuous iv infusion (increased to 3 g/m^2 from cycle 3 if tolerated) over 46 hours.	14 days	Colorectal cancer	69
5FU/Folinic acid	Fluorouracil 370 mg/m^2 iv days 1–5 and folinic acid 200 mg/m^2 iv days 1–5.	28–35 days	Colorectal cancer	42

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
5FU/Folinic acid (Mayo regimen, Poon regimen)	Fluorouracil 425 mg/m^2 iv days 1–5 and folinic acid 20 mg/m^2 iv day 1–5.	28–35 days	Stomach cancer, colorectal cancer	42, 43
5FU/Folinic acid (de Gramont regimen)	Fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2 and folinic acid 200 mg/m^2 iv days 1, 2.	14 days	Colorectal cancer	44
Gemcitabine + cisplatin	Gemcitabine 1 g/m^2 iv days 1, 8, 15 and cisplatin 70 mg/m^2 iv day 2.	28 days	Bladder cancer (metastatic)	45
Hyper-CVAD	*Course A:* Cyclophosphamide 300 mg/m^2 iv every 12 hrs, days 1–3; doxorubicin 50 mg/m^2 iv day 4; vincristine 2 mg iv days 4, 11; and dexamethasone 40 mg iv or oral, days 1–4, 11–14. *CNS prophylaxis* Methotrexate 12 mg intrathecal, day 2 and cytarabine 100 mg intrathecal, day 8. *Course B:* Methotrexate 200 mg/m^2 iv over 2 hrs, then 800 mg/m^2 iv over 24 hrs, day 1; folinic acid 15 mg iv every 6 hrs for 8 doses, from 24 hrs after methotrexate (increased to 50 mg iv every 6 hrs if methotrexate levels are high); methylprednisolone 50 mg iv every 12 hrs, days 1–3; and cytarabine 3 g/m^2 every 12 hrs, days 2, 3.	4 cycles of A alternated with 4 cycles of B, given over as short a period as possible; the number of A cycles in which CNS prophylaxis is given varies with expected risk of CNS disease	Lymphomas, adult acute lymphoblastic leukaemia (some variants of this regimen exist, including the substitution of daunorubicin 60 mg/m^2 for doxorubicin in course A, the omission of methylprednisolone and addition of oral bicarbonate in course B, and simplification of methotrexate and folinic acid dosing; mesna, which was given in course A of the original regimen, is usually omitted)	48
ICE (ICbE)	Ifosfamide 5 g/m^2 iv over 24 hrs, day 1 (with mesna); carboplatin 400 mg/m^2 iv day 1; and etoposide 100 mg/m^2 iv days 1–3.	28 days (for 6 cycles)	Small cell lung cancer	46
IFL (Douillard 1-week regimen)	Irinotecan 80 mg/m^2 iv, day 1; fluorouracil 2.3 g/m^2 continuous iv infusion, day 1; folinic acid 500 mg/m^2 iv, day 1.	7 days	Colorectal cancer	71
IFL (Douillard 2-week regimen)	Irinotecan 180 mg/m^2 iv, day 1; fluorouracil 400 mg/m^2 iv bolus then 600 mg/m^2 continuous iv infusion, days 1, 2; folinic acid 200 mg/m^2 iv, days 1, 2.	14 days	Colorectal cancer	71
IFL (Saltz regimen)	Irinotečan 125 mg/m^2 iv; fluorouracil 500 mg/m^2 iv; and folinic acid 20 mg/m^2 iv all once a week for 4 weeks.	42 days	Colorectal cancer	47
M2	Vincristine 30 micrograms/kg iv[a] day 1; carmustine 500 micrograms/kg iv day 1; cyclophosphamide 10 mg/kg iv day 1; melphalan 250 micrograms/kg oral days 1–4 *or* 100 micrograms/kg oral days 1–7 *or* 1–10; and prednisone 1 mg/kg oral, days 1–7, then taper and discontinue by day 21 unless hypercalcaemia or bone disease persist.	35 days	Multiple myeloma	49
MACOP-B	Methotrexate 400 mg/m^2 iv days 8, 36, 64 (as 100 mg/m^2 iv bolus, then 300 mg/m^2 iv over 4 hrs); folinic acid 15 mg oral every 6 hrs for 6 doses, from 24 hrs after methotrexate; doxorubicin 50 mg/m^2 iv days 1, 15, 29, 43, 57, 71; cyclophosphamide 350 mg/m^2 iv days 1, 15, 29, 43, 57, 71; vincristine 1.4 mg/m^2 iv[a] days 8, 22, 36, 50, 64, 78; bleomycin 10 000 IU/m^2 iv[b] days 22, 50, 78; and prednisone 75 mg oral, daily for 10 weeks then tapered over 15 days.	12 weeks	Lymphomas	50
MCF	Mitomycin 7 mg/m^2 (max 14 mg) iv day 1; cisplatin 60 mg/m^2 iv days 1, 22; fluorouracil 300 mg/m^2 daily continuous iv.	42 days	Oesophagogastric cancer	76

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
MIC	Mitomycin 6 mg/m^2 iv day 2; ifosfamide 3 g/m^2 iv day 2; and cisplatin 120 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	51
MIC	Mitomycin 6 mg/m^2 iv day 1; ifosfamide 3 g/m^2 iv day 1; and cisplatin 50 mg/m^2 iv day 1.	21 days	Non-small cell lung cancer	52
MOPP	Chlormethine 6 mg/m^2 iv days 1, 8; vincristine 1.4 mg/m^2 (max. 2 mg), days 1, 8; procarbazine 100 mg/m^2 oral days 1–14; and prednisone 40 mg/m^2 oral days 1–14, cycles 1, 4.	28 days (for 6 cycles)	Lymphomas, Hodgkin's disease	3, 53
M-VAC	Methotrexate 30 mg/m^2 iv days 1, 15, 22; vinblastine 3 mg/m^2 iv days 2, 15, 22; doxorubicin 30 mg/m^2 iv day 2; and cisplatin 70 mg/m^2 iv day 2.	usually 28 days	Bladder cancer	45, 54, 55
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vinblastine 4 mg/m^2 iv day 1, cycle 1 2 mg/m^2 iv day 8, cycle 1 4.5 mg/m^2 iv days 15, 22, cycle 1 4.5 mg/m^2 iv days 1, 15, cycle 2 and later; and cisplatin 120 mg/m^2 iv day 1	28 days	Non-small cell lung cancer (neoadjuvant)	56
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vindesine 3 mg/m^2 iv days 1, 8, 15, 22, day 1 of cycle 2, then every 2 weeks until the 15th week; and cisplatin 120 mg/m^2 iv day 1, for 3 cycles.	28 days	Non-small cell lung cancer (neoadjuvant)	56, 57
MVP	Mitomycin 8 mg/m^2 iv day 1, cycles 1 and 2, day 15 cycle 3; vinorelbine 25 mg/m^2 iv once a week for 16 weeks; and cisplatin 120 mg/m^2 iv day 1, for 3 cycles.	28 days	Non-small cell lung cancer (neoadjuvant)	57
PAC	Cisplatin 50 mg/m^2 iv day 1; doxorubicin 50 mg/m^2 iv day 1; and cyclophosphamide 500 mg/m^2 iv day 1.	21 days (for up to 8 cycles)	Thymoma	58
Paclitaxel and carboplatin	Paclitaxel 175 mg/m^2 iv day 1 and carboplatin – adjust dose to AUC of 7.5 mg/mL/minute by Calvert formula, iv day 1.	21 days (for 6 cycles)	Ovarian cancer	59
Paclitaxel and cisplatin	Paclitaxel 135 mg/m^2 continuous iv over 24 hrs, day 1 and cisplatin 75 mg/m^2 iv day 1.	21 days (for 6 cycles)	Ovarian cancer	60
Paclitaxel (standard) and trastuzumab	Paclitaxel 175 mg/m^2 iv on day 1 and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	21 days	Breast cancer (HER2 overexpressing)	8
Paclitaxel (weekly) and trastuzumab	Paclitaxel 90 mg/m^2 iv on day 1 and trastuzumab 4 mg/kg iv loading dose on day 1 then 2 mg/kg once each week.	7 days	Breast cancer (HER2 overexpressing)	61
PCV	Procarbazine 60 mg/m^2 oral days 8–21; lomustine 110 mg/m^2 oral day 1; and vincristine 1.4 mg/m^2 iv[a] days 8, 29.	42–56 days	Gliomas (adjuvant)	62
PE	*See* EP			
Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous				

Table 1. Common chemotherapy regimens for malignant disease. *(Continued)*

Regimen	Drugs and Administration	Cycle	Typically used for	References
ProMACE-CytaBOM	Prednisone 60 mg/m^2 oral days 1–14; doxorubicin 25 mg/m^2 iv day 1; cyclophosphamide 650 mg/m^2 iv day 1; etoposide 120 mg/m^2 iv day 1; cytarabine 300 mg/m^2 iv day 8; bleomycin 5000 IU/m^2 iv[b] day 8; vincristine 1.4 mg/m^2 iv[a] day 8; methotrexate 120 mg/m^2 iv day 8; and folinic acid 25 mg/m^2 oral every 6 hrs for 4 doses, from 24 hrs after methotrexate.	21 days	Lymphomas	63
PVB	See VBP			
SMF	Streptozocin 1 g/m^2 iv days 1, 8, 29, 36; mitomycin 10 mg/m^2 iv day 1; and fluorouracil 600 mg/m^2 iv days 1, 8, 29, 36.	56 days	Pancreatic cancer	41
Stanford V regimen	Doxorubicin 25 mg/m^2 iv days 1, 15; vinblastine 6 mg/m^2 iv days 1, 15; chlormethine 6 mg/m^2 iv day 1; vincristine 1.4 mg/m^2 iv (max 2mg) days 8, 22; bleomycin 5000 IU/m^2 iv[b] days 8, 22; etoposide 60 mg/m^2 iv days 15, 16; prednisone 40 mg/m^2 oral on alternate days for 10 weeks then tapered by 10 mg on alternate days.	28 days (for 3 cycles)	Hodgkin's disease	64
TAP	Doxorubicin 45 mg/m^2 iv day 1; cisplatin 50 mg/m^2 iv day 1; paclitaxel 160 mg/m^2 iv day 2.	21 days[c] (up to 7 cycles)	Endometrial cancer	73
VAD	Vincristine 400 micrograms iv days 1–4; doxorubicin 9 mg/m^2 iv days 1–4; and dexamethasone 40 mg oral days 1–4, 9–12, 17–20.	28 days (usually for 4 cycles)	Multiple myeloma	65
VBAP	Vincristine 1 mg iv day 1; carmustine 30 mg/m^2 iv day 1; doxorubicin 30 mg/m^2 iv day 1; and prednisone 60 mg/m^2 oral or parenteral (may be rounded to 100 mg oral) days 1–4.	21 or 28 days	Multiple myeloma	66, 67
VBP	Vinblastine 150 micrograms/kg iv days 1, 2; bleomycin 30 000 IU iv[b] days 2, 9, 16; and cisplatin 20 mg/m^2 iv days 1–5.	21 days	Germ-cell (ovarian, testicular) cancer	11
VCMP	Vincristine 1 mg iv day 1; melphalan 9 mg/m^2 oral days 1–4; cyclophosphamide 500 mg/m^2 iv day 1; and prednisone 60 mg/m^2 oral or parenteral, days 1–4.	28 days	Multiple myeloma	67
VeIP	Vinblastine 110 micrograms/kg iv days 1, 2; ifosfamide 1.2 g/m^2 iv days 1–5 (with mesna); and cisplatin 20 mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Germ-cell (especially testicular) cancer	68
VIP	Etoposide 75mg/m^2 iv days 1–5; ifosfamide 1.2 g/m^2 iv days 1–5 (with mesna); and cisplatin 20 mg/m^2 iv days 1–5.	21 days (for 4 cycles)	Germ-cell (especially testicular) cancer	68

Key to abbreviations: hrs – hours; im – intramuscular; iv – intravenous

(a) Although not always reflected in the original papers it is now generally accepted that the total dose of vincristine should not exceed 2 mg, in order to minimise neurotoxicity

(b) Doses of bleomycin have been given in international units (IU) in this table, but doses in the original papers may be quoted in mg-potency or USP units. One mg-potency or one USP unit is equivalent to 1000 international units

(c) This regimen is invariably given with haematological support using subcutaneous filgrastim on days 3–12

References.

1. MacLennan ICM, *et al.* Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis. *Lancet* 1992; **339:** 200–205.
2. Bonadonna G, Santoro A. ABVD chemotherapy in the treatment of Hodgkin's disease. *Cancer Treat Rev* 1982; **9:** 21–35.
3. Canellos GP, *et al.*. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992; **327:** 1478–84.
4. Pouillart P, *et al.* Final results of a phase II randomized, parallel study of doxorubicin/cyclophosphamide (AC) and doxorubicin/Taxol® (paclitaxel) (AT) as neoadjuvant treatment of local-regional breast cancer. *Proc Am Soc Clin Oncol* 1999; **18:** 73.
5. Nabholtz J-M, *et al.* Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. *J Clin Oncol* 2003; **21:** 968–75.
6. Fisher B, *et al.* Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol.* 1990; **8:** 1483–96.
7. Henderson IC, *et al.* Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003; **21:** 976–83.
8. Slamon DJ, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783–92.
9. Aisner J, *et al.* Doxorubicin, cyclophosphamide and VP16-213 (ACE) in the treatment of small cell lung cancer. *Cancer Chemother Pharmacol* 1982; **7:** 187–93.
10. Colwill R, *et al.* Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease before intensive therapy and autologous bone marrow transplantation. *J Clin Oncol* 1995; **13:** 396–402.
11. Williams SD, *et al.* Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med* 1987; **316:** 1435–40.
12. Smalley RV, *et al.* A comparison of cyclophosphamide, adriamycin, 5-fluorouracil (CAF) and cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone (CMFVP) in patients with metastatic breast cancer: a Southeastern Cancer Study Group project. *Cancer* 1977; **40:** 625–32.
13. The French Cooperative Group on Chronic Lymphocytic Leukemia. Comparison of fludarabine, cyclophosphamide/doxorubicin/prednisone, and cyclophosphamide/doxorubicin/vincristine/prednisone in advanced forms of chronic lymphocytic leukemia: preliminary results of a controlled clinical trial. *Semin Oncol* 1993; **20** (suppl 7): 21–3.
14. de Oliveira CF, *et al.* Randomized comparison of cyclophosphamide, doxorubicin and cisplatin (CAP) versus cyclophosphamide and doxorubicin (CA) for the treatment of advanced ovarian cancer (ADOVCA): a EORTC Gynecological Cancer Cooperative Group study. *Eur J Gynaecol Oncol* 1990; **11:** 323–30.
15. The ICON Collaborators. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. *Lancet* 1998; **352:** 1571–6.
16. Feld R, *et al.* Combined modality induction therapy without maintenance chemotherapy for small cell carcinoma of the lung. *J Clin Oncol* 1984; **2:** 294–304.
17. McKelvey EM, *et al.* Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. *Cancer* 1976; **38:** 1484–93.
18. Fisher RI, *et al.* Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993; **328:** 1002–6.
19. Bonadonna G, *et al.* Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976; **294:** 405–10.
20. Weiss RB, *et al.* Adjuvant chemotherapy after conservative surgery plus irradiation versus modified radical mastectomy: analysis of drug dosing and toxicity. *Am J Med* 1987; **83:** 455–63.
21. Harker WG, *et al.* Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. *J Clin Oncol* 1985; **3:** 1463–70.
22. Luce JK, *et al.* Combined cyclophosphamide, vincristine, and prednisone therapy of malignant lymphoma. *Cancer* 1971; **28:** 306–17.
23. Alberts DS, *et al.* Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report by the Southwest Oncology Group of a phase III randomized trial in stages III and IV ovarian cancer. *J Clin Oncol* 1992; **10:** 706–17.
24. Yap B-S, *et al.* Cyclophosphamide, vincristine, adriamycin, and DTIC (CYVADIC) combination chemotherapy for the treatment of advanced sarcomas. *Cancer Treat Rep* 1980; **64:** 93–8.
25. McClay EF, *et al.* Combination chemotherapy and hormonal therapy in the treatment of malignant melanoma. *Cancer Treat Rep* 1987; **71:** 465–9.
26. Chapman PB, *et al.* Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 1999; **17:** 2745–51.
27. Velasquez WS, *et al.* Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). *Blood* 1988; **71:** 117–22.
28. Preusser P, *et al.* Phase II study with the combination etoposide, doxorubicin and cisplatin in advanced measurable gastric cancer. *J Clin Oncol* 1989; **7:** 1310–17.
29. Kelsen D, *et al.* FAMTX versus etoposide, doxorubicin, and cisplatin: a random assignment trial in gastric cancer. *J Clin Oncol* 1992; **10:** 541–8.
30. Viren M, *et al.* Carboplatin and etoposide in extensive small cell lung cancer. *Acta Oncol* 1994; **33:** 921–4.
31. Klastersky J, *et al.* A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small-cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07861. *J Clin Oncol* 1990; **8:** 1556–62.
32. Waters JS, *et al.* Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. *Br J Cancer* 1999; **80:** 269–72.
33. Barlogie B, *et al.* Etoposide, dexamethasone, cytarabine, and cisplatin in vincristine, doxorubicin, and dexamethasone-refractory myeloma. *J Clin Oncol* 1989; **7:** 1514–17.
34. Newlands ES, *et al.* Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumours, 1979 to 1989. *Br J Obstet Gynaecol* 1991; **98:** 550–7.
35. Ihde DC, *et al.* Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994; **12:** 2022–34.
36. Sundström S, *et al.* Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol* 2002; **20:** 4665–72.
37. Gutierrez M, *et al.* Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: an 8-year follow-up study of EPOCH. *J Clin Oncol* 2000; **18:** 3633–42.
38. Velasquez WS, *et al.* ESHAP—an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. *J Clin Oncol* 1994; **12:** 1169–76.
39. Macdonald JS, *et al.* 5-Fluorouracil, doxorubicin and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980; **93:** 533–6.
40. Cullinan SA, *et al.* A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma: fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. *JAMA* 1985; **253:** 2061–7.
41. The Gastrointestinal Tumor Study Group. Phase II studies of drug combinations in advanced pancreatic carcinoma: fluorouracil plus doxorubicin plus mitomycin C and two regimens of streptozotocin plus mitomycin C plus fluorouracil. *J Clin Oncol* 1986; **4:** 1794–8.
42. Poon MA, *et al.* Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989; **7:** 1407–18.
43. Rubin J, *et al.* Phase II trials of 5-fluorouracil and leucovorin in patients with metastatic gastric or pancreatic carcinoma. *Cancer* 1996; **78:** 1888–91.
44. de Gramont A, *et al.* A review of GERCOD trials of bimonthly leucovorin plus 5-fluorouracil 48-h continuous infusion in advanced colorectal cancer: evolution of a regimen. *Eur J Cancer* 1998; **34:** 619–26.
45. von der Maase H, *et al.* Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; **17:** 3068–77.
46. Smith IE, *et al.* Carboplatin, etoposide, and ifosfamide as intensive chemotherapy for small-cell lung cancer. *J Clin Oncol* 1990; **8:** 899–905.
47. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
48. Kantarjian HM, *et al.* Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol* 2000; **18:** 547–61.
49. Case DC, *et al.* Improved survival times in multiple myeloma treated with melphalan, prednisone, cyclophosphamide, vincristine and BCNU: M-2 protocol. *Am J Med* 1977; **63:** 897–903.
50. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. *Ann Intern Med* 1985; **102:** 596–602.
51. Crinò L, *et al.* Chemotherapy of advanced non-small-cell lung cancer: a comparison of three active regimens. A randomized trial of the Italian Oncology Group for Clinical Research. *Ann Oncol* 1995; **6:** 347–53.
52. Cullen MH, *et al.* Mitomycin, ifosfamide and cis-platin in non-small cell lung cancer: treatment good enough to compare. *Br J Cancer* 1988; **58:** 359–61.
53. DeVita VT, *et al.* Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 1970; **73:** 881–95.
54. Sternberg CN, *et al.* Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. *J Urol (Baltimore)* 1985; **133:** 403–7.
55. Loehrer PJ, *et al.* A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992; **10:** 1066–73.
56. Pisters KMW, *et al.* Pathologic complete response in advanced non-small-cell lung cancer following preoperative chemotherapy: implications for the design of future non-small-cell lung cancer combined modality trials. *J Clin Oncol* 1993; **11:** 1757–62.
57. Pérol M, *et al.* Multicenter randomized trial comparing cisplatin-mitomycin-vinorelbine versus cisplatin-mitomycin-vindesine in advanced non-small cell lung cancer. *Lung Cancer* 1996; **14:** 119–34.
58. Loehrer PJ, *et al.* Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. *J Clin Oncol* 1994; **12:** 1164–8.
59. Coleman RL, *et al.* Carboplatin and short-infusion paclitaxel in high-risk and advanced-stage ovarian carcinoma. *Cancer J Sci Am* 1997; **3:** 246–53.
60. McGuire WP, *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996; **334:** 1–6.
61. Seidman AD, *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001; **19:** 2587–95.
62. Levin VA, *et al.* Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. *Int J Radiat Oncol Biol Phys* 1990; **18:** 321–4.
63. Longo DL, *et al.* Superiority of ProMACE-CytaBOM over ProMACE-MOPP in the treatment of advanced diffuse aggressive lymphoma: results of a prospective randomized trial. *J Clin Oncol* 1991; **9:** 25–38.
64. Bartlett NL, *et al.* Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J Clin Oncol* 1995; **13:** 1080–8.
65. Barlogie B, *et al.* Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med* 1984; **310:** 1353–6.
66. Bonnet J, *et al.* Vincristine, BCNU, doxorubicin, and prednisone (VBAP) combination in the treatment of relapsing or resistant multiple myeloma: a Southwest Oncology Group study. *Cancer Treat Rep* 1982; **66:** 1267–71.
67. Bladé J, *et al.* Increased conventional chemotherapy does not improve survival in multiple myeloma: long-term results of two PETHEMA trials including 914 patients. *Hematol J* 2001; **2:** 272–8.
68. Loehrer PJ, *et al.* Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. *Ann Intern Med* 1988; **109:** 540–6.
69. Tournigand C, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22:** 229–37.
70. Rothenberg ML, *et al.* Superiority of oxaliplatin and fluorouracil–leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil–leucovorin: interim results of a phase III trial. *J Clin Oncol* 2003; **21:** 2059–69.
71. Douillard JY, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355:** 1041–7.
72. Long HJ, *et al.* Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix; a Gynecologic Oncology Group Study. *J Clin Oncol* 2005; **23:** 4626–33.
73. Fleming GF, *et al.* Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 2004; **22:** 2159–66.
74. Cunningham D, *et al.* Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358:** 36–46.
75. Van Cutsem E, *et al.* V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24:** 4991–7.
76. Ross P, *et al.* Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002; **20:** 1996–2004.

Surgery is used for localised, resectable disease arising in the gastrointestinal tract, although this does not routinely cure GISTs; median time to recurrence after resection is about 2 years. Imatinib produces durable clinical benefit and objective responses in most patients with GISTS, including those with metastatic or unresectable disease. If the tumour responds to imatinib, surgical resection may be indicated. In patients with imatinib-resistant GIST, or who experience life-threatening adverse effects such as hepatotoxicity and fluid retention with imatinib, sunitinib may be considered.[4,8,11,19,21,22] Regorafenib is an option when both imatinib and sunitinib have failed.

1. Mankin HJ, Hornicek PJ. Diagnosis, classification, and management of soft tissue sarcomas. *Cancer Control* 2005; **12**: 5–21.
2. Windham TC, Pisters PWT. Retroperitoneal sarcomas. *Cancer Control* 2005; **12**: 36–43.
3. Hartmann JT, Patel S. Recent developments in salvage chemotherapy for patients with metastatic soft tissue sarcoma. *Drugs* 2005; **65**: 167–78.
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: soft tissue sarcoma (version 2.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf (accessed 13/07/10)
5. Clark MA, *et al.* Soft-tissue sarcomas in adults. *N Engl J Med* 2005; **353**: 701–11.
6. McDowell HP. Update on childhood rhabdomyosarcoma. *Arch Dis Child* 2003; **88**: 354–7.
7. Breitfeld PP, Meyer WH. Rhabdomyosarcoma: new windows of opportunity. *Oncologist* 2005; **10**: 518–27.
8. Skubitz KM, D'Adamo DR. Sarcoma. *Mayo Clin Proc* 2007; **82**: 1409–32.
9. Casali PG, Blay J-Y. ESMO/CONTICANET/EUROBONET Consensus Panel of Experts. Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v198–v203. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v198.full.pdf+html (accessed 28/10/10)
10. Pellitteri PK, *et al.* Management of sarcomas of the head and neck in adults. *Oral Oncol* 2003; **39**: 2–12.
11. Judson I. State-of-the-art approach in selective curable tumours: soft tissue sarcoma. *Ann Oncol* 2008; **19** (suppl 7): vii166–vii169.
12. Sarcoma Meta-analysis Collaboration (SMAC). Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 01/04/10).
13. Bramwell V, *et al.* Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 01/04/10).
14. Cormier JN, *et al.* Cohort analysis of patients with localized, high-risk, extremity soft tissue sarcoma treated at two cancer centers: chemotherapy-associated outcomes. *J Clin Oncol* 2004; **22**: 4567–74.
15. Frustaci S, *et al.* Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *J Clin Oncol* 2001; **19**: 1238–47.
16. Le Cesne A, *et al.* Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 2000; **18**: 2676–84.
17. Carli M, *et al.* European intergroup studies (MMT4-89 and MMT4-91) on childhood metastatic rhabdomyosarcoma: final results and analysis of prognostic factors. *J Clin Oncol* 2004; **22**: 4787–94. Correction. *ibid.* 2005; **23**: 248.
18. Pappo AS, *et al.* Up-front window trial of topotecan in previously untreated children and adolescents with metastatic rhabdomyosarcoma: an intergroup rhabdomyosarcoma study. *J Clin Oncol* 2001; **19**: 213–19.
19. Rubin BP, *et al.* Gastrointestinal stromal-tumour. *Lancet* 2007; **369**: 1731–41. Correction. *ibid.*; **370**: 388.
20. D'Amato G, *et al.* Update on the biology and therapy of gastrointestinal stromal tumors. *Cancer Control* 2005; **12**: 44–56.
21. Cowie F. Treatment of rare cancers: gastrointestinal stromal tumours. *Br J Hosp Med* 2006; **67**: 361–4.
22. Casali PG, Blay J-Y. ESMO/CONTICANET/EUROBONET Consensus Panel of Experts. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v98–v102. Also available at: http://annonc.oxfordjournals.org/content/21/suppl_5/v98.full.pdf+html (accessed 28/10/10)

Adverse Effects

The acute effects of antineoplastic drugs often include nausea and vomiting, sometimes extremely severe. In addition, many of these compounds are irritant or vesicant, and produce local pain, irritation, and inflammation at the administration site; extravasation may lead to ulceration and necrosis. Hypersensitivity reactions may also occur.

Many of the adverse effects of antineoplastics are an extension of their therapeutic action, which is generally not selective for malignant cells but affects all rapidly-dividing cells: antineoplastic therapy is then made possible only by increased sensitivity or less effective recovery of malignant cells compared with normal cells, and dosage is carefully controlled and timed, and, where possible, localised, to maximise the differences.

In consequence, adverse effects may be expected from most antineoplastics in tissues where normal cell division is fairly rapid, e.g. the bone marrow, lymphoreticular tissue, gastrointestinal mucosa, skin, and gonads, as well as in the fetus. The effects may not manifest for days or weeks, depending both on the drugs used and the rate of division in the tissue concerned, and may sometimes be cumulative. Perhaps the most common serious effect, and one which has often limited the doses that can be given, is bone-marrow depression. Because of their effects on the various types of white blood cell many antineoplastics also cause profound suppression of normal immunity, and patients may be at greatly increased risk of severe and disseminated infection.

The rapid destruction of large numbers of cells during antineoplastic therapy of certain highly sensitive tumours, and the consequent release of breakdown products, may also lead to problems with hyperuricaemia and acute renal failure due to uric acid nephropathy (the 'tumour lysis syndrome').

Additionally, some drugs may have specific toxicities that are not necessarily related to their therapeutic action, such as cardiotoxicity due to anthracycline antibiotics, nephrotoxicity with cisplatin, or the effects of bleomycin on the lung. Again these can be cumulative, and may limit the total lifetime dose that can be given.

In the very long term, patients who have undergone successful antineoplastic chemotherapy may develop secondary malignancies, suggesting that antineoplastics may themselves be carcinogenic. In addition, most are potentially mutagenic and teratogenic, and use in pregnancy, particularly in the first trimester, may lead to fetal abortion, stunting, or malformation.

Carcinogenicity. There is clear evidence that some antineoplastic drugs may themselves be carcinogenic, although it is difficult to control for the possible effects of primary disease, combination chemotherapy, and combined treatment with radiotherapy.[1]

Most convincingly associated with secondary malignancies are the various **alkylating agents**[2-5] including the nitrosoureas, the topoisomerase II inhibitor **podophyllotoxin derivatives** such as etoposide and teniposide,[2,3,5,6] and the **anthracyclines**.[7] Leukaemias, particularly acute myeloid leukaemia, are the most common forms of secondary disease.[1-3] Leukaemia associated with alkylating agents usually occurs about 5 to 7 years after treatment, and is often preceded by a preleukaemic myelodysplasia.[2,3] The nitrosoureas are associated with a relatively high frequency of secondary leukaemia, and busulfan and melphalan are considered to be more leukaemogenic than cyclophosphamide.[3] Another drug that has been associated with the development of secondary leukaemia is procarbazine.[3,4,8,9] Leukaemia associated with the podophyllotoxin derivatives has a shorter latency period of 2 to 3 years, with sudden onset and no myelodysplastic phase.[2,3] There is little evidence of carcinogenicity associated with **antimetabolites** such as methotrexate, although it has been suggested that they may act as co-carcinogens.[10] Fludarabine therapy has been reported to be associated with the development of myelodysplasia and acute myeloid leukaemias,[11] although a review of the purine nucleoside analogues, cladribine and fludarabine, concluded that no significant increase in the risk of secondary malignancy had been shown, but also that long-term follow-up of patients was needed.[12] Immunosuppression caused by antimetabolites including methotrexate, cladribine, and fludarabine, may also allow the development of Epstein-Barr virus-related lymphoma.[12,13]

Solid tumours can also occur as secondary malignancies and include bladder cancer associated with cyclophosphamide used to treat non-Hodgkin's lymphoma,[4,14] and bone sarcomas, and breast and lung cancers after the use of various alkylating agents.[4,7,15] Higher doses of anthracyclines also increase the risk of sarcoma. Podophyllotoxin derivatives are associated with a greater risk of lung carcinoma, while the risk of subsequent colorectal and kidney cancer increases with **platinum** therapy.[7] Platinum derivatives such as carboplatin and cisplatin have also been found in large cohort studies[16,17] to have a dose-response relationship with the development of secondary leukaemia. **Combinations** that may also be associated with leukaemias include cisplatin with doxorubicin,[18] and other anthracycline-based regimens.[19]

Estimates of **risk** have varied very widely between studies, and have been calculated in various ways, making direct comparison impossible. Factors influencing the incidence of secondary malignancy include the use of combination chemotherapy regimens, combined treatment modalities, exposure to environmental carcinogens, predisposing genetic risk factors, ethnicity, age at time of diagnosis and treatment, gender, and spontaneous occurrence.[2,3,20]

The risk of secondary acute myeloid leukaemia appears to be associated mainly with the **cumulative dose** of antineoplastics.[2] Of patients at risk for secondary leukaemias, those with Hodgkin's disease have been most extensively studied. The cumulative 10-year incidence of secondary myeloid leukaemia has been reported to range from less than 1% up to 10%.[2,3] The highest risk is associated with the use of MOPP (chlormethine, vincristine, procarbazine, prednisone) and relative risk increases with cumulative dose of chlormethine.[2,3] Splenectomy or radiation of the spleen doubles the risk of leukaemia, as does an age of more than 45 years at the time of treatment.[2] Secondary solid tumours, such as lung cancer, in patients with Hodgkin's disease have also been attributed to the use of regimens such as MOPP.[4] The risk of secondary acute myeloid leukaemia, in patients treated with adjuvant chemotherapy for breast cancer, increases with cumulative doses of melphalan and cyclophosphamide, and high-dose regimens of doxorubicin with cyclophosphamide.[2,3] In patients treated for multiple myeloma, the increased risk of secondary leukaemia has been attributed to the prolonged use of melphalan.[2,3] Patients treated for testicular cancer appear to be at increased risk of secondary leukaemia associated with cumulative doses of podophyllotoxin derivatives (more than 2 g/m^2 etoposide), and the addition of high cisplatin doses may increase this risk.[2,3] Another review[21] of studies using etoposide or teniposide for various cancers found no relationship between the cumulative dose of these and secondary leukaemia, and suggested that other drugs used in treatment regimens had a greater effect on the development of secondary malignancy. There is growing evidence that the use of high-dose therapy with alkylating agents and/or anthracyclines, followed by autologous stem cell transplantation, is associated with an increased risk of secondary myelodysplasias and leukaemias, and a cumulative incidence of about 9% at 5 years.[2] However, it is unclear whether this is due to the high-dose therapy or to previous chemotherapy that has caused bone-marrow damage.[2,3]

Radiotherapy is an established cause of secondary malignancy. It remains unclear, however, to what extent the use of chemotherapy combined **with radiotherapy** could have an additive effect on the risk of secondary leukaemias, and how dose and treatment regimen influence this effect.[3] Similarly, the role of combined modality treatment in the development of secondary solid tumours has not been defined, even though the radiation-enhancing effect of some antineoplastics is known and used in chemoradiation regimens for this reason.[4]

In many cases the risk of secondary malignancy is far less than that of undertreating, or of failing to treat, the primary disease.[2,4] However, secondary malignancies may be more resistant to treatment and more aggressive than primary disease,[3,22] and the risk of inducing malignant neoplasia is certainly a consideration in the use of alkylating agents and podophyllotoxin derivatives to treat non-malignant disease,[3] and is an increasing challenge in the design of suitable treatment regimens for primary neoplastic disease.

1. Curtis RE, *et al.* Risk of leukemia associated with the first course of cancer treatment: an analysis of the surveillance, epidemiology, and end results program experience. *J Natl Cancer Inst* 1984; **72**: 531–44.
2. Kollmannsberger C, *et al.* Risk of secondary myeloid leukemia and myelodysplastic syndrome following standard-dose chemotherapy or high-dose chemotherapy with stem cell support in patients with potentially curable malignancies. *J Cancer Res Clin Oncol* 1998; **124**: 207–14.
3. Leone G, *et al.* Therapy related leukemias: susceptibility, prevention and treatment. *Leuk Lymphoma* 2001; **41**: 255–76.
4. Travis LB. Therapy-associated solid tumors. *Acta Oncol* 2002; **41**: 323–33.
5. Dickerman JD. The late effects of childhood cancer therapy. *Pediatrics* 2007; **119**: 554–68. Correction. *ibid.*; 1045.
6. Hawkins MM, *et al.* Epipodophyllotoxins, alkylating agents and radiation and risk of secondary leukaemia after childhood cancer. *BMJ* 1992; **304**: 951–8.
7. Hudson MM, *et al.* High-risk populations identified in Childhood Cancer Survivor Study investigations: implications for risk-based surveillance. *J Clin Oncol* 2009; **27**: 2405–14.
8. Kaldor JM, *et al.* Leukemia following Hodgkin's disease. *N Engl J Med* 1990; **322**: 7–13.
9. Lee IP, Dixon RL. Mutagenicity, carcinogenicity and teratogenicity of procarbazine. *Mutat Res* 1978; **55**: 1–14.
10. Zumtobel U, *et al.* Widespread cutaneous carcinomas associated with human papillomaviruses 5, 14 and 20 after introduction of methotrexate in two long-term PUVA-treated patients. *Dermatology* 2001; **202**: 127–30.
11. Micallef INM, *et al.* Therapy-related myelodysplasia and secondary acute myelogenous leukemia after high-dose therapy with autologous hematopoietic progenitor-cell support for lymphoid malignancies. *J Clin Oncol* 2000; **18**: 947–55.
12. Van Den Neste E, *et al.* Second primary tumors and immune phenomena after fludarabine or 2-chloro-2′-deoxyadenosine treatment. *Leuk Lymphoma* 2001; **40**: 541–50.
13. Kamel OW, *et al.* Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993; **328**: 1317–21.
14. Nilsson S, Ullén A. Chemotherapy-induced bladder cancer. *Scand J Urol Nephrol* 2008; **42** (suppl 218): 89–92.
15. Neglia JP, *et al.* Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2001; **93**: 618–29.
16. Travis LB, *et al.* Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med* 1999; **340**: 351–7.
17. Travis LB, *et al.* Treatment-associated leukemia following testicular cancer. *J Natl Cancer Inst* 2000; **92**: 1165–71.
18. Kaldor JM, *et al.* Leukemia following chemotherapy for ovarian cancer. *N Engl J Med* 1990; **322**: 1–6.
19. Levine MN, *et al.* Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. *J Clin Oncol* 1998; **16**: 2651–8.
20. Meadows AT, *et al.* Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol* 2009; **27**: 2356–62.
21. Smith MA, *et al.* Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. *J Clin Oncol* 1999; **17**: 569–77.
22. Neugut AI, *et al.* Poor survival of treatment-related acute nonlymphocytic leukemia. *JAMA* 1990; **264**: 1006–8.

EFFECTS ON CHROMOSOMES. Visible chromosome gaps, breaks, and structural rearrangements are found in blood lymphocytes from patients who have received substantial doses of combination chemotherapy, and the changes persist for years after the end of treatment. A more sensitive, if transient, measure of genetic damage is the increased rate of sister chromatid exchange (SCE) that occurs with even quite small doses of cytotoxic drugs.[1] Evidence from

All cross-references refer to entries in Volume A

a study[2] in patients given chlorambucil suggests that as the dose increases so the capacity of the cells to cope with induced genetic damage is progressively exceeded, and thus SCE frequency reflects cumulative toxicity throughout the course of treatment.

In patients who develop acute myeloid leukaemia after alkylating agent therapy, the most common chromosomal losses involve deletions of chromosome 13, loss of the entire chromosomes 5 and 7, or deletions of part or the whole long arm of chromosomes 5 and 7. Molecular alterations of the suppressor gene p53 have also been found.[3] Balanced translocations, usually involving chromosomes 11 and 21, are associated with treatment using topoisomerase II inhibitors.[3,4]

See also under Effects on Reproductive Potential, p. 729.2.

1. Anonymous. Drugs that can cause cancer. *Lancet* 1984; **i**: 261–2.
2. Palmer RG, *et al.* Chlorambucil-induced chromosome damage to human lymphocytes is dose-dependent and cumulative. *Lancet* 1984; **i**: 246–9.
3. Leone G, *et al.* Therapy related leukemias: susceptibility, prevention and treatment. *Leuk Lymphoma* 2001; **41**: 255–76.
4. Rowley JD, Olney HJ. International workshop on the relationship of prior therapy to balanced chromosome aberrations in therapy-related myelodysplastic syndromes and acute leukemia: overview report. *Genes Chromosomes Cancer* 2002; **33**: 331–45.

Effects on the bladder. Cyclophosphamide (p. 772.3) and ifosfamide (p. 806.2) are the antineoplastics most frequently associated with adverse effects on the bladder, but see also Busulfan, p. 755.2, Chlorambucil, p. 764.3, Dacarbazine, p. 776.2, and Mitomycin, p. 831.3.

Effects on the blood. *BONE-MARROW DEPRESSION.* Bone-marrow depression, or myelosuppression, is common to the majority of cytotoxic antineoplastics, and is probably the single most important dose-limiting adverse effect, although its significance has been somewhat reduced in recent years by improvements in supportive care, including the availability of colony-stimulating factors and the development of techniques such as peripheral blood stem cell transfusion.

All the cellular elements of blood (see Haematopoiesis, p. 1121.1) may be affected by antineoplastic therapy, resulting in pancytopenia, but in many cases the toxicity appears to be greater for particular cell types. In addition, white blood cells and platelets tend to have shorter half-lives in circulation than erythrocytes. Hence the most usual manifestation of bone-marrow depression is leucopenia, leading to an increased risk of infection; thrombocytopenia is also fairly common. Anaemia is somewhat less frequent, and may be associated with megaloblastic changes in the bone marrow.

The onset, duration, and severity of bone-marrow depression vary considerably with different antineoplastics. For details, see under the individual monographs. For the management of bone-marrow depression, including discussion of the appropriate thresholds for treatment, see under Treatment of Adverse Effects, p. 730.3.

See also Effects on Immune Response, p. 728.3.

Effects on body-weight. The effects of antineoplastics on the gastrointestinal tract (p. 728.1) may lead to anorexia, malabsorption, and malnutrition, and hence to weight loss. A large cohort study[1] in survivors of childhood cancer found that treatment with total body irradiation, alkylating agents, or anthracyclines was associated with being underweight in females; in males, being underweight was associated with abdominal radiotherapy, younger age at treatment, and treatment with alkylating agents or anthracyclines. Antineoplastic therapy for breast cancer has however also been associated with weight gain, sometimes dramatic.[2] Weight gain appeared to be more likely in premenopausal women, in those receiving multidrug regimens, and in those treated for longer periods of time. A study of premenopausal women found that reduced physical activity may be a contributing factor to the development of this form of weight gain.[3] A subsequent small study has suggested that adjuvant regimens based on doxorubicin and cyclophosphamide, with or without a taxane, may not be associated with significant weight gain, although patients may undergo unfavourable changes in body-mass composition.[4] Weight gain has also been noted after long-term follow-up of paediatric leukaemia patients.[1,5,6] Causes include cranial irradiation[1,7] and corticosteroid therapy,[7] although some have suggested that weight gain depends more on inherent characteristics of the patients than the treatment given.[8]

1. Diller L, *et al.* Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. *J Clin Oncol* 2009; **27**: 2339–55.
2. Demark-Wahnefried W, *et al.* Why women gain weight with adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1993; **11**: 1418–29.
3. Demark-Wahnefried W, *et al.* Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 2001; **19**: 2381–9.
4. Freedman RJ, *et al.* Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. *J Clin Endocrinol Metab* 2004; **89**: 2248–53.
5. Birkebaek NH, Clausen N. Height and weight pattern up to 20 years after treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1998; **79**: 161–4.
6. Nysom K, *et al.* Degree of fatness after treatment for acute lymphoblastic leukaemia in childhood. *J Clin Endocrinol Metab* 1999; **84**: 4591–6.
7. Dickerman JD. The late effects of childhood cancer therapy. *Pediatrics* 2007; **119**: 554–68. Correction. *ibid.*; 1045.
8. Razzouk BI, *et al.* Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma. *J Clin Oncol* 2007; **25**: 1183–9.

Effects on bones and joints. Osteoporosis occurs as both an acute[1] and late[2] complication of chemotherapy, but as multicomponent regimens are used and because the pathogenesis of osteoporosis is likely to be multifactorial, it is difficult to assess the impact of individual drugs.[3] A main cause of bone loss is hypogonadism induced by irradiation, surgical gonadal ablation, hormonal therapy, or chemotherapy.[2] These form part of treatment regimens for a variety of neoplasms, including breast, prostate and testicular cancers, lymphomas, and haematological malignancies. In particular, regimens containing cyclophosphamide, chlormethine, chlorambucil, busulfan, mitomycin, or procarbazine may cause ovarian insufficiency and therefore have the potential to lead to osteoporosis in females.[2,3] Males may be somewhat protected from the effects of chemotherapy-induced hypogonadism, as the cells that produce testosterone only replicate slowly.[3] Endocrine therapies for breast cancer such as selective oestrogen-receptor modulators and aromatase inhibitors, and androgen deprivation therapy for prostate cancer can also cause bone loss.[2,4,5]

In addition, several drugs may exert direct effects on the bone. Methotrexate has been found to increase bone resorption and inhibit bone formation to produce a massive uncoupling of bone turnover.[2,3] Repeated doses of methotrexate, given as monotherapy to children with acute lymphoblastic leukaemia in remission, have been associated with pain, osteoporosis, and fractures.[6] Other drugs, including doxorubicin, have been shown to be toxic to bone in *animals*.[3] High-dose conditioning regimens used for bone marrow transplantation may have a direct dose-dependent toxicity on bone marrow osteoprogenitor cells, contributing to osteopenia.[7]

Corticosteroids are believed to cause bone loss by decreasing osteoblast activity, an effect which may be alleviated by chlorambucil. Surprisingly, corticosteroids have not been implicated in bone loss for most chemotherapy regimens, perhaps because the duration of treatment is short.[3] Nevertheless, osteoporosis and fractures have occurred in young patients with acute lymphoblastic leukaemia, treated with regimens containing high total doses of corticosteroids.[6,8,9] However, the disease itself, other chemotherapy, and radiotherapy are also likely to be contributory factors in the development of osteopenia in these patients. Osteonecrosis has also been reported with high doses of corticosteroids used in the treatment of leukaemias and solid tumours in adults and children.[8,10-12] Adolescent patients may be at increased risk because their bones are in the process of maturation.[8,10]

Indirect effects of cancer therapies may also affect bone health. These effects include hyperparathyroidism, hypovitaminosis D, hypophosphataemia, gastrointestinal complications, and hyperprolactinaemia.[2] A study in children with leukaemia has suggested that the effects of chemotherapy on gastrointestinal and renal handling of nutrients may lead to alterations in calcium and magnesium homoeostasis and hence to abnormal turnover of bone mineral.[13] Renal phosphate loss following damage to the renal tubule caused by ifosfamide can lead to osteomalacia.[2,3] Hypophosphataemia, with associated changes in bone and mineral metabolism, has been seen with tyrosine kinase inhibitors such as imatinib, sorafenib, and sunitinib.[2]

1. Arikoski P, *et al.* Reduced bone density at completion of chemotherapy for a malignancy. *Arch Dis Child* 1999; **80**: 143–8.
2. Stava CJ, *et al.* Skeletal sequelae of cancer and cancer treatment. *J Cancer Surviv* 2009; **3**: 75–88.
3. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol* 2000; **18**: 1570–93.
4. Gulse TA. Bone loss and fracture risk associated with cancer therapy. *Oncologist* 2006; **11**: 1121–31.
5. Bjarnason NH, *et al.* Adverse bone effects during pharmacological breast cancer therapy. *Acta Oncol* 2008; **47**: 747–54.
6. Sala A, Barr RD. Osteopenia and cancer in children and adolescents: the fragility of success. *Cancer* 2007; **109**: 1420–31.
7. Banfi A, *et al.* High-dose chemotherapy shows a dose-dependent toxicity to bone marrow osteoprogenitors: a mechanism for post-bone marrow transplantation osteopenia. *Cancer* 2001; **92**: 2419–28.
8. Strauss AJ, *et al.* Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol* 2001; **19**: 3066–72.
9. van der Sluis IM, *et al.* Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. *J Pediatr* 2002; **141**: 204–10.
10. Mattano LA, *et al.* Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol* 2000; **18**: 3262–72.
11. Winquist EW, *et al.* Nontraumatic osteonecrosis after chemotherapy for testicular cancer: a systematic review. *Am J Clin Oncol* 2001; **24**: 603–6.
12. Diller L, *et al.* Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. *J Clin Oncol* 2009; **27**: 2339–55.
13. Atkinson SA, *et al.* Mineral homeostasis and bone mass in children treated for acute lymphoblastic leukemia. *J Pediatr* 1989; **114**: 793–800.

Effects on the cardiovascular system. *THROMBOEMBOLISM.* Patients with cancer are at increased risk of thromboembolic disease, and thrombosis can be the earliest clinical sign of malignancy.[1,2] Clinical risk factors for cancer-associated venous thromboembolism include type of cancer, stage of disease, presence of comorbidities, and treatment-related factors such as hospitalisation, and use of systemic chemotherapy.[3] Deep-vein thrombosis and pulmonary embolism have been reported with a variety of chemotherapeutic regimens. Studies in patients with breast cancer have found that adjuvant chemotherapy can significantly increase the risk of venous thromboembolism.[4] An increase in venous thromboembolism, including CNS thromboses, has also been found with the use of asparaginase in the treatment of acute lymphoblastic leukaemia[4] (see also Effects on the Blood, under Asparaginase, p. 744.2). Regimens that include bevacizumab, lenalidomide, or thalidomide have also reported high rates of venous thromboembolism.[3,5] Arterial thrombosis, including acute myocardial infarction, angina, stroke, and peripheral artery thrombosis, has also been reported with various regimens.[4,5] Mechanisms proposed for the possible role of antineoplastics in these effects include activation of coagulation, suppression of anticoagulant proteins and fibrinolysis, and a direct toxic effect on vascular endothelium.[1,4]

Several reports of arterial and venous thromboembolism have implicated combinations of bleomycin with cisplatin and another drug such as a vinca alkaloid or etoposide.[6-8] Such combinations, widely used for testicular cancer, have also been implicated in producing vasospastic reactions including angina[9] and Raynaud's syndrome,[10,11] although there is no evidence of a relationship between thromboembolism and vasospasm.[6]

In men with germ cell cancer there is some evidence that those with liver metastases, or receiving high-dose dexamethasone as antiemetic therapy, are at increased risk of thromboembolic complications.[12]

Various organisations have addressed the problems of prevention and treatment of cancer-associated venous thromboembolism. Generally, unless contra-indicated, most recommend prophylactic anticoagulation for hospitalised or surgical cancer patients; low-molecular-weight or unfractionated heparin or fondaparinux may be used. Prophylaxis is not recommended for the ambulatory cancer patient, with the exception of patients with multiple myeloma given thalidomide- or lenalidomide-based regimens.[13] Treatment of venous thrombosis usually consists of low-molecular-weight or unfractionated heparin therapy and long-term secondary prophylaxis with warfarin,[14] but a multicentre, randomised study found that a low-molecular-weight heparin was more effective than an oral anticoagulant in reducing the risk of recurrent venous thromboembolism without increasing the risk of bleeding,[15] and many now recommend low-molecular-weight heparin therapy for both initial and continuing treatment of cancer patients with venous thromboembolism.[13,14] Patients with arterial thrombosis may require heparin and warfarin, or anti-platelet therapy.[16]

Thromboembolic complications may also be associated with the indwelling catheters used to provide vascular access for antineoplastic therapy.[17,18] Prophylaxis with low-dose warfarin or a low-molecular-weight heparin may reduce the risk.[18]

1. Falanga A, Donati MB. Pathogenesis of thrombosis in patients with malignancy. *Int J Hematol* 2001; **73**: 137–44.
2. Lyman GH, Khorana AA. Cancer, clots and consensus: new understanding of an old problem. *J Clin Oncol* 2009; **27**: 4821–6.
3. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol* 2009; **27**: 4839–47.
4. Lee AYY, Levine MN. The thrombophilic state induced by therapeutic agents in the cancer patient. *Semin Thromb Hemost* 1999; **25**: 137–45.
5. Zangari M, *et al.* Thrombotic events in patients with cancer receiving antiangiogenesis agents. *J Clin Oncol* 2009; **27**: 4865–73.
6. Cantwell BMJ, *et al.* Thromboembolic events during combination chemotherapy for germ cell malignancy. *Lancet* 1988; **ii**: 1086–7.
7. Hall MR, *et al.* Thromboembolic events during combination chemotherapy for germ cell malignancy. *Lancet* 1988; **ii**: 1259.
8. Garstin JWH, *et al.* Arterial thrombosis after treatment with bleomycin and cisplatin. *BMJ* 1990; **300**: 1018.
9. Rodriguez J, *et al.* Angina pectoris following cisplatin, etoposide, and bleomycin in a patient with advanced testicular cancer. *Ann Pharmacother* 1995; **29**: 138–9.
10. Vogelzang NJ, *et al.* Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. *Ann Intern Med* 1981; **95**: 288–92.
11. Pechère M, *et al.* Fingertip necrosis during chemotherapy with bleomycin, vincristine and methotrexate for HIV-related Kaposi's sarcoma. *Br J Dermatol* 1996; **134**: 378–9.
12. Weiji NI, *et al.* Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. *J Clin Oncol* 2000; **18**: 2169–78.
13. Khorana AA, *et al.* Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. *J Clin Oncol* 2009; **27**: 4919–26.
14. Lee A, Levine M. Treatment of venous thromboembolism in cancer patients. *Cancer Control* 2005; **12** (suppl 1): 17–21.
15. Lee AYY, *et al.* Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; **349**: 146–53.
16. Sutherland DE, *et al.* Thromboembolic complications of cancer: epidemiology, pathogenesis, diagnosis, and treatment. *Am J Hematol* 2003; **72**: 43–52.

17. Monreal M, Davant E. Thrombotic complications of central venous catheters in cancer patients. *Acta Haematol (Basel)* 2001; 106: 69–72.
18. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol* 2003; 21: 3665–75.

Effects on electrolytes. Fluid and electrolyte disturbances are common in patients with cancer.[1-4] These can be caused by the disease process, or adverse effects of treatment such as surgery, chemotherapy, antibacterials and diuretics. Mechanisms of chemotherapy-induced electrolyte disturbances include loss of appetite, gastrointestinal electrolyte loss due to vomiting and diarrhoea, impaired intestinal absorption due to mucosal damage, direct nephrotoxicity causing renal electrolyte loss, and a syndrome of inappropriate antidiuretic hormone secretion or a condition resembling it. Hypoparathyroidism, which may be a complication of neck surgery, also affects electrolyte balance and is associated with hyperphosphataemia and hypocalcaemia. As well as the acute signs and symptoms of electrolyte disturbances, changes in electrolyte homoeostasis may result in abnormal bone turnover (see Effects on Bones and Joints, p. 727.2). Release of the contents of cells destroyed by chemotherapy is well-known to be associated with hyperuricaemia, hyperphosphataemia, hyperkalaemia, and hypocalcaemia (see Tumour Lysis Syndrome, p. 730.2).

Disturbances of electrolyte homoeostasis have been reported particularly with cisplatin (p. 767.2), cyclophosphamide (p. 772.3), and ifosfamide (see Effects on the Kidneys, p. 806.3). Hypomagnesaemia has been seen with cetuximab (p. 763.3).

1. Kapoor M, Chan GZ. Fluid and electrolyte abnormalities. *Crit Care Clin* 2001; 17: 503–29.
2. Filippatos TD, *et al.* Alterations in electrolyte equilibrium in patients with acute leukemia. *Eur J Haematol* 2005; 75: 449–60.
3. Miltiadous G, *et al.* Causes and mechanisms of acid-base and electrolyte abnormalities in cancer patients. *Eur J Intern Med* 2008; 19: 1–7.
4. Lameire N, *et al.* Acute renal problems in the critically ill cancer patient. *Curr Opin Crit Care* 2008; 14: 635–46.

Effects on the gastrointestinal tract. Apart from anorexia, and nausea and vomiting (see below), many antineoplastics produce gastrointestinal disturbances, sometimes severe. Mucosal inflammation (mucositis), notably as stomatitis and sometimes proctitis, is quite common, as are mucosal cellular changes, xerostomia, impaired absorption, and diarrhoea. In some cases gastrointestinal damage may progress to ulceration, haemorrhage, and perforation. Constipation may be a problem with the vinca alkaloids.

Use with radiotherapy may increase the toxicity of some drugs on the gastrointestinal tract. The neutropenia induced by many antineoplastic regimens can also lead to secondary gastrointestinal effects, such as stomatitis and gastrointestinal inflammation, associated with infection.

References.

1. Gibson RJ, Keefe DMK. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. *Support Care Cancer* 2006; 14: 890–900.
2. Richardson G, Dobish R. Chemotherapy induced diarrhea. *J Oncol Pharm Pract* 2007; 13: 181–98.
3. Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage* 2008; 36: 413–25.
4. Sonis ST. Regimen-related gastrointestinal toxicities in cancer patients. *Curr Opin Support Palliat Care* 2010; 4: 26–30.

CLOSTRIDIUM DIFFICILE INFECTION. Antineoplastic therapy has occasionally been associated with the development of *Clostridium difficile*-induced gastrointestinal disease, even in the absence of concomitant antibacterial therapy.[1] Most patients had received multiple drug regimens. Methotrexate, fluorouracil, cyclophosphamide, and doxorubicin have all been associated with a number of cases but this may simply reflect the frequency of their use. A retrospective analysis[2] of a group of patients treated for acute leukaemia or receiving bone marrow transplantation found that predictive variables for *C. difficile* diarrhoea included the use of low intensity chemotherapy, but speculated that patients receiving high intensity chemotherapy may be subjected to more strict isolation and infection control procedures, thereby reducing the risk of nosocomial transmission. Another review[3] of 875 courses of myelosuppressive chemotherapy found 61 episodes of *C. difficile* diarrhoea, and that in 36% of those episodes the patients had received high-dose cytarabine. In 35 of the 61 episodes, patients had also received prior intravenous antibacterials.

For discussion of the treatment of such disease, see Antibiotic-associated Colitis, p. 183.1

1. Anand A, Glatt AE. Clostridium difficile infection associated with antineoplastic chemotherapy: a review. *Clin Infect Dis* 1993; 17: 109–13.
2. Hornbuckle K, *et al.* Determination and validation of a predictive model for Clostridium difficile diarrhea in hospitalized oncology patients. *Ann Oncol* 1998; 9: 307–11.
3. Gorschlüter M, *et al.* Clostridium difficile infection in patients with neutropenia. *Clin Infect Dis* 2001; 33: 786–91.

MUCOSITIS. The suffering associated with oral mucositis is by far the worst part of treatment for many patients undergoing curative chemotherapy or bone marrow transplantation, and for those undergoing oral radiotherapy.[1-3] Apart from pain and dysphagia the ulcerated mucosa provides a portal of entry for infection; loss of weight and malnutrition can further impair immune function, and if symptoms are severe enough the treatment cycle may have to be interrupted. Before the patient starts any intensive chemotherapy or local or systemic radiotherapy the oral cavity must be assessed with a view to eliminating sources of infection and chronic irritation. Established risk factors for mucotoxicity include smoking, poor oral hygiene, age, female gender, and previous antineoplastic therapy. However, the most significant risk factor is the treatment itself. Drugs such as fluorouracil, methotrexate, and etoposide are associated with an increased risk for mucositis, as are the more aggressive, dose-intense regimens such as TAC (docetaxel, doxorubicin, and cyclophosphamide). Infusional fluorouracil-based regimens appear to have less risk than standard-dose CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or bolus fluorouracil regimens. Drug dosing and scheduling are important in modulating the risk for mucositis.[4] For further comment on the prophylaxis and treatment of mucositis, see under Treatment of Adverse Effects, p. 732.1.

1. Calman FMB, Langdon J. Oral complications of cancer. *BMJ* 1991; 302: 485–6.
2. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol* 1998; 34: 39–43.
3. Sonis ST, *et al.* The Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 2004; 100 (suppl): 1995–2025.
4. Jones JA, *et al.* Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer. *Support Care Cancer* 2006; 14: 505–15.

NAUSEA AND VOMITING. Nausea and vomiting are common adverse effects of antineoplastic therapy, and for many patients, represent a major drawback to treatment. Once experienced, anticipatory vomiting may occur at the sight of medical staff, or a needle. The problem may be severe enough in some cases to hinder or completely prevent further treatment.

Antineoplastic or cytotoxic drugs may induce vomiting by both a central action on the chemoreceptor trigger zone and a peripheral action on the gastrointestinal tract. Several neurotransmitters have been implicated over the years including acetylcholine, histamine, enkephalins, dopamine, and serotonin or 5-hydroxytryptamine (5-HT). The cerebral cortex is probably responsible for anticipatory vomiting. Antineoplastics may not all induce emesis by a common pathway, but 5-HT_3-receptor mechanisms are clearly important in the pathogenesis of *acute* cisplatin-associated vomiting. This was suspected when the antiemetic metoclopramide, a dopamine antagonist, was found to have serotonin (5-HT) antagonist activity at the high doses used against cisplatin emesis and confirmed when specific 5-HT_3 antagonists such as ondansetron proved to be effective. Different mechanisms are probably involved in *delayed* emesis since 5-HT_3 antagonists are less effective.

Some patients are more susceptible to emesis than others. The emetic potential of antineoplastics also varies in terms of severity and incidence, and may depend to some extent on the dose, route, and schedule of administration. Some combination therapy has resulted in a higher incidence of vomiting than would be expected from the constituents.

- Vomiting may be *very severe* with cisplatin, dacarbazine, dactinomycin, chlormethine, high-dose cyclophosphamide, and streptozocin, and occurs in most patients.
- *Moderate* vomiting is likely with the taxanes, doxorubicin, more modest doses of cyclophosphamide, and high-dose methotrexate.
- Vinca alkaloids, fluorouracil, lower doses of methotrexate, chlorambucil, bleomycin, and etoposide have *low* emetogenic potential.

The *onset and duration* of vomiting also varies from drug to drug. With cisplatin the onset may be between 4 and 8 hours after a dose, while the duration may be up to 48 hours or occasionally even longer; a persistent feeling of nausea, and sometimes vomiting, lasting for several days may also occur. After chlormethine, vomiting may begin within a half to 2 hours, whereas after cyclophosphamide there may be a latent interval of 9 to 18 hours, but in both cases vomiting is generally less prolonged than with cisplatin. Acute emesis (that occurring within 24 hours) has generally been easier to control than delayed emesis (that occurring more than 24 hours after chemotherapy) or anticipatory emesis.

The management of chemotherapy-induced nausea and vomiting is discussed on p. 1814.3.

Effects on the heart. The cardiotoxicity of antineoplastics has been reviewed.[1-6] Common cardiovascular complications include left ventricular dysfunction, heart failure, myocardial ischaemia or infarction, QT interval prolongation, arrhythmias, or bradycardia; thromboembolism (see Effects on the Cardiovascular System, p. 727.2) and hypertension are also common. Cardiotoxicity is the major dose-limiting toxicity with anthracyclines such as doxorubicin and daunorubicin (see Effects on the Heart, under Doxorubicin, p. 784.1). Cardiotoxicity has also been associated with other antineoplastics, such as the alkylating agents cyclophosphamide and ifosfamide, antimetabolites such as capecitabine and fluorouracil, taxanes, tyrosine kinase inhibitors, and the monoclonal antibodies bevacizumab and trastuzumab. Amsacrine has been associated with arrhythmias, sometimes fatal. As well as cardiac effects associated with a capillary leak syndrome, arrhythmias can occur with interleukin-2. Occasional reports of cardiotoxicity associated with busulfan, carmustine, cisplatin, cytarabine, etoposide, mitomycin, pentostatin, and vincristine also exist.

1. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Safety* 2000; 22: 263–302.
2. Floyd JD, *et al.* Cardiotoxicity of cancer therapy. *J Clin Oncol* 2005; 23: 7685–96.
3. Simbre VC, *et al.* Cardiotoxicity of cancer chemotherapy: implications for children. *Paediatr Drugs* 2005; 7: 187–202.
4. Sereno M, *et al.* Cardiac toxicity: old and new issues in anti-cancer drugs. *Clin Transl Oncol* 2008; 10: 35–46.
5. Anderson B, Sawyer DB. Predicting and preventing the cardiotoxicity of cancer therapy. *Expert Rev Cardiovasc Ther* 2008; 6: 1023–33.
6. Yeh ETH, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009; 53: 2231–47.

Effects on immune response. Lymphocytes are produced by stem cells in the bone marrow and at other sites including the thymus, and are involved in humoral and cell-mediated immunity. Most antineoplastics have a depressant effect on bone marrow (see Effects on the Blood, p. 727.1) and many have immunosuppressant properties although the degree of suppression varies considerably and may depend on the dose and schedule used. Immunosuppression decreases the patient's resistance to infection and has been implicated in the development of malignancies. Response to vaccines may also be reduced, and there is a possibility of generalised infections with live viral vaccines (see Interactions, p. 2375.3).

For a discussion on the effects of immunosuppressant therapy on the immune response and the infections associated with it, see Corticosteroids, p. 1617.2.

Effects on the kidneys. Nephrotoxicity is well-recognised as an adverse effect of cisplatin (p. 767.2), ifosfamide (p. 806.3), and methotrexate (p. 825.2), but renal toxicity may occur with other antineoplastics including the nitrosoureas (such as carmustine and streptozocin), mitomycin (due to haemolytic-uraemic syndrome, see p. 831.3), azacitidine, gemcitabine, and pentostatin.[1] See also under individual monographs—other antineoplastics with which nephrotoxicity has been reported include aldesleukin (p. 811.3), bevacizumab (p. 748.2), and imatinib (p. 808.3).

1. Kintzel PE. Anticancer drug-induced kidney disorders: incidence, prevention and management. *Drug Safety* 2001; 24: 19–38.

Effects on the liver. The range of hepatotoxic reactions that can occur with antineoplastics is wide. Toxic hepatitis (hepatocellular injury) can range from asymptomatic elevations of aminotransferases to signs of overt liver failure with hepatocellular necrosis. Other manifestations of hepatotoxicity include cholestatic injury, steatosis, hepatic veno-occlusive disease (VOD), and hepatic tumours. The important indicator of toxicity is liver biopsy rather than liver function tests as the latter may be normal in this setting.[1] The hepatotoxicity of various chemotherapy drugs has been reviewed.[1-4] Occasional reports of hepatotoxicity exist for many antineoplastics including anastrozole (p. 743.1), aminoglutethimide (p. 739.3), bicalutamide (p. 749.2), busulfan (p. 755.2), dacarbazine (p. 776.2), dactinomycin (p. 777.2), doxorubicin (p. 784.3), erlotinib (p. 789.2), floxuridine (p. 793.3), flutamide (p. 798.3), gemtuzumab, (p. 802.3), hydroxycarbamide (p. 804.2), imatinib (p. 808.2), methotrexate (p. 825.3), mitomycin (p. 832.1), mitoxantrone (p. 833.3), oxaliplatin (p. 838.3), tamoxifen (p. 862.3), tioguanine (p. 872.1), and trastuzumab (p. 877.1). However, the relationship of the drug to the adverse effect is not always easy to establish. The temporal relationship between drug use and the appearance of symptoms is important; rechallenge in most cases is not recommended as liver toxicity may be more severe on re-exposure.[1] Use with radiotherapy may increase the risk of hepatotoxicity.[4,5] Liver toxicity may not be confined to patients: one report described 3 cases of liver damage in nurses working on an oncology ward.[6]

VOD has occurred after the use of high doses of chemotherapy for conditioning regimens before haematopoietic stem cell transplantation.[3-5] Other antineoplastic drugs involved in the development of VOD include the alkylating agents, antimetabolites, and combination chemotherapy, typically with drugs that undergo hepatic metabolism.[4]

1. Rodriguez-Frias EA, Lee WM. Cancer chemotherapy I: hepatocellular injury. *Clin Liver Dis* 2007; 11: 641–62.
2. Ménard DB, *et al.* Antineoplastic agents and the liver. *Gastroenterology* 1980; 78: 142–64.

3. Field KM, *et al.* Part I: Liver function in oncology: biochemistry and beyond. *Lancet Oncol* 2008; **9**: 1092–1101.
4. Floyd J, *et al.* Hepatotoxicity of chemotherapy. *Semin Oncol* 2006; **33**: 50–67.
5. King PD, Perry MC. Hepatotoxicity of chemotherapy. *Oncologist* 2001; **6**: 162–76.
6. Sotaniemi EA, *et al.* Liver damage in nurses handling cytostatic agents. *Acta Med Scand* 1983; **214**: 181–9.

Effects on the lungs. Lung injury leading to pulmonary fibrosis occurs in about 10% of all patients who receive bleomycin, being fatal in 1 to 2%. Clinically, the reaction usually presents several months after completion of therapy as non-productive cough and dyspnoea. The reaction is dose-related, being more likely at total doses over 400 000 international units (*400 USP units*), although it has occurred at much lower doses, and is more common in elderly patients. Injury may be exacerbated by the use of combination chemotherapy regimens and radiotherapy, and supplemental oxygen given even years after the use of bleomycin may precipitate pulmonary oedema.[1] Hypersensitivity pneumonitis, which is more amenable to treatment, has also been reported.[2]

Pulmonary damage has also been reported with an increasing number of antineoplastics apart from bleomycin.[1,3,4] Among the alkylating agents cyclophosphamide has been reported to produce lung injury in less than 1% of cases, although this may be increased where it is a component of combination regimens or given with radiotherapy. Busulfan may produce lung toxicity including insidious pulmonary fibrosis in as many as 4% of patients, usually developing several years after initiation of therapy, and with increased risk the longer that therapy lasts. A few reports exist of interstitial pneumonitis and fibrosis associated with chlorambucil and melphalan, but these appear to be extremely rare. The prognosis in patients with alkylating-agent-induced fibrosis is often poor, with mortality rates of 50% or more.

The antimetabolite methotrexate can produce symptoms similar to hypersensitivity pneumonitis in up to 7% of patients, sometimes with pleuritis and acute respiratory failure due to pulmonary oedema, but it is not clear whether a true hypersensitivity mechanism is involved, and symptoms are usually reversible even without stopping therapy. High-dose cytarabine has also been associated with pulmonary oedema. Gemcitabine (p. 801.3) has been associated with interstitial pneumonitis and potentially life-threatening symptoms have occurred when given with thoracic radiotherapy.

Other antineoplastics known to be associated with pulmonary toxicity include mitomycin (usually in less than 10% of patients though the incidence may be much higher in combination regimens); the vinca alkaloids (generally in combination, and usually producing acute respiratory failure); chlorozotocin; procarbazine; and possibly teniposide. The nitrosoureas, and particularly carmustine, have also emerged as pulmonary toxins. Carmustine has been associated with an insidious chronic pulmonary fibrosis, which in some early studies occurred in as many as 30% of patients and had a high mortality. Symptoms are associated particularly with cumulative doses in excess of about 1.4 g/m^2, although toxicity has occurred at cumulative doses as low as 240 mg/m^2. The onset of symptoms may be very delayed: some workers reported fibrosis occurring up to 17 years after treatment in patients who received carmustine as children.[5] Pneumonia and fibrosis have also been reported in patients receiving rituximab (p. 854.2), and fatal lung disease has occurred in patients given erlotinib (p. 789.2).

1. Abid SH, *et al.* Radiation-induced and chemotherapy-induced pulmonary injury. *Curr Opin Oncol* 2001; **13**: 242–8.
2. Holoye PY, *et al.* Bleomycin hypersensitivity pneumonitis. *Ann Intern Med* 1978; **88**: 47–9.
3. Twohig KJ, Matthay RA. Pulmonary effects of cytotoxic agents other than bleomycin. *Clin Chest Med* 1990; **11**: 31–54.
4. Fennell DA, Rudd RM. Pulmonary toxicity and cancer treatment. *Hosp Med* 2004; **65**: 462–5.
5. O'Driscoll BR, *et al.* Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med* 1990; **323**: 378–82.

Effects on mental function. Combination chemotherapy has been associated with psychiatric morbidity (anxiety, depression, behavioural changes) in both adults[1] and children.[2] It has been pointed out that patients receiving cancer chemotherapy inevitably suffer emotional distress, associated in part with the adverse effects of treatment. Patients should be fully informed of aims and likely outcomes of treatment, and adverse effects minimised, in order to keep emotional distress to a minimum.[3] Chemotherapy can also cause cognitive impairment,[4-7] affecting functions such as memory, reasoning, concentration, and language skills. Drugs may have direct central neurological toxic effects, or may indirectly affect brain function through adverse effects such as anaemia. Most studies have examined cognitive impairment in women being treated with chemotherapy for breast cancer, but many other cancer patients develop cognitive impairment, which has been described as 'chemo-brain' or 'chemo-fog'.

Some antineoplastics have been associated with mental symptoms, including methotrexate (p. 826.2), mitotane (p. 832.3), and the vinca alkaloids (see Vinblastine, p. 882.1). In many cases such symptoms can be attributed to direct central neurotoxicity (see also under Effects on the Nervous System, below).

1. Maguire GP, *et al.* Psychiatric morbidity and physical toxicity associated with adjuvant chemotherapy after mastectomy. *BMJ* 1980; **281**: 1179–80.
2. Dolgin MJ, *et al.* Behavioral distress in pediatric patients with cancer receiving chemotherapy. *Pediatrics* 1989; **84**: 103–10.
3. Brinkley D. Emotional distress during cancer chemotherapy. *BMJ* 1983; **286**: 663–4.
4. Tannock IF, *et al.* Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *J Clin Oncol* 2004; **22**: 2233–9.
5. Minisini A, *et al.* What is the effect of systemic anticancer treatment on cognitive function? *Lancet Oncol* 2004; **5**: 273–82.
6. Cavallere R, Schiff D. Neurologic toxicities of cancer therapies. *Curr Neurol Neurosci Rep* 2006; **6**: 218–26.
7. Weiss B. Chemobrain: a translational challenge for neurotoxicology. *Neurotoxicology* 2008; **29**: 891–8.

Effects on the nervous system. The neurotoxicity of various antineoplastic drugs has been reviewed.[1-5] Effects can be central or peripheral, and can be dose-limiting.[3,5] For further details see under the individual monographs.

CNS toxicity is usually manifested as encephalopathy of various severities.[5,6] Drugs that can cause CNS toxicity include methotrexate, vincristine, ifosfamide, cytarabine, fludarabine, fluorouracil, cisplatin, and the taxanes.[3] Some drugs cause mental status changes, see Effects on Mental Function, above. Drugs that commonly cause peripheral neuropathy include the platinum compounds, the vinca alkaloids, taxanes, and other agents such as bortezomib.[3,4,7] Peripheral neuropathy can manifest as sensory, motor, or sensorimotor (combination) neuropathies.[8] Two patterns are common: a painful sensory neuropathy (seen with platinum compounds) and a mixed sensorimotor neuropathy with or without autonomic involvement (such as that seen with vincristine and taxanes).[3,8]

In some cases these effects may be associated with particular routes such as the intrathecal.[4] Radiotherapy can also cause damage to the nervous system so its use with chemotherapy may lead to additive effects.[6]

For discussion on management, see Neurotoxicity, p. 732.2.

1. Verstappen CCP, *et al.* Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs* 2003; **63**: 1549–63.
2. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol* 2006; **24**: 1633–42.
3. Cavallere R, Schiff D. Neurologic toxicities of cancer therapies. *Curr Neurol Neurosci Rep* 2006; **6**: 218–26.
4. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst* 2008; **13**: 27–46.
5. Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. *Cancer Chemother Pharmacol* 2009; **63**: 761–7.
6. Perry A, Schmidt RE. Cancer therapy-associated CNS neuropathology: an update and review of the literature. *Acta Neuropathol* 2006; **111**: 197–212.
7. Visovsky C, *et al.* Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. *Clin J Oncol Nurs* 2007; **11**: 901–13.
8. Walker M, Ni O. Neuroprotection during chemotherapy: a systematic review. *Am J Clin Oncol* 2007; **30**: 82–92.

EFFECTS ON THE EARS. Several antineoplastics have been associated with ototoxicity,[1] including vincristine and vinblastine, but cisplatin in particular is associated with high-frequency hearing loss and tinnitus. In addition, agents such as the nitrogen mustards and bleomycin are potentially ototoxic.

1. Seligmann H, *et al.* Drug-induced tinnitus and other hearing disorders. *Drug Safety* 1996; **14**: 198–212.

Effects on reproductive potential. *CHROMOSOMES.* If patients are fertile after treatment with antineoplastics, no significant increase has been seen in fetal chromosome damage, fetal abnormality, or the miscarriage rate. A review[1] of reports of survivors of *childhood cancers* found that adverse pregnancy outcomes were limited to particular groups of survivors. Female survivors of Wilms' tumours who had been treated with abdominal radiation, with or without chemotherapy, appeared to be at increased risk of complications including miscarriage, low birth-weight neonates, and neonatal death. After treatment of childhood Hodgkin's disease using both radiotherapy and chemotherapy, female survivors and partners of male survivors might be at increased risk of miscarriage; however, treatment with radiotherapy or chemotherapy alone did not increase this risk. For other cancers, data were more limited, but suggested that the risk of adverse pregnancy outcomes was not increased in survivors. The Childhood Cancer Survivor study[2] found that the offspring of women whose treatment included pelvic irradiation were more likely to be premature, to be of low birth-weight, and small for gestational age. Treatment with doxorubicin or daunorubicin increased the risk of low birth-weight independently of radiotherapy. The risk of miscarriage was increased in those women treated with high-dose cranial or craniospinal radiotherapy. In general, the pregnancy outcome of the partners of male survivors was unaffected by the men's previous treatment; however, non-alkylating agent chemotherapy increased the risk of low birth-weight neonates.

Regarding the risk of congenital abnormalities in the offspring of survivors of childhood cancers, most studies have shown no excess of major or minor malformations.[1-3] There was also no evidence that the risk of cancer is increased in the offspring. However, because of the small numbers in many studies and heterogeneity regarding treatments used, it is possible that effects of individual drugs could have been masked. Long-term follow-up is needed as increasing numbers of children survive to adulthood after successful chemotherapy.

For *adult patients*, there is also a lack of evidence of adverse pregnancy outcomes and congenital abnormalities in offspring after chemotherapy. In a large series[4] of women treated with methotrexate, alone or in combination, for gestational trophoblastic tumours, there was no evidence of an increase in adverse outcomes or abnormalities, although women who had received three or more drugs in combination were less likely to have a live birth. A large case-control study carried out in Canada, and involving over 85 000 parents of children with congenital anomalies, also failed to confirm a higher incidence of congenital abnormality in the offspring of patients treated with radiotherapy or alkylating agents.[5] However, despite these generally reassuring results, it has been suggested that women should delay conception for a year after cessation of chemotherapy to allow mature ova that might have been damaged to be eliminated,[6] and that monitoring outcomes in patients who become pregnant shortly after exposure to cytotoxic drugs is desirable.[3]

See also Effects on Chromosomes under Carcinogenicity, p. 726.3.

1. Blatt J. Pregnancy outcome in long-term survivors of childhood cancer. *Med Pediatr Oncol* 1999; **33**: 29–33.
2. Green DM, *et al.* Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009; **27**: 2374–81.
3. Meirow D, Schiff E. Appraisal of chemotherapy effects on reproductive outcome according to animal studies and clinical data. *J Natl Cancer Inst Monogr* 2005; **34**: 21–5.
4. Rustin GJS, *et al.* Pregnancy after cytotoxic chemotherapy for gestational trophoblastic tumours. *BMJ* 1984; **288**: 103–6.
5. Dodds L, *et al.* Case-control study of congenital anomalies in children of cancer patients. *BMJ* 1993; **307**: 164–8.
6. Walden PAM, Bagshawe KD. Pregnancies after chemotherapy for gestational trophoblastic tumours. *Lancet* 1979; **ii**: 1241.

GONADS. The effects of cytotoxic drugs on the gonads have been reviewed.[1-7] In male patients, antineoplastic drugs may damage the seminiferous tubules, resulting in testicular atrophy with decreased sperm count and motility. Testosterone secretion may also be reduced after damage to Leydig cells. In women, cytotoxic drugs act on the ovary to produce loss of primordial follicles with failure of ovulation, oligomenorrhoea or amenorrhoea, and failure of endocrine function resulting in loss of libido and menopausal symptoms. The degree of damage and its reversibility depend on the drug and its dose and the age and sex of the patient. Age is particularly important for women at the time of treatment, with older women (35 to 40 or over) being more sensitive, probably a reflection of the decrease in oocyte numbers with age.

Although dose also plays a role, estimates of the toxicity of various antineoplastics (as single agents) have been published.[4-6] The risk of gonadal dysfunction is high with alkylating agents (busulfan, chlorambucil, chlormethine, cyclophosphamide, ifosfamide, melphalan), nitrosoureas (carmustine, lomustine), and procarbazine. Medium risk drugs include carboplatin, cisplatin, and doxorubicin. Low risk drugs include bleomycin, dactinomycin, fluorouracil, mercaptopurine, methotrexate, vinblastine, and vincristine.

Severe gonadal dysfunction in both men and women has been associated with combination chemotherapy regimens for Hodgkin's disease. Chlormethine and procarbazine are thought to be mainly responsible for the infertility produced. There is some evidence that currently favoured regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) result in less damage to gonadal cells than the earlier MOPP regimen (chlormethine, vincristine, procarbazine, and prednisone). Prolonged gonadal dysfunction has also been seen in patients given combination chemotherapy for acute lymphoblastic leukaemia; girls appear to be at less risk than boys, especially if treated in the prepubertal period.

Techniques for fertility preservation have been reviewed.[3-6,8] Established methods with the highest likelihood of success are sperm cryopreservation (sperm banking) for men and IVF with embryo cryopreservation for women. Other methods for women, for which there is less experience and investigation is underway, include oocyte cryopreservation for future IVF, gonadal tissue cryopreservation for autologous transplantation, and ovarian suppression using oral contraceptives or gonadotrophin-releasing hormone analogues. Such techniques are of little

benefit for the preservation of fertility in patients treated as young children, however, because of gonadal immaturity.

1. Goldman S, Johnson FL. Effects of chemotherapy and irradiation on the gonads. *Endocrinol Metab Clin North Am* 1993; 22: 617–29.
2. Kovacs GT, Stern K. Reproductive aspects of cancer treatment: an update. *Med J Aust* 1999; 170: 495–7.
3. Thomson AB, *et al.* Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. *Best Pract Res Clin Endocrinol Metab* 2002; 16: 311–34.
4. Wallace WHB, *et al.* Fertility preservation for young patients with cancer: who is at risk and what can be offered? *Lancet Oncol* 2005; 6: 209–18. Correction. *ibid.*: 922.
5. Magelssen H, *et al.* The effects of cancer and cancer treatments on male reproductive function. *Nat Clin Pract Urol* 2006; 3: 312–22.
6. Lee SJ, *et al.* American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006; 24: 2917–31. Correction. *ibid.*: 5790.
7. Walshe JM, *et al.* Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2006; 24: 5769–79.
8. Fallat ME, Hutter J. American Academy of Pediatrics Committee on Bioethics. American Academy of Pediatrics Section on Hematology/Oncology. American Academy of Pediatrics Section on Surgery. Preservation of fertility in pediatric and adolescent patients with cancer. *Pediatrics* 2008; 121: e1461–e1469. Also available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/e1461 (accessed 23/02/10)

SEXUAL FUNCTION. Loss of libido and decline in sexual performance seem to be relatively common in men receiving combination chemotherapy,[1,2] and may persist after chemotherapy has ended.[1] However, it may sometimes be difficult to distinguish the effects of chemotherapy from those of the disease and the patient's reaction to it: at least one study has shown that gonadal function is disturbed in patients with Hodgkin's disease before treatment.[2] Erectile dysfunction can also result from local damage caused by pelvic surgery or irradiation.[3] Evidence for decreased libido in women is harder to find, but failure of endocrine function after chemotherapy may lead to loss of libido and menopausal symptoms.[4]

1. Chapman RM, *et al.* Cyclical combination chemotherapy and gonadal function: retrospective study in males. *Lancet* 1979; i: 285–9.
2. Chapman RM, *et al.* Male gonadal dysfunction in Hodgkin's disease: a prospective study. *JAMA* 1981; 245: 1323–8.
3. Costabile RA. Cancer and male sexual dysfunction. *Oncology (Huntingt)* 2000; 14: 195–205.
4. Shalet SM. Effects of cancer chemotherapy on gonadal function of patients. *Cancer Treat Rev* 1980; 7: 141–52.

Effects on the skin, hair, and nails. Alopecia occurs with many antineoplastics, and may be severe with doxorubicin and other anthracyclines, cyclophosphamide, ifosfamide, etoposide, or teniposide, the taxanes docetaxel and paclitaxel, and topotecan. The alkylating agents and some antibiotic antineoplastics are often associated with hyperpigmentation, most commonly of skin, although pigmentation of nails, hair, and teeth has occurred. Some drugs, such as the taxanes, cause dystrophic changes in the nails. Certain drugs may interact with UV light or x-ray radiation to enhance its effects on the skin and may cause radiation recall, photosensitivity, or, in the case of methotrexate, reactivation of UV light burns. Hypersensitivity to antineoplastics may produce cutaneous reactions including allergic rashes, angioedema, and pruritus. In addition to the above there may be local reactions to irritant and vesicant drugs after extravasation. Finally, certain drugs are associated with specific dermatological reactions: acneform follicular rashes have been reported with cetuximab, bleomycin may produce hyperkeratotic and sclerotic lesions, dactinomycin is associated with an erythematous papular or pustular rash mimicking septic emboli, fluorouracil may produce inflammation of solar keratoses, and plicamycin is associated with a distinctive flushing phenomenon. A palmar-plantar erythrodysesthesia syndrome has been seen with some antineoplastics (see below).

See also Local Toxicity, below. References may also be found under individual monographs.

PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME. Palmar-plantar erythrodysesthesia (PPE; hand-foot syndrome) associated with chemotherapy[1,2] usually presents as a tingling sensation in the palms and soles, which progresses in a few days to burning pain and well-defined swelling and erythema. In severe cases there is desquamation, ulceration, blistering, and severe pain. The reaction appears to be caused by a direct toxic effect and seems to be dose-dependent, affected by both peak drug concentration and total cumulative dose. The drugs most often associated with PPE or similar syndromes are capecitabine (p. 758.3), cytarabine (p. 775.2), docetaxel (p. 782.1), doxorubicin—particularly liposomal doxorubicin (p. 785.1), and fluorouracil (p. 797.2). PPE also occurs with the tyrosine kinase inhibitors, such as lapatinib (p. 815.2), sorafenib (p. 858.1), and sunitinib (p. 859.2). It has also been reported for bevacizumab (p. 747.3), cisplatin (see under Hypersensitivity, p. 768.1), cyclophosphamide (p. 773.1), ixabepilone (p. 815.1), and methotrexate (p. 826.2). PPE is usually managed by reducing the drug dose, increasing the dosage interval, or withdrawing the drug, along with symptomatic treatment and wound care. Systemic corticosteroids and pyridoxine have been used in prophylaxis and treatment. Topical dimethyl sulfoxide has been used for PPE caused by liposomal doxorubicin.

1. Nagore E, *et al.* Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome: incidence, recognition and management. *Am J Clin Dermatol* 2000; 1: 225–34.
2. Webster-Gandy JD, *et al.* Palmar-plantar erythrodysesthesia (PPE): a literature review with commentary on experience in a cancer centre. *Eur J Oncol Nurs* 2007; 11: 238–46.

Hyperuricaemia. Overproduction of purines is a known complication of antineoplastic therapy and may result in hyperuricaemia (p. 600.1). Hyperuricaemia is also an important part of the tumour lysis syndrome—see below.

Local toxicity. Local toxicity due to intravenous cancer chemotherapy may include local irritation, extravasation necrosis, and hypersensitivity. **Venous irritation**, presenting as vasospasm and pain or endothelial chemical burn of the vessel, resulting in a painful, streaky, long-lasting sterile phlebitis, may be due to the drug, or, as with carmustine, due to the diluent (alcohol). Irritation and phlebitis have been reported particularly with fluorouracil, carmustine, vinorelbine, and chlormethine.

Some patients treated with peripheral intravenous chemotherapy experience **extravasation** (see p. 731.3), usually with pain, erythema, and swelling at the site of injection. Severe necrosis requiring surgical intervention can develop, particularly with antibiotic antineoplastics such as doxorubicin.

Local **hypersensitivity** reactions, usually self-limiting, must be distinguished from extravasation. In hypersensitivity reactions there is no swelling at the injection site, and pain is felt as a dull ache along the course of the vein, as opposed to the stinging commonly noted after extravasation.

Tumour lysis syndrome. The tumour lysis syndrome represents a biochemical disturbance due to massive release of cellular breakdown products from tumour cells sensitive to therapy. The amount of breakdown products is sufficient to overwhelm normal excretory and metabolic mechanisms for their clearance, and the cardinal features of the syndrome are hyperkalaemia, hyperuricaemia, and hyperphosphataemia accompanied by hypocalcaemia. Clinical symptoms may include urate nephropathy or nephrocalcinosis leading to renal impairment, and cardiac arrhythmias associated with the potassium abnormalities. The syndrome is seen particularly when bulky chemosensitive disease is present, and may be more likely in patients with pre-existing renal impairment or hyperuricaemia. It is most frequent in patients with Burkitt's or lymphoblastic lymphoma, or an acute leukaemia. Of patients with solid tumours, reports have implicated those with germ-cell tumours, small-cell lung cancer, or neuroblastoma although, surprisingly, the syndrome has also been reported in patients with breast cancer, which is normally less rapidly responsive to chemotherapy. For comment on prevention and treatment, see under Treatment of Adverse Effects, p. 732.2.

References.

1. Kalemkerian GP, *et al.* Tumor lysis syndrome in small cell carcinoma and other solid tumors. *Am J Med* 1997; 103: 363–7.
2. Jeha S. Tumor lysis syndrome. *Semin Hematol* 2001; 38 (suppl 10): 4–8.
3. Baeksgaard L, Sørensen JB. Acute tumor lysis syndrome in solid tumors—a case report and review of the literature. *Cancer Chemother Pharmacol* 2003; 51: 187–92.

Treatment of Adverse Effects

Intensive supportive care may be necessary to prevent or control the adverse effects of antineoplastic therapy. Antiemetic therapy should be given to reduce, and if possible prevent, nausea and vomiting, since once experienced it may become a conditioned response, and may not respond to antiemetics. Intensive oral care is desirable to minimise the effects of stomatitis (see also Mucositis, p. 732.1), while corticosteroids, and if necessary nutritional supplements, may be of some help in patients with anorexia. Chemotherapy-induced diarrhoea may also require treatment (see p. 731.3).

Techniques attempting to prevent the occurrence of alopecia have met with varying success (see below). Scalp tourniquets and local hypothermia have been used to minimise concentrations of antineoplastics in the scalp after intravenous injection. However, such methods may allow the development of a cancer-cell sanctuary and should not be used in patients with leukaemia or other conditions with circulating malignant cells.

Of particular importance is the management of bone-marrow depression. Colony-stimulating factors and epoetins can be used to promote the formation of replacement blood elements (see Anaemia, p. 731.1). Active measures may be necessary to combat infection and bleeding. Transfusions of blood products may be required; granulocyte transfusions have been given for infections unresponsive to antibiotics, although their value is a matter of debate, while transfusion of blood platelets or use of growth factors such as oprelvekin (interleukin-11) may be of value in preventing thrombocytopenia-induced bleeding.

Extravasation of antineoplastics can pose serious problems. Infusion should be stopped immediately once extravasation is noticed and any drug remaining at the site aspirated if possible but the details of treatment are controversial (see p. 731.3). If ulceration occurs plastic surgery may be required.

Hyperuricaemia secondary to tumour lysis in patients with leukaemias or lymphomas can be prevented by the addition of allopurinol or rasburicase to treatment schedules, and by adequate hydration and, if necessary, alkalinisation of the urine (see Tumour Lysis Syndrome, p. 732.2). Good hydration is also important to minimise the nephrotoxic effects of drugs such as cisplatin and methotrexate.

Specific treatments exist for the toxicity of certain antineoplastics (for example the use of calcium folinate to reduce methotrexate toxicity, or mesna to control the bladder toxicity of cyclophosphamide or ifosfamide). For further details of the treatment of specific adverse effects see under the individual monographs.

Alopecia. Attempts to prevent or reduce chemotherapy-induced alopecia have relied on either restriction of scalp blood flow with a tourniquet or the use of local hypothermia.[1] Both of these techniques have been based on the rationale that a temporary decrease in blood flow to the scalp will decrease the exposure of hair follicles to the antineoplastic. Therefore, most benefit would be expected for alopecia caused by drugs with a short half-life and for which both active drug and metabolites are rapidly cleared from the circulation.

Studies of scalp tourniquets carried out in the 1970s found head discomfort to be the main adverse effect. They used different chemotherapy regimens, definitions for success, and tourniquet techniques, making conclusions difficult, and tourniquets were largely replaced by local hypothermia techniques.

Regimens vary in their propensity to cause alopecia: drugs that normally produce hair loss include the anthracyclines, cyclophosphamide and ifosfamide, etoposide and topotecan, irinotecan, the taxanes, and vindesine or vinorelbine.[2] Most studies of local hypothermia have attempted to prevent doxorubicin-induced alopecia.[1] Again, chemotherapy regimens, devices used, and exposure times have varied between studies. Varying degrees of efficacy have been reported, but hypothermia has generally been of benefit, particularly with single-agent chemotherapy. The dose of chemotherapy may be relevant, with hypothermia being less effective at doxorubicin doses above 50 mg.[1] Better results have also been reported when cooling is continued for 90 minutes or more; theoretically, cooling time should be related to the half-life of the drugs used and any active metabolites.[2] Headache and cold intolerance may occur, but scalp hypothermia is generally well tolerated.

Despite the successes there is concern that this technique may provide a sanctuary for circulating malignant cells, with the potential risk of metastasis, and there are reports of scalp metastases after the use of hypothermia.[1-3] The technique is considered contra-indicated in patients with haematological malignancies and use is controversial where curative chemotherapy can be given.[2] It has been suggested that the use of scalp hypothermia might therefore be restricted to patients receiving single-agent chemotherapy with a palliative intent, or those with solid tumours that rarely metastasise to the scalp.[1]

In the USA commercial distribution of cooling caps designed to produce localised scalp hypothermia was halted by the FDA in 1990 because of concerns about their efficacy and their potential to create sanctuary sites and interfere with drug distribution elsewhere in the head. However, they continue to be available in many countries.

There has been limited investigation of pharmacological management.[2] For reference to the use of minoxidil to decrease the duration of alopecia after doxorubicin-containing chemotherapy, see p. 1439.1.

1. Dorr VJ. A practitioner's guide to cancer-related alopecia. *Semin Oncol* 1998; 25: 562–70.
2. Trüeb RM. Chemotherapy-induced alopecia. *Semin Cutan Med Surg* 2009; 28: 11–14.
3. Forsberg SA. Scalp cooling therapy and cytotoxic treatment. *Lancet* 2001; 357: 1134.

Bone-marrow depression. Bone-marrow depression in patients receiving chemotherapy may require a modification of the dose regimen in subsequent cycles, either by delaying or reducing doses, although it is recognised that this may sometimes reduce efficacy.

Licensed product information for several myelosuppressive antineoplastics recommends that if neutropenia or thrombocytopenia occurs subsequent doses should be withheld until white cell counts have returned to 3000 to 3500 cells/mm^3 or more, and blood platelets to about 100 000 cells/mm^3. In practice, however, improved supportive care means that many expert centres routinely give treatment at lower blood counts than these. The values at which it is acceptable to treat will be influenced by whether the regimen is likely to result in further significant falls, and

whether the intent is curative (in which case maintaining treatment intensity is particularly important) or palliative (when avoiding toxicity becomes a prime consideration); local protocols may contain further guidance and should be consulted where available. However, it has been suggested[1] that with appropriate management treatment is usually possible at neutrophil counts of 1500 cells/mm³ and platelet counts above 100 000 cells/mm³.

For guidelines on the use of haematopoietic growth factors in the management of anaemia, neutropenia, and thrombocytopenia, see below.

1. Summerhayes M, Daniels S. *Practical chemotherapy: a multidisciplinary guide*. Oxford: Radcliffe Medical Press, 2003.

ANAEMIA. Chemotherapy-induced anaemia can be managed with transfusion of red cells (p. 1162.1), or treatment with epoetin (p. 1141.1) or darbepoetin (p. 1137.1).[1-4] Iron supplementation may be of benefit in anaemic cancer patients receiving erythropoietic therapy, even in those who are iron-replete.[3]

Guidelines for the use of epoetins and darbepoetin have been issued jointly by the American Society of Clinical Oncology and the American Society of Hematology,[5] and guidelines have also been issued by the US National Comprehensive Cancer Network.[4] In the treatment of chemotherapy-induced anaemia, the use of epoetins or darbepoetin can improve haemoglobin concentration and reduce the need for transfusion of red cells, but whether this improves symptoms and quality of life requires further study. The use of epoetins or darbepoetin is recommended as an option when haemoglobin has fallen to less than 10 g per 100 mL. For patients with a concentration between 10 and 12 g per 100 mL, the decision to use epoetins depends on clinical circumstances and patient preference.[5] In the UK, the use of epoetins or their analogues is not generally recommended[3] for chemotherapy-related anaemia except, in combination with intravenous iron, in patients in whom anaemia is profound and likely to affect survival, and who cannot be given blood transfusions, or in women given platinum-based chemotherapy for ovarian cancer in whom haemoglobin has fallen to 8 g per 100 mL or less.

1. Littlewood TJ. Management options for cancer therapy-related anaemia. *Drug Safety* 2002; **25**: 525–35.
2. Bohlius J, *et al.* Erythropoietin or darbepoetin for patients with cancer. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2006 (accessed 26/01/10).
3. NICE. Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia (TA 142, issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA142Guidance.pdf (accessed 26/01/10)
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: cancer- and chemotherapy-induced anemia (version 1.2011). Available at: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf (accessed 12/07/10)
5. Rizzo JD, *et al.* American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood* 2010; **116**: 4045–59. Also published in *J Clin Oncol* 2010; **28**: 4996–5010. Also available at: http://bloodjournal.hematologylibrary.org/cgi/reprint/116/20/4045 (accessed 16/12/10)

NEUTROPENIA. Use of granulocyte or granulocyte-macrophage colony-stimulating factors (G-CSF or GM-CSF), alone or with autologous bone marrow transplants or peripheral blood stem-cells, can markedly reduce the period of neutropenia after high-dose chemotherapy regimens (see Filgrastim, p. 1152.1, and Molgramostim, p. 1156.2). The use of filgrastim and pegfilgrastim has been reviewed;[1,2] it was considered that prophylactic use of these agents has enabled the use of more aggressive chemotherapy regimens, including dose-dense regimens (but see below), and treatment of a broader range of patients.

The American Society of Clinical Oncology has issued detailed guidelines for the use of colony-stimulating factors (CSFs) in patients receiving chemotherapy.[3] These point out that in current practice infectious mortality resulting from febrile neutropenia is rare, and that the incidence with common chemotherapy regimens seldom exceeds 20% in previously untreated patients; however, episodes of febrile neutropenia prolong hospital stay, expose the patient to further interventions, and may result in delay or dose-reduction of further chemotherapy cycles. Unfortunately, although CSFs can markedly reduce the incidence of febrile neutropenia, there was little evidence of improved clinical outcomes from the use of CSFs in most situations.

- Use of CSFs for **primary prophylaxis** in previously untreated patients should not normally be considered except where the risk of febrile neutropenia was 20% or more, or where the risk was less than 20% but bone-marrow compromise or comorbidity indicated a patient at high risk (and even here the evidence for improved clinical outcome was modest).
- There was no evidence of clinical benefit from the use of CSFs in **secondary prophylaxis**. In patients with a previous episode of febrile neutropenia the usual option (except where it would compromise the chances of cure) was dose reduction of the chemotherapy regimen.
- For adjunctive **treatment** of episodes of neutropenia, it was recommended that CSFs should not be routinely used for patients who were *afebrile*; there was also strong and consistent evidence against routine use for uncomplicated fever and neutropenia in *febrile* patients. Use might be considered in high-risk patients with febrile neutropenia.
- Although CSFs could permit **increased dose-density or dose-intensity** of chemotherapy, this was considered only justified within the context of a clinical study, since the limited data suggest survival benefit from dose-dense regimens with CSF support in only a few specific settings. Use in patients receiving combined **chemoradiotherapy** was not recommended.
- In patients with **haematological malignancies**, CSFs should be considered after induction chemotherapy in patients with acute myeloid leukaemias (patients aged over 55 may be most likely to benefit), after consolidation chemotherapy, and after initial induction or postremission chemotherapy in patients with acute lymphoblastic leukaemia; a subset of patients with myelodysplastic syndrome, severe neutropenia, and recurrent infection, might also benefit, but use in patients with refractory or relapsed myeloid leukaemia was not thought to be of benefit.
- CSFs were recommended as adjuncts to **progenitor cell transplantation** to help mobilise peripheral blood stem cells and to speed autologous engraftment.
- As **older patients** treated with curative chemotherapy for diffuse aggressive lymphoma are at increased risk of febrile neutropenia and infections, and dose reduction strategies have been associated with a reduced response rate and survival, prophylactic CSF was recommended for such patients aged 65 and older.
- Although the guidelines in adults were held to be generally applicable to **children**, it was noted that the potential for secondary myeloid leukaemia or myelodysplastic syndrome associated with CSFs was of concern in children with acute lymphoblastic leukaemia.

Guidelines issued by the US National Comprehensive Cancer Network[4] adopt a similar attitude to the use of CSFs, and suggest that they should be used for prophylaxis in all patients with a more than 20% risk of febrile neutropenia or neutropenia sufficient to compromise treatment, and may be considered in patients in whom this risk is judged to be between 10 and 20%. Factors that contribute to risk categorisation include the type of chemotherapy regimen and patient risk factors such as age, type of disease, disease stage, previous chemotherapy or irradiation, general health, and performance status.

For details on the management of infections in neutropenic patients, see Infections in Immunocompromised Patients, p. 186.3.

1. Marangolo M, *et al.* Dose and outcome: the hurdle of neutropenia (Review). *Oncol Rep* 2006; **16**: 233–48.
2. Renwick W, *et al.* Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. *BioDrugs* 2009; **23**: 175–86.
3. Smith TJ, *et al.* American Society of Clinical Oncology. 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://www.jco.org/cgi/reprint/24/19/3187 (accessed 18/01/10)
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: myeloid growth factors (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf (accessed 18/01/10)

THROMBOCYTOPENIA. Chemotherapy-induced thrombocytopenia can be managed by chemotherapy dose reductions or delaying the next cycle of chemotherapy; treatment modifications depend on the drug used and the severity of the thrombocytopenia.[1] Severe thrombocytopenia can be rapidly treated with transfusion of platelets (p. 1159.3). Recombinant thrombopoietin[2] (p. 1164.1), interleukin-3 (p. 1155.2), and interleukin-6 have been evaluated for their ability to increase platelet numbers *in vivo*. Interleukin-11 has also been studied and is now available as oprelvekin (p. 1157.2), which can reduce chemotherapy-induced thrombocytopenia.[1,3,4] Interleukin-1 (p. 2533.3) has also been investigated in the prevention or treatment of thrombocytopenia. Eltrombopag (p. 1140.1) and romiplostim (p. 1162.2) are also under investigation.[1]

The American Society of Clinical Oncology has issued guidelines for the use of platelet transfusion.[5] They recommend that prophylactic platelet transfusion be given for thrombocytopenia resulting from impaired bone-marrow function to reduce the risk of haemorrhage when the platelet count falls below a predefined threshold. This threshold will vary depending on the patient's diagnosis, clinical condition, and treatment modality. A threshold of 10 000 cells/mm³ has been recommended for patients being treated for acute leukaemia, with haematopoietic stem cell transplantation, or for solid tumours. A higher threshold of 20 000 cells/mm³ may need to be considered for patients with signs of haemorrhage, high fever, rapid fall of platelet count, coagulation abnormalities, patients receiving aggressive therapy for bladder tumours, or those with necrotic solid tumours who are at increased risk of bleeding from these sites.

1. Vadhan-Raj S. Management of chemotherapy-induced thrombocytopenia: current status of thrombopoietic agents. *Semin Hematol* 2009; **46** (suppl 2): S26–S32.
2. Vadhan-Raj S, *et al.* Recombinant human thrombopoietin attenuates carboplatin-induced severe thrombocytopenia and the need for platelet transfusions in patients with gynecologic cancer. *Ann Intern Med* 2000; **132**: 364–8.
3. Gordon MS, *et al.* A phase I trial of recombinant human interleukin-11 (Neumega rhIL-11 growth factor) in women with breast cancer receiving chemotherapy. *Blood* 1996; **87**: 3615–24.
4. 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.
5. 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://www.jco.org/cgi/reprint/19/5/1519.pdf (accessed 18/01/10)

Diarrhoea. Patients receiving chemotherapy should be monitored for onset, duration, and severity of diarrhoea. Uncomplicated mild to moderate diarrhoea may be managed conservatively with dietary modification and loperamide. Severe diarrhoea, and mild to moderate cases that are complicated by moderate to severe cramping, nausea and vomiting, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration, may require more aggressive management including intravenous fluids, octreotide, and antibacterials.[1-3]

1. Benson AB, *et al.* Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004; **22**: 2918–26.
2. Richardson G, Dobish R. Chemotherapy induced diarrhea. *J Oncol Pharm Pract* 2007; **13**: 181–98.
3. Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage* 2008; **36**: 413–23.

Extravasation. Extravasation is the leakage of a drug into subcutaneous tissue during parenteral dosage. Extravasation injuries can range from mild erythema to ulceration, and severe necrosis in some cases if not dealt with promptly. Antineoplastics vary in their propensity to cause extravasation injury:[1]

- *vesicant antineoplastics* cause pain, inflammation and blistering of the local skin, tissue death and necrosis; they include amsacrine, the anthracyclines (doxorubicin and its derivatives), carmustine, dacarbazine, dactinomycin, mitomycin, chlormethine, paclitaxel, plicamycin, streptozocin, and the vinca alkaloids
- *exfoliants* can cause inflammation and exfoliation, but are less likely to cause tissue death, and include cisplatin, docetaxel, mitoxantrone, oxaliplatin, and topotecan
- carboplatin, irinotecan, and the podophyllotoxin derivatives (etoposide and teniposide) are examples of *irritant drugs* which may cause inflammation and irritation, but rarely cause breakdown of tissue. Fluorouracil, methotrexate, and raltitrexed can cause mild to moderate inflammation of local tissue.

Measures to prevent the occurrence of extravasation include giving vesicant or irritant drugs via a central line, or peripherally via a recently sited cannula; vesicants are generally given by intravenous injection into a fast-running infusion. Glyceryl trinitrate patches applied distally to the cannula may be used to dilate veins where venous access is a problem. The site of administration should be regularly checked, and the patient asked to report any untoward sensations.

If extravasation should occur the infusion should be stopped immediately and as much as possible of the infiltrating drug removed by aspiration. Beyond this, however, the management of extravasation is not well standardised and there has been disagreement as to the most appropriate course; there is little data from controlled studies and much practice is based on anecdotal reports and individual experience. Intravenous and subcutaneous injection of a corticosteroid (usually hydrocortisone) has been suggested, although some consider it ineffective or possibly even disadvantageous. Topical application of a 1% hydrocortisone cream to inflamed skin has also been suggested, and antihistamines and, if necessary, analgesics, may be given orally. In most cases application of a cold dressing or ice pack is appropriate. However, after extravasation of the taxanes, vinca alkaloids, or cisplatin, the use of warm packs with hyaluronidase to enhance uptake from the skin has been recommended; a similar procedure has been suggested for large volume extravasations of the podophyllotoxin derivatives.

The use of specific antidotes is a particularly contentious area, since few are clinically validated and some (such as the use of sodium bicarbonate 8.4% for anthracycline extravasations) may do more harm than good. Brief infiltration of a less concentrated (2.1%) sodium bicarbonate solution, followed after a few minutes by aspiration, is still, however, advocated by some in the management of extravasations of the anthracyclines, carmustine, and plicamycin. Better accepted in the management of anthracycline and mitomycin extravasation is the topical application of dimethyl sulfoxide about every 6 hours,

sometimes alternated with hydrocortisone 1% cream. Dexrazoxane is also used for the management of anthracycline extravasation. Sodium thiosulfate 3 or 4% has been used to infiltrate the site of extravasations of cisplatin, dactinomycin, or chlormethine.

The role of surgery is also important. It is unequivocally necessary in cases where other methods have failed to prevent evolving tissue damage, but there is some dispute as to the role of early surgery to remove drug-laden tissue and prevent the development of more serious ulceration and necrosis. Techniques of saline flushout and liposuction have been developed for removing drug and non-viable tissue while preserving overlying skin.

Some references to the management of extravasation are given below.[1-6]

1. Stanley A. Managing complications of chemotherapy administration. In: Allwood M, *et al.*, eds. *The Cytotoxic Handbook*. 4th ed. Oxford: Radcliffe Medical Press, 2002: 119–93.
2. Dorr RT. Antidotes to vesicant chemotherapy extravasations. *Blood Rev* 1990; 4: 41–60.
3. Gault DT. Extravasation injuries. *Br J Plast Surg* 1993; 46: 91–6.
4. Bertelli G. Prevention and management of extravasation of cytotoxic drugs. *Drug Safety* 1995; 12: 245–55.
5. Kassner E. Evaluation and treatment of chemotherapy extravasation injuries. *J Pediatr Oncol Nurs* 2000; 17: 135–48.
6. Ener RA, *et al.* Extravasation of systemic hemato-oncological therapies. *Ann Oncol* 2004; 15: 858–62.

Hypersensitivity. Desensitisation protocols have been described for cancer patients with hypersensitivity reactions to chemotherapy, including taxanes, platinum agents, and monoclonal antibodies.[1]

1. Castells M. Rapid desensitization for hypersensitivity reactions to chemotherapy agents. *Curr Opin Allergy Clin Immunol* 2006; 6: 271–7.

Mucositis. Many drugs have been tried for the *prophylaxis* of mucositis caused by antineoplastic therapy, by modifying exposure of the oral mucosa to chemotherapy, modifying epithelial proliferation, or reducing the potential for infection and inflammatory complications of mucositis.[1] Some drugs showed limited evidence of benefit in small studies, including benzydamine, betacarotene, granulocyte-macrophage colony-stimulating factor, povidone-iodine, propantheline bromide, vitamin E, and tretinoin. There are conflicting reports of benefit from studies of sucralfate and chlorhexidine. Other options that have been tried with less success include aciclovir, allopurinol, dinoprostone, glutamine, misoprostol, pentoxifylline, and bacterial and fungal decontamination.

A large systematic review[2] considered many of these and found that some drugs showed evidence of benefit, albeit weak, including amifostine, benzydamine, calcium phosphate, honey, hydrolytic enzymes, iseganan, and zinc sulfate; local cooling with ice chips and Chinese medicinal herb mixtures also showed some benefit. Practice guidelines[3] also suggested that local cooling may prevent oral mucositis associated with bolus fluorouracil or edatrexate and that ranitidine or omeprazole may prevent epigastric pain after treatment with cyclophosphamide, methotrexate, and fluorouracil, or after fluorouracil with or without folinic acid. Palifermin may prevent oral mucositis in patients with haematological neoplasms given high-dose chemotherapy and total body irradiation before autologous stem cell transplantation. Local cooling may be used in patients given high-dose melphalan. Amifostine may prevent radiation proctitis in those receiving standard-dose radiotherapy for rectal cancer, and although it has been suggested that it may reduce oesophagitis associated with chemoradiotherapy for non-small cell lung cancer,[3] others feel that data are insufficient to recommend routine use in such patients.[4]

There will be some overlap between measures for prophylaxis and treatment of mucositis, and another systematic review[5] of *treatment* strategies found that there was some evidence that topical allopurinol or granulocyte-macrophage colony-stimulating factor might improve chemotherapy-induced oral mucositis, but the evidence was weak and unreliable. Given the number of variables involved in the development of mucositis it is unlikely that any one prophylactic or treatment regimen will prove suitable for all patients.

1. Knox JJ, *et al.* Chemotherapy-induced oral mucositis: prevention and management. *Drugs Aging* 2000; 17: 257–67.
2. Worthington HV, *et al.* Interventions for preventing oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 16/07/08).
3. Keefe DM, *et al.* The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; 109: 820–31. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/114078093/PDFSTART (accessed 16/07/08).
4. Hensley ML, *et al.* American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009; 27: 127–45.
5. Clarkson JE, *et al.* Interventions for treating oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 26/01/10).

Nausea and vomiting. For a detailed discussion of the management of chemotherapy-induced nausea and vomiting, see p. 1814.3.

Neurotoxicity. Overall management of neurotoxicity comprises prevention, restoration of function, and symptomatic treatment.[1] Many agents have been tried for neuroprotection, including amifostine, carnitine, erythropoietin, glutamine, glutathione, and vitamin E.[1-4] Drug regimes have also been modified in an attempt to prevent neurotoxicity.[1] Treatment is supportive and symptomatic; pain management is similar to the management of other types of neuropathic pain.[1] Non-pharmacological interventions have also been investigated.[2]

1. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst* 2008; 13: 27–46.
2. Visovsky C, *et al.* Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. *Clin J Oncol Nurs* 2007; 11: 901–13.
3. Walker M, Ni O. Neuroprotection during chemotherapy: a systematic review. *Am J Clin Oncol* 2007; 30: 82–92.
4. Cavaletti G, Marmiroli P. The role of growth factors in the prevention and treatment of chemotherapy-induced peripheral neurotoxicity. *Curr Drug Saf* 2006; 1: 35–42.

Osteoporosis. Bone loss that occurs with cancer therapy is generally more rapid and severe than postmenopausal bone loss in women or normal age-related osteoporosis in men. However, treatment principles are generally the same. For a detailed discussion on the management of osteoporosis, see p. 1168.1.

Further references.

1. Michaud LB, Goudin S. Cancer-treatment-induced bone loss, part 1. *Am J Health-Syst Pharm* 2006; 63: 419–30.
2. Michaud LB, Goudin S. Cancer-treatment-induced bone loss, part 2. *Am J Health-Syst Pharm* 2006; 63: 534–46.
3. Guise TA. Bone loss and fracture risk associated with cancer therapy. *Oncologist* 2006; 11: 1121–31.

Thromboembolism. For discussion on the management of venous or arterial thrombosis, see Effects on the Cardiovascular System, p. 727.2.

Tumour lysis syndrome. Management of tumour lysis syndrome is based on hydration, correction of metabolic abnormalities, and supportive treatment of renal failure.[1-3] Aggressive hydration with isotonic sodium chloride reduces concentrations of uric acid, phosphate, and potassium, and should be considered in all patients at risk of the syndrome, except those at risk of volume overload. Management of acute hyperkalaemia may include cardiac membrane stabilisation with calcium gluconate, intracellular shift of potassium using insulin (with glucose) or inhaled beta$_2$ agonists, and increased excretion of potassium by diuretics or dialysis. In the management of hyperuricaemia[1,3,4] allopurinol may be given prophylactically to reduce the formation of uric acid, and rasburicase may be used for both prophylaxis and treatment by increasing uric acid oxidation. Adequate hydration, sometimes with urinary alkalinisation using sodium bicarbonate, also improves the solubility and hence renal excretion of uric acid.

1. Davidson MB, *et al.* Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med* 2004; 116: 546–54.
2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004; 127: 3–11.
3. Coiffier B, *et al.* Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008; 26: 2767–78.
4. Holdsworth MT, Nguyen P. Role of i.v. allopurinol and rasburicase in tumor lysis syndrome. *Am J Health-Syst Pharm* 2003; 60: 2213–24.

Precautions

In view of their severe toxicity and possible carcinogenicity these drugs should generally be reserved for severe or life-threatening disease, and it is widely suggested that their use should be confined to experienced staff in specialised centres.

Immunosuppression and bone-marrow depression are features of many of these drugs and their use is associated with an increased risk of infections caused by pathogenic or opportunistic micro-organisms, and a reduced capacity to cope with them. Where possible, immunosuppressant drugs should not be given to patients with acute infections, and dosage reduction or withdrawal should be considered if infection develops, until the infection has been controlled. For cautions regarding the use of vaccines in patients receiving these drugs see Interactions, p. 733.3. For discussion of the treatment of infections in immunosuppressed patients, see p. 186.3. Special care is necessary in debilitated patients.

Blood counts and measurement of haemoglobin concentrations should be carried out routinely to help predict the onset of bone-marrow depression. Great caution is needed when the marrow is already depressed from radiotherapy or therapy with other antineoplastics, and modification of dosage regimens may be required. The blood counts below which treatment is contra-indicated will vary depending on the regimen to be used and the therapeutic intent of that treatment (see Bone-Marrow Depression, p. 730.3); local protocols, including those for the use of colony-stimulating factors, should always be consulted.

Although positive evidence of teratogenicity in humans is not available for all antineoplastics, pregnancy should be avoided in women receiving them: in particular they should not be given, if possible, during the first trimester. Mothers receiving antineoplastic therapy should not breast feed. Because some regimens may result in permanent infertility, the storage of semen samples for male patients, and embryos for females before such therapy may be desirable.

Many antineoplastics are vesicant or irritant. Care must be taken to avoid extravasation since severe pain and tissue damage may ensue. They must be handled with great care and contact with skin and eyes avoided; they should not be inhaled. In many countries official or professional guidelines on precautions for the safe handling of cytotoxic drugs have been issued.

For precautions specific to particular drugs, see under the individual monographs.

Administration. Oral antineoplastic drugs have the same potential for treatment-related toxicity and serious medication errors as intravenous antineoplastic drugs.[1] The National Patient Safety Agency (NPSA) in the UK received 3 reports of fatalities and 400 safety incidents with oral antineoplastic drugs between November 2003 and July 2007. Errors included the incorrect dose, frequency, quantity, or duration of medication.[2] The NPSA has recommended that the prescribing, dispensing, and use of oral antineoplastics (excluding hormonal therapy) should be carried out and monitored to the same standard as that of parenteral therapy, requiring the inclusion of some of the following procedures:

- treatment should be started by a cancer specialist
- prescription in the context of a written protocol and treatment plan, including guidance on monitoring and treatment of toxicity
- access to the written protocol and treatment plan, and access to advice from an experienced cancer pharmacist, for non-specialist prescribers and dispensers
- patients should be provided with written information, including details of the original regimen and treatment plan and arrangements for monitoring

Recommendations for the dispensing and supply of oral chemotherapy in the primary care setting have been made by specialist organisations.[1]

Doses of antineoplastics are determined using different methods, including body-surface area or body-weight; alternatively, doses may be fixed. Doses are further adjusted after consideration of a patient's individual health status. Dose regimens may be complex and may differ depending on its indication, or on whether a drug is used as monotherapy or as part of a combination regimen. The *BNF* omits some dose statements of antineoplastic drugs for this reason, while stating that, even where dose statements are given, specialist literature, chemotherapy protocols, or local cancer networks should be consulted before prescribing, dispensing, and giving these drugs; furthermore, they advocate that prescriptions for these drugs should not be repeated without specialist instruction.

1. Williamson S. British Oncology Pharmacy Association, Royal Pharmaceutical Society, National Pharmacy Association. A report on the dispensing and supply of oral chemotherapy and systemic anticancer medicines in primary care (issued January 2011). Available at: http://www.rpharms.com/support-pdfs/providing-oral-chemotherapy-in-the-community.pdf (accessed 07/07/11)
2. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR001 (issued 22nd January, 2008): risks of incorrect dosing of oral anti-cancer medicines. Available at: www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60278&type=full&servicetype=Attachment (accessed 07/07/11)

Administration in the elderly. The use of antineoplastics in the elderly should take into consideration age-related physiological changes including decline in renal and hepatic function, reduced haematopoietic reserve, and reduced gastrointestinal and cardiac function. Other factors to consider are comorbid conditions and potential drug interactions with associated medications.[1-9] Neoplastic disorders in the elderly have been undertreated because of an impression that these diseases are less aggressive,[10] and the effects of chemotherapy more likely to be severe.[1,2,10,11] Elderly patients have often been excluded from clinical studies for reasons that included physician bias, protocol eligibility criteria with restrictions on comorbidities, and poor patient functional status.[2] There is evidence, however, that healthy older patients can tolerate chemotherapy as well as younger patients.[1,2] However, there have been few studies of chemotherapy specifically in elderly patients,[4,10] and selection of a suitable dosage regimen is more difficult as a consequence, although there is increasing effort to address this lack of data.[2,10,11] Old people vary as much as any other group in their response to drugs, and the consensus is that they should not be excluded from any form of treatment on the grounds of age alone.

1. Kimmick GG, *et al.* Cancer chemotherapy in older adults: a tolerability perspective. *Drugs Aging* 1997; 10: 34–49.
2. Lichtman SM, Skirvin JA. Pharmacology of antineoplastic agents in older cancer patients. *Oncology (Huntingt)* 2000; 14: 1743–55.
3. Wildiers H, *et al.* Pharmacology of anticancer drugs in the elderly population. *Clin Pharmacokinet* 2003; 42: 1213–42.

4. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25**: 1832–43.
5. Hurria A, Lichtman SM. Pharmacokinetics of chemotherapy in the older patient. *Cancer Control* 2007; **14**: 32–43.
6. Lichtman SM, Boparai MK. Anticancer drug therapy in the older cancer patient: pharmacology and polypharmacy. *Curr Treat Options Oncol* 2008; **9**: 191–203.
7. Balducci L. Pharmacology of antineoplastic medications in older cancer patients. *Oncology (Williston Park)* 2009; **23**: 78–85.
8. Balducci L. Supportive care in elderly cancer patients. *Curr Opin Oncol* 2009; **21**: 310–17.
9. Gillison TL, Chatta GS. Cancer chemotherapy in the elderly patient. *Oncology (Williston Park)* 2010; **24**: 76–85.
10. Balducci L, Beghe' C. Cancer and age in the USA. *Crit Rev Oncol Hematol* 2001; **37**: 137–45.
11. Muss HB. Older age—not a barrier to cancer treatment. *N Engl J Med* 2001; **345**: 1128–9.
12. Townsley CA, *et al.* Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; **23**: 3112–24.

Administration at home. Outpatients taking oral antineoplastic therapy (such as capecitabine or tegafur with uracil) at home do not receive the same level of monitoring as inpatients, and should be cautioned to report any adverse effects, since such treatments may still produce severe toxicity. Problems with home administration include non-compliance, interactions with other drugs and food, and medication errors. However, many patients prefer oral therapy to intravenous administration, and such problems can be managed with better communication and patient education. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Bleyer WA, Danielson MG. Oral cancer chemotherapy in paediatric patients: obstacles and potential for development and utilisation. *Drugs* 1999; **58** (suppl 3): 133–40.
2. Hollywood E, *et al.* Nursing strategies for patients on oral chemotherapy. *Oncology (Williston Park)* 2001; **15** (1 suppl 2): 37–9.
3. Borner M, *et al.* 'Answering patients' needs: oral alternatives to intravenous therapy. *Oncologist* 2001; **6** (suppl 4): 12–16.
4. Gerbrecht B-M. Current Canadian experience with capecitabine: partnering with patients to optimize therapy. *Cancer Nurs* 2003; **26**: 161–7.
5. Gerbrecht B-M, Kangas T. Implications of capecitabine (Xeloda) for cancer nursing practice. *Eur J Oncol Nurs* 2004; **8** (suppl 1): S63–S71.
6. Bartel SB. Safe practices and financial considerations in using oral chemotherapeutic agents. *Am J Health-Syst Pharm* 2007; **64** (9 suppl 5): S8–S14.
7. Aisner J. Overview of the changing paradigm in cancer treatment: oral chemotherapy. *Am J Health-Syst Pharm* 2007; **64** (9 suppl 5): S4–S7.

Contraception. The *BNF* recommends that intra-uterine devices for contraception be used with caution in patients with drug- or disease-induced immunosuppression, because of the risk of infection; such devices are contra-indicated in marked immunosuppression.

Handling and disposal. Antineoplastics are usually potent and potentially highly toxic drugs that must be handled with due care. In many countries official or professional guidelines are available for the handling, reconstitution, and disposal of antineoplastics, and most centres or institutions in which these drugs are used will have individual handling policies based on these.[1]

Recommendations generally include:

- that these drugs be reconstituted by trained personnel;
- that reconstitution take place in designated areas, designed to protect personnel and the environment—for example, the use of safety cabinets;
- that protective clothing be worn, including gloves, eye protection, and masks if necessary (it should be noted that gloves may vary in their resistance to penetration, depending upon their thickness, the material of which they are made, and the drug in question[1,2]);
- that waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (it should be noted that the patient's body fluids and excreta may contain appreciable amounts of antineoplastic agents and it has been suggested that they and materials such as bed linen contaminated with them should also be treated as hazardous waste[3,4]);
- that adequate procedures should be in place for accidental contamination due to spillages;
- that staff exposure to antineoplastic agents be recorded and monitored;
- that pregnant staff should avoid handling these drugs if possible.

1. Allwood M, *et al.* eds. *The Cytotoxic Handbook.* 4th ed. Oxford: Radcliffe Medical Press,2002.
2. Connor TH. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. *Am J Health-Syst Pharm* 1999; **56**: 2430–3.
3. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235**: 289–91.
4. Cass Y, Musgrave CF. Guidelines for the safe handling of excreta contaminated by cytotoxic agents. *Am J Hosp Pharm* 1992; **49**: 1957–8.

Pregnancy. Antineoplastics may be used during pregnancy for their immunosuppressant properties in auto-immune disease, and for the treatment of cancer, which can complicate 1 in 1000 pregnancies.[1-3] Although the use of potentially teratogenic drugs would normally be avoided during pregnancy, the risk to the mother of inadequate treatment may outweigh whatever risks exist of abnormality in the fetus.[1]

The highest incidence of adverse effects appears to occur after exposure during the first trimester:[1-4] about 10 to 20% of fetuses exposed to cytotoxics during this period have major malformations, compared with 3% in the general population.[1] Malformations reflect the gestational age at exposure. The fetus is particularly vulnerable when exposed during organogenesis (weeks 2 to 8 after conception), and the heart, neural tube, and limbs are affected earlier than the palate and ear; after organogenesis, the eyes, genitalia, haematopoietic system, and CNS remain vulnerable to continued exposure.[3]

The risk of fetal malformations after exposure during the second and third trimesters is probably no higher than the background rate, but there may still be an increased risk of still-birth, fetal growth restriction, premature birth, and maternal or fetal myelosuppression.[1-3]

The delayed effects of antineoplastics on development have not been well-documented. Despite concerns that premature birth and low birth-weight could contribute to retardation of growth, development, and intellect,[5] long-term follow-up of a limited number of children has not shown any evidence of abnormalities.[3-5] Similarly, although maternal antineoplastic therapy has been implicated in a case of childhood neuroblastoma and papillary thyroid cancer, the child's fraternal twin, exposed to the same drugs *in utero*, was healthy.[3] There have been no reports of secondary leukaemias in exposed offspring, but the longer term risk is unknown.[3]

The teratogenicity of any drug depends on the timing of exposure, the dose, and the characteristics affecting placental transfer,[3] as well as the actions of the drug. Of the antineoplastics, the greatest risk seems to be associated with alkylating agents and antimetabolites, in particular aminopterin, fluorouracil, and methotrexate.[1,2,6] The vinca alkaloids and doxorubicin (but not epirubicin or idarubicin) may entail less risk,[2,3] although the former have produced malformations in *animals*.[1] Other drugs reported to be teratogenic or potentially teratogenic include busulfan,[1] chlorambucil,[1,6] chlormethine,[1] cyclophosphamide,[1,6] cytarabine,[1] and the podophyllotoxin derivatives.[1] The problems with thalidomide and its congeners are well known.

There are no specific dosage recommendations for the use of antineoplastics during pregnancy, but physiological changes occurring in the mother can alter the pharmacokinetics of drugs.[1-3] This could potentially increase the toxicity of the antineoplastic, or decrease its efficacy.[2] Anecdotal evidence suggests that adverse effects may be less marked during pregnancy, perhaps reflecting reduced peak or free-drug concentrations in the blood.[3] Myelosuppressive chemotherapy should be avoided 3 weeks before the anticipated delivery so that the mother is neither neutropenic nor thrombocytopenic.[1-3] For the same reason, chemotherapy should be avoided after 35 weeks of gestation, when spontaneous delivery is more likely to occur.[3] The timing of delivery is also critical for the neonate, as chemotherapy given shortly before delivery may not be eliminated through the placenta, prolonging exposure in the newborn.[1,3]

There has also been concern that long-term *occupational exposure* to antineoplastics might have an adverse effect on the fetus of pregnant healthcare workers: a study in 650 Finnish nurses found that women who experienced fetal loss were more than twice as likely to have had first trimester exposure to antineoplastic drugs as women who successfully gave birth.[7] These results have been criticised on the grounds that such results are not generally seen in cancer patients,[8,9] who presumably are exposed to much higher doses of antineoplastics. However, similar results were seen in a cross-sectional analysis of 7094 pregnancies involving 2815 nursing and pharmacy staff.[10] Another study[11] has suggested that the rate of ectopic pregnancy may be increased in nurses occupationally exposed to antineoplastics, but the small number of ectopic pregnancies involved (15 in 734 pregnancies) means that the association with antineoplastics may be due to chance. A further, larger, case-control study[12] by the same investigators found no evidence of an increased rate of ectopic pregnancy, and suggested that occupational exposure to higher levels of antineoplastics in the past possibly explained the earlier findings. Again, such an effect does not appear to have been reported in women treated with antineoplastics.

See also Effects on Reproductive Potential, p. 729.2.

1. Buekers TE, Lallas TA. Chemotherapy in pregnancy. *Obstet Gynecol Clin North Am* 1998; **25**: 323–9.
2. Falkenberry SS. Cancer in pregnancy. *Surg Oncol Clin N Am* 1998; **7**: 375–97.
3. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004; **5**: 283–91.
4. Gwyn K. Children exposed to chemotherapy in utero. *J Natl Cancer Inst Monogr* 2005; 69–71.
5. Partridge AH, Garber JE. Long-term outcomes of children exposed to antineoplastic agents in utero. *Semin Oncol* 2000; **27**: 712–26.
6. Østensen M, Ramsey-Goldman R. Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? *Drug Safety* 1998; **19**: 389–410.
7. Selevan SG, *et al.* A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. *N Engl J Med* 1985; **313**: 1173–8.
8. Kalter H. Antineoplastic drugs and spontaneous abortion in nurses. *N Engl J Med* 1986; **314**: 1048–9.
9. Mulvihill JJ, Stewart KR. Antineoplastic drugs and spontaneous abortion in nurses. *N Engl J Med* 1986; **314**: 1049.
10. Valanis B, *et al.* Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med* 1999; **41**: 632–8.
11. Saurel-Cubizolles MJ, *et al.* Ectopic pregnancy and occupational exposure to antineoplastic drugs. *Lancet* 1993; **341**: 1169–71.
12. Bouyer J, *et al.* Ectopic pregnancy and occupational exposure of hospital personnel. *Scand J Work Environ Health* 1998; **24**: 98–103.

Interactions

Because of their effects on the gastrointestinal mucosa antineoplastics have the potential to interfere with the absorption of drugs given orally. Antineoplastics that have an immunosuppressant effect may reduce the response to vaccines, and there is a possibility of generalised infection with live vaccines. Use with live vaccines should generally be avoided.

Many antineoplastics are inhibitors of certain isoenzymes of cytochrome P450 and some antineoplastics are also metabolised by these enzymes, and in consequence the possibility of interactions between antineoplastics, or between antineoplastics and other medication, cannot be discounted.

Interactions affecting specific drugs are covered under the individual monographs.

References.

1. Le Blanc GA, Waxman DJ. Interaction of anticancer drugs with hepatic monooxygenase enzymes. *Drug Metab Rev* 1989; **20**: 395–439.
2. Loadman PM, Bibby MC. Pharmacokinetic drug interactions with anticancer drugs. *Clin Pharmacokinet* 1994; **26**: 486–500.
3. Kivistö KT, *et al.* The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. *Br J Clin Pharmacol* 1995; **40**: 523–30.
4. McLeod HL. Clinically relevant drug-drug interactions in oncology. *Br J Clin Pharmacol* 1998; **45**: 539–44.
5. Beijnen JH, Schellens JHM. Drug interactions in oncology. *Lancet Oncol* 2004; **5**: 489–96.
6. Singh BN, Malhotra BK. Effects of food on the clinical pharmacokinetics of anticancer agents: underlying mechanisms and implications for oral chemotherapy. *Clin Pharmacokinet* 2004; **43**: 1127–56.
7. Riechelmann RP, Saad ED. A systematic review on drug interactions in oncology. *Cancer Invest* 2006; **24**: 704–12.
8. Harmsen S, *et al.* The role of nuclear receptors in pharmacokinetic drug-drug interactions in oncology. *Cancer Treat Rev* 2007; **33**: 369–80.
9. Riechelmann RP, Del Giglio A. Drug interactions in oncology: how common are they? *Ann Oncol* 2009; **20**: 1907–12.

Antiepileptics. Retrospective review of outcomes in children treated for acute lymphoblastic leukaemia indicated that long-term antiepileptic therapy increased the clearance of several antileukaemic drugs and reduced the efficacy of therapy.[1] Management of patients with brain tumours or metastases, which may predispose patients to convulsions, thus poses particular problems in the choice of antiepileptic treatment if interactions are to be avoided; the topic has been reviewed.[2,3]

1. Relling MV, *et al.* Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet* 2000; **356**: 285–90.
2. Vecht CJ, *et al.* Treating seizures in patients with brain tumors: drug interactions between antiepileptic and chemotherapeutic agents. *Semin Oncol* 2003; **30** (suppl 19): 49–52.
3. Ruggiero A, *et al.* Interactions between antiepileptic and chemotherapeutic drugs in children with brain tumors: is it time to change treatment? *Pediatr Blood Cancer* 2010; **54**: 193–8.

Antivirals. The potential for interaction between antiretrovirals and antineoplastics has been reviewed.[1] Although clinical evidence of interactions is scanty, various HIV-protease inhibitors and NNRTIs can inhibit or induce cytochrome P450 isoenzymes, and thus have the potential to interact with some antineoplastics including taxanes, vinca alkaloids, and cyclophosphamide.

1. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet* 2005; **44**: 111–45.

Antoxidants. The potential for interactions between antoxidants and antineoplastics has been reviewed.[1] Theoretically, antoxidants might reduce the efficacy of antineoplastic chemotherapy. The authors raised three concerns regarding this effect:

- *acetylcysteine* should not be used with *cisplatin* or *doxorubicin*;
- *tangeretin*, a flavonoid, should not be used with *tamoxifen*; and
- *betacarotene* should not be used with *fluorouracil*.

Aside from these possible interactions, no *in-vivo* evidence was found to suggest that natural antoxidants interfere with conventional cancer chemotherapy.

1. Lamson DW, Brignall MS. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. *Altern Med Rev* 1999; **4**: 304–29.

Effects on other drugs. Antineoplastics have been reported to affect several drugs including:

- digoxin (reduced absorption, see p. 1357.1)

- oral anticoagulants (increased or decreased effect, see Warfarin, p. 1532.2)
- phenytoin (increased or decreased effect, see p. 544.1)
- suxamethonium (prolonged effect, see p. 2039.3)
- vaccines (decreased response, see p. 2375.3).

Herbal medicines. The potential for interactions between antineoplastics and herbal medicines has been reviewed.[1,2] There is a general lack of information and reports, and warnings are largely based on theory and extrapolation from herbal interactions with other drugs.

1. Sparreboom A, *et al.* Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol* 2004; **22**: 2489–2503.
2. Yeung KS, Gubili J. Clinical guide to herb-drug interactions in oncology. *J Soc Integr Oncol* 2007; **5**: 113–17.

Pharmacokinetics

Many antineoplastics have intra- and interindividual pharmacokinetic variability that can be influenced by various factors. Patient age, disease state, and drug interactions can affect drug absorption, distribution, metabolism, and excretion. Genetic polymorphisms also affect drug disposition and are under investigation, but the clinical use of such information is currently limited. Various methods have been tried or are being investigated as ways of tailoring initial drug dosage and therapeutic drug monitoring for individual patients in order to improve treatment efficacy and minimise toxicity. Such methods include population pharmacokinetic modelling and individual pharmacogenetic typing; examples include carboplatin dosing based on glomerular filtration rate (see Administration, p. 759.2) and genotyping of patients thought to be at increased risk of irinotecan toxicity (see Genetic Factors, p. 813.3).

Reviews.

1. Schrijvers D. Role of red blood cells in pharmacokinetics of chemotherapeutic agents. *Clin Pharmacokinet* 2003; **42**: 779–91.
2. Tomita M, *et al.* Effect of haemodialysis on the pharmacokinetics of antineoplastic drugs. *Clin Pharmacokinet* 2004; **43**: 515–27.
3. Fleischhack G, *et al.* Pharmacokinetics following intraventricular administration of chemotherapy in patients with neoplastic meningitis. *Clin Pharmacokinet* 2005; **44**: 1–31.
4. de Jonge ME, *et al.* Individualised cancer chemotherapy: strategies and performance of prospective studies on therapeutic drug monitoring with dose adaptation: a review. *Clin Pharmacokinet* 2005; **44**: 147–73.
5. Undevia SD, *et al.* Pharmacokinetic variability of anticancer agents. *Nat Rev Cancer* 2005; **5**: 447–58.
6. Scripture CD, *et al.* Modulation of cytochrome P450 activity: implications for cancer therapy. *Lancet Oncol* 2005; **6**: 780–9.
7. Bosch TM, *et al.* Genetic polymorphisms of drug-metabolising enzymes and drug transporters in the chemotherapeutic treatment of cancer. *Clin Pharmacokinet* 2006; **45**: 253–85.
8. Yong WP, *et al.* The role of pharmacogenetics in cancer therapeutics. *Br J Clin Pharmacol* 2006; **62**: 35–46.
9. Hurria A, Lichtman SM. Pharmacokinetics of chemotherapy in the older patient. *Cancer Control* 2007; **14**: 32–43.
10. Alnaim L. Therapeutic drug monitoring of cancer chemotherapy. *J Oncol Pharm Pract* 2007; **13**: 207–21.
11. Hunter RJ, *et al.* Dosing chemotherapy in obese patients: actual versus assigned body surface area (BSA). *Cancer Treat Rev* 2009; **35**: 69–78.
12. Phan VH, *et al.* Ethnic differences in drug metabolism and toxicity from chemotherapy. *Expert Opin Drug Metab Toxicol* 2009; **5**: 243–57.

Action

Much of the development of cancer chemotherapy has been based on an understanding of the way in which tumour cells grow, and the way in which the drugs affect this growth.

After cell division the daughter cells enter a period of growth, G_1, which lasts for different lengths of time in different tissues. This is followed by a period of DNA synthesis, **S**, in which the amount of chromosomal material is doubled, then a postsynthetic, or premitotic, phase, G_2, then finally by mitotic cell division, **M**. As an alternative to re-entering the cycle, the products of cell division may enter a kinetically-dormant, nonproliferative stage, G_0, although it is not exactly clear what recruits such 'resting' cells back into the cell cycle.

The rate of cell division varies for different tumours; the doubling time for Burkitt's lymphoma and acute lymphoblastic leukaemia is less than 5 days, whereas the mean doubling time for seminoma is about 20 days, that for small-cell lung cancer about 50 days, and those for colon cancer and advanced breast cancer about 100 and 150 days respectively. The range of reported doubling times may also vary widely for a particular tumour type. Most common cancers increase very slowly in size in comparison with sensitive normal tissues, including those from which they derive, and the rate may decrease further in large tumours. This difference allows normal cells to recover more quickly than malignant ones from chemotherapy, and is the rationale behind cyclic dosage schedules. The lethal body tumour burden is reached when the tumour cell mass approaches or exceeds 1×10^{12} cells, equivalent to about 1 kg of tissue, and representing about 40 doublings.

Cell killing by cytotoxic agents is generally a first order process, so a given dose or course of antineoplastic kills a fixed percentage of tumour cells rather than a fixed number. Thus a drug that killed 99% of tumour cells would leave behind 10^{10} cells from a tumour containing 10^{12} cells, but only 10^2 cells from one containing 10^4, reinforcing the importance of treating malignant neoplasms as early as possible.

Cytotoxic drugs act to damage the reproductive integrity of cells. Some are active at a particular stage of the cell cycle. The antimetabolites interfere with DNA synthesis, as does hydroxycarbamide, and are thus active against cells in S phase, while the vinca alkaloids inhibit microtubular function and act on cells in phase M. Other drugs such as the alkylating agents, the anthracyclines, and cisplatin are not phase-specific, but since their actions are dependent at least in part on damaging DNA they are more effective against proliferating cells, particularly in S phase. It is now thought that many antineoplastics exert their ultimate effect by inducing cellular apoptosis (programmed cell death). Some drugs, such as bleomycin or vinblastine also have the property of arresting the cycle in a particular phase, and attempts have been made to synchronise tumour cell division in this way, to maximise the number of cells in a sensitive phase when a particular drug is used. However, in practice this approach has been less successful than early experimental results suggested.

Some drugs used in the treatment of neoplasms do not attack the tumour cells directly but are given in order to increase cell vulnerability to other modalities: these include radiosensitisers (which have proved of only limited benefit to date), and photosensitisers such as porfimer sodium, used in photodynamic therapy (PDT).

Apart from attacking cell division, increased understanding of the molecular biology of tumour cells has begun to open the possibility of other approaches to the treatment of malignant neoplasms. Some monoclonal antibodies are designed to bind to specific cell-surface proteins or receptors, enabling the immune system to recognise and attack tumour cells (targeted therapy); anti-tumour vaccines have also been developed. Control of tumour growth through inhibition of angiogenesis is also being used. Other areas of investigation include inducing tumour cells to differentiate into non-malignant forms, manipulation of cellular apoptosis and signal transduction, inhibiting the expression of abnormal growth factors, telomerases and other oncogene products (including the use of ribozymes or of 'antisense' compounds which inhibit oncogenic messenger RNA), and prevention or inhibition of metastasis. Gene therapy (p. 2511.2) is another form of treatment under consideration.

Some references to newer modes of cancer therapy.

1. Cox AD. Farnesyltransferase inhibitors: potential role in the treatment of cancer. *Drugs* 2001; **61**: 723–32.
2. Miller KD, *et al.* Redefining the target: chemotherapeutics as antiangiogenics. *J Clin Oncol* 2001; **19**: 1195–1206.
3. Kerbel RS. Clinical trials of antiangiogenic drugs: opportunities, problems, and assessment of initial results. *J Clin Oncol* 2001; **19** (suppl): 45s–51s.
4. Dermime S, *et al.* Cancer vaccines and immunotherapy. *Br Med Bull* 2002; **62**: 149–62.
5. Pirollo KF, *et al.* Antisense therapeutics: from theory to clinical practice. *Pharmacol Ther* 2003; **99**: 55–77.
6. Kerbel RS. Antiangiogenic drugs and current strategies for the treatment of lung cancer. *Semin Oncol* 2004; **31** (suppl 1): 54–60.
7. Blanco R, *et al.* Key cancer cell signal transduction pathways as therapeutic targets. *Eur J Cancer* 2006; **42**: 290–4.
8. Chernajovsky Y, *et al.* Fighting cancer with oncolytic viruses. *BMJ* 2006; **332**: 170–2.
9. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. *J Clin Oncol* 2006; **24**: 1770–83.
10. Eastman A, Perez RP. New targets and challenges in the molecular therapeutics of cancer. *Br J Clin Pharmacol* 2006; **62**: 5–14.
11. Dangoor A, *et al.* Cancer vaccines: a clinical perspective. *Br J Hosp Med* 2006; **67**: 365–9.
12. Jordan CT, *et al.* Cancer stem cells. *N Engl J Med* 2006; **355**: 1253–61.
13. Eccles SA, Welch DR. Metastasis: recent discoveries and novel treatment strategies. *Lancet* 2007; **369**: 1742–57.
14. Hinnen P, Eskens FALM. Vascular disrupting agents in clinical development. *Br J Cancer* 2007; **96**: 1159–65.
15. Hsieh AC, Moasser MM. Targeting HER proteins in cancer therapy and the role of the non-target HER3. *Br J Cancer* 2007; **97**: 453–7.
16. Press MF, Lenz H-J. EGFR, HER2 and VEGF pathways: validated targets for cancer treatment. *Drugs* 2007; **67**: 2045–75.
17. Croce CM. Oncogenes and cancer. *N Engl J Med* 2008; **358**: 502–11.
18. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med* 2008; **358**: 1160–74.
19. Newsome BW, Ernstoff MS. The clinical pharmacology of therapeutic monoclonal antibodies in the treatment of malignancy: have the magic bullets arrived? *Br J Clin Pharmacol* 2008; **66**: 6–19.
20. Roy R, *et al.* Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer. *J Clin Oncol* 2009; **27**: 5287–97.
21. Lane AA, Chabner BA. Histone deacetylase inhibitors in cancer therapy. *J Clin Oncol* 2009; **27**: 5459–68.
22. Kim LC, *et al.* Src kinases as therapeutic targets for cancer. *Nat Rev Clin Oncol* 2009; **6**: 587–95.
23. Schwock J, *et al.* Targeting focal adhesion kinase signaling in tumor growth and metastasis. *Expert Opin Ther Targets* 2010; **14**: 77–94.

Resistance

Resistance to antineoplastics is one of the greatest limitations to the use of chemotherapy in malignant disease. Resistance may be intrinsic to the tumour or may be acquired during chemotherapy, which effectively acts to select resistant cells from a heterogeneous population; the latter is one reason that relapses, or malignancies in heavily-pretreated patients, may be particularly difficult to treat.

The mechanisms of resistance in cancer cells are complex and imperfectly understood, but appear to include:

- hypoxia and imperfect drug penetration in the centre of large, solid tumours
- the small proportion of cells actively dividing and thus vulnerable to antineoplastics (particularly in slow-growing tumours)
- decreased cellular uptake or increased efflux of antineoplastic
- increased metabolic breakdown or decreased activation of antineoplastic
- increased expression of target enzymes
- metabolism via alternative biochemical pathways to those blocked by the antineoplastic
- more efficient repair of damaged DNA
- possibly the expression of genes which inhibit drug-induced apoptosis.

Several of these mechanisms may be in operation at one time. Much interest has been expressed in the potential use of drugs which can modulate or inhibit mechanisms of resistance, and in particular in compounds such as valspodar, verapamil, quinidine, and ciclosporin, which have the ability to block the action of P-glycoprotein, a membrane glycoprotein which acts as an efflux pump for a range of cytotoxic substances and which is one of a group of so-called ATP-binding cassette (ABC) drug transporters responsible for the multidrug resistant (MDR) phenotype. However, for sustained benefit it seems likely that several drugs would be required, each to overcome a different mechanism of resistance, and it would be necessary to ensure that toxicity of antineoplastics to normal cells was not also enhanced.

If the emergence of heritable resistant phenotypes is a natural part of tumour-cell biology (the Goldie-Coldman hypothesis) it implies that the larger and older the tumour, the more likely is resistance to occur. This would confirm the benefits of surgery and radiotherapy to shrink the primary tumour, and of starting chemotherapy as soon as possible after (a preferably early) diagnosis.

Antiresistance agents. Some drugs have been reported to partially abolish multidrug resistance to antineoplastics *in vitro*.[1,2] These include:

- verapamil, its enantiomers and analogues such as Ro-11-2933
- other calcium-channel blockers including prenylamine, diltiazem, nifedipine analogues such as nicardipine and bepridil
- various phenothiazines and thioxanthenes including trifluoperazine and the *trans*-isomer of flupentixol
- structural analogues of the anthracyclines and vinca alkaloids
- progesterone and other steroid hormones, as well as, to some extent, anti-oestrogens such as tamoxifen
- ciclosporin and various of its nonimmunosuppressive analogues (such as valspodar)
- miscellaneous drugs including amiodarone, quinidine, propranolol, reserpine, yohimbine, dipyridamole, erythromycin, cefoperazone, and ceftriaxone

However, despite reported effects on resistance *in vitro* clinical results may be less impressive: studies in which verapamil was added to therapy for small cell lung cancer[3] or multiple myeloma[4] failed to show any benefit, and second-generation P-glycoprotein inhibitors such as valspodar have unpredictable pharmacokinetic interactions with cytotoxics.[5] Nevertheless, there is ongoing development of inhibitors of P-glycoprotein and other ATP-binding cassette drug transporters,[6] and drugs such as tariquidar are undergoing clinical studies.[5] It has been suggested that tumour growth may rely on a malignant equivalent of stem cells, with innate multidrug resistance, and that this may make overcoming resistance without damaging normal stem cells particularly difficult.[7]

1. Ford JM, Bait WN. Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev* 1990; **42**: 155–99.
2. Krishna R, Mayer LD. Multidrug resistance (MDR) in cancer: mechanisms, reversal using modulators of MDR and the role of MDR modulators in influencing the pharmacokinetics of anticancer drugs. *Eur J Pharm Sci* 2000; **11**: 265–83.
3. Milroy R, *et al.* A randomised clinical study of verapamil in addition to combination chemotherapy in small cell lung cancer. *Br J Cancer* 1993; **68**: 813–18.
4. Dalton WS, *et al.* A phase III randomized study of oral verapamil as a chemosensitizer to reverse drug resistance in patients with refractory myeloma: a Southwest Oncology Group Study. *Cancer* 1995; **75**: 815–20.
5. Thomas H, Coley HM. Overcoming multidrug resistance in cancer: an update on the clinical strategy of inhibiting P-glycoprotein. *Cancer Control* 2003; **10**: 159–65.
6. Lee CH. Reversing agents for ATP-binding cassette drug transporters. *Methods Mol Biol* 2010; **596**: 325–40.
7. Donnenberg VS, Donnenberg AD. Multiple drug resistance in cancer revisited: the cancer stem cell hypothesis. *J Clin Pharmacol* 2005; **45**: 872–7.

Abiraterone Acetate (BANM, USAN, rINNM)

Abirateron-azetat; Abiratérone, Acétate d'; Abirateroni Acetas; Acetato de abiraterona; CB-7630; Абиратерона Ацетат.

17-(Pyridin-3-yl)androsta-5,16-dien-3β-yl acetate.

$C_{26}H_{33}NO_2$=391.6

CAS — 154229-19-3 (abiraterone); 154229-18-2 (abiraterone acetate).

UNII — EMSOCB9YJ6.

Uses and Administration

Abiraterone acetate suppresses testosterone production by inhibiting the enzyme CYP17, which plays a key role in sex hormone synthesis, and is given orally with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate cancer (p. 712.3). It is used in patients given previous docetaxel-based chemotherapy, and in those where androgen deprivation therapy has failed but chemotherapy is not yet indicated. Medical castration therapy with a gonadorelin (LHRH) analogue should be continued. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The recommended dose is 1 g daily as a single dose, plus prednisone or prednisolone 5 mg twice daily (or 10 mg daily). Abiraterone should be taken on an empty stomach, at least 2 hours after and one hour before any food. For doses in patients who develop hepatotoxicity or with pre-existing hepatic impairment, see below.

References.
1. Salem M, Garcia JA. Abiraterone acetate, a novel adrenal inhibitor in metastatic castration-resistant prostate cancer. *Curr Oncol Rep* 2011; 13: 92–6.
2. de Bono JS, *et al.* COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; 364: 1995–2005.
3. Yang LPH. Abiraterone acetate: in metastatic castration-resistant prostate cancer. *Drugs* 2011; 71: 2067–77. Correction. *ibid.* 2012; 72: 192.
4. Beckett RD, *et al.* Abiraterone for the treatment of metastatic castrate-resistant prostate cancer. *Ann Pharmacother* 2012; 46: 1016–24.
5. Ryan CJ, *et al.* COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; 368: 138–48. Correction. *ibid.*; 584.

Administration in hepatic impairment. No dose adjustment of abiraterone is necessary for patients with pre-existing mild hepatic impairment (Child-Pugh class A). In patients with baseline moderate hepatic impairment (Child-Pugh class B), US licensed product information recommends that the oral dose of abiraterone acetate be reduced to 250 mg daily. Use in patients with severe hepatic impairment (Child-Pugh class C) should be avoided since data are lacking.

For patients who develop increases in liver enzymes above 5 times the upper limit of normal (ULN) or total bilirubin >3 times ULN during treatment, US licensed product information states that therapy should be interrupted, and only restarted (at a reduced dose of 750 mg daily) once these values have fallen to acceptable levels (baseline or no more than half the increased values above). If hepatotoxicity recurs at the lower dose, a dose of 500 mg daily is recommended once values have fallen to acceptable levels, but if it recurs again, treatment should be stopped.

UK licensed product information states that, for patients who develop increases in liver enzymes above 5 times the ULN, therapy should be stopped, and advocates restarting at 500 mg daily once values return to baseline levels; if hepatotoxicity recurs at this reduced dose, treatment should be stopped. If patients develop increases in enzymes 20 times the ULN at any time while on therapy, abiraterone should be stopped permanently and patients should not be re-treated.

Adverse Effects, Treatment, and Precautions

Abiraterone acetate inhibits the enzyme CYP17, which can result in mineralocorticoid excess, very often leading to hypertension, hypokalaemia, and fluid retention or oedema; patients should be monitored at least monthly for these effects, and treated appropriately. Use with a glucocorticoid can reduce the incidence and severity of these adverse effects. However, adrenocortical insufficiency has been reported in those treated with abiraterone acetate plus prednisone or prednisolone, and patients should be monitored for manifestations of this, particularly after withdrawal from the corticosteroid.

Caution is needed when treating patients with heart failure, recent myocardial infarction, ventricular arrhythmia, or any underlying medical condition likely to be adversely affected by mineralocorticoid effects. Cardiac disorders are common with abiraterone acetate, and include cardiac failure, chest pain, angina pectoris, arrhythmias, atrial fibrillation, and tachycardia.

Hepatotoxicity can occur, and treatment may need to be stopped, or the dose adjusted (see Administration in Hepatic Impairment, above). Serum transaminases and bilirubin levels should be measured before starting treatment, then every two weeks for the first three months, and monthly thereafter.

Joint swelling or discomfort, muscle discomfort, hot flushes, dyspepsia, diarrhoea, cough, urinary-tract infection, urinary frequency, nocturia, and upper respiratory-tract infection are common, as is hypertriglyceridaemia.

Interactions

Abiraterone inhibits the cytochrome P450 isoenzyme CYP2D6; caution is advised when abiraterone acetate is used with drugs activated or metabolised by CYP2D6, especially those with a narrow therapeutic index. *In-vitro studies have shown that abiraterone is also an inhibitor of CYP2C8.*

Abiraterone is metabolised by the cytochrome P450 isoenzyme CYP3A4. Strong inhibitors or inducers of CYP3A4 should be avoided, or used with caution, during treatment with abiraterone acetate.

Pharmacokinetics

Abiraterone acetate is hydrolysed to abiraterone, which is active. Peak plasma concentrations of abiraterone occur about 2 hours after an oral dose of abiraterone acetate. Systemic exposure to abiraterone is increased when abiraterone acetate is given with food. Abiraterone is over 99% bound to plasma proteins. Abiraterone is metabolised via sulfation, hydroxylation, and oxidation, mainly in the liver. The two main metabolites are abiraterone sulfate and *N*-oxide abiraterone sulfate, which are inactive; these are formed by the enzymes SULT2A1, and cytochrome P450 isoenzyme CYP3A4 and SULT2A1, respectively. The mean terminal plasma half-life of abiraterone is reported to be about 15 hours in healthy subjects, and about 12 hours in patients with metastatic castration-resistant prostate cancer. About 88% of a dose is excreted in the faeces, of which about 55% is unchanged abiraterone acetate and about 22% is abiraterone; about 5% of a dose is excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Zytiga; *Canad.*: Zytiga; *Denm.*: Zytiga; *Fr.*: Zytiga; *Ger.*: Zytiga; *Irl.*: Zytiga; *Israel*: Zytiga; *Neth.*: Zytiga; *Norw.*: Zytiga; *Spain*: Zytiga; *Swed.*: Zytiga; *Switz.*: Zytiga; *UK*: Zytiga; *USA*: Zytiga.

Aceglatone (rINN)

Aceglatona; Acéglatone; Aceglatonum; Ацеглатон.

D-Glucaric acid 1,4:6,3-dilactone diacetate.

$C_{10}H_{10}O_8$=258.2

CAS — 642-83-1.

UNII — 347Q3OOJ13.

Profile

Aceglatone inhibits the activity of β-glucuronidase and has an anti-inflammatory action. It has been given orally to prevent relapse after surgery for carcinoma of the bladder. Adverse effects have included anorexia, gastric discomfort, and diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Glucaron.

Aclarubicin (BAN, USAN, rINN)

Aclacinomycin A; Aclarubicina; Aclarubicine; Aclarubicinum; Aklarubicin; Aklarubisilni; Aklarubisin; NSC-208734; Акларубицин.

Methyl (1*R*,2*R*,4*S*)-4-(*O*-2,6-dideoxy-4-*O*-[(2*R*,6*S*)-tetrahydro-6-methyl-5-oxopyran-2-yl]-α-L-*lyxo*-hexopyranosyl-(1→4)-2,3,6-trideoxy-3-dimethylamino-L-*lyxo*-hexopyranosyloxy)-2-ethyl-1,2,3,4,6,11-hexahydro-2,5,7-trihydroxy-6,11-dioxonaphthacene-1-carboxylate.

$C_{42}H_{53}NO_{15}$=811.9

CAS — 57576-44-0.

ATC — L01DB04.

ATC Vet — QL01DB04.

UNII — 74KXF8I502.

Description. Aclarubicin is an anthracycline antineoplastic antibiotic isolated from *Streptomyces galilaeus*.

Aclarubicin Hydrochloride (BANM, rINNM)

Aclarubicina, hidrocloruro de; Aclarubicine, Chlorhydrate d'; Aclarubicini Hydrochloridum; Hidrocloruro de aclarubicina; Акларубицина Гидрохлорид.

$C_{42}H_{53}NO_{15}$.HCl=848.3

CAS — 75443-99-1.

ATC — L01DB04.

ATC Vet — QL01DB04.

UNII — 501948RI66.

Pharmacopoeias. In *Jpn*.

Profile

Aclarubicin is an anthracycline antibiotic with actions similar to those of other anthracyclines such as doxorubicin (p. 782.3), although it inhibits RNA synthesis more strongly than DNA synthesis. It has been given by intravenous infusion as the hydrochloride in the treatment of malignant blood disorders, such as acute myeloid leukaemia. Alopecia and cardiotoxicity may be less pronounced than with doxorubicin, and extravasation of aclarubicin causes less local tissue inflammation.

Stability. In a study of the stability of anthracycline antineoplastic agents in 4 infusion fluids—glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid—stability appeared to be partly related to pH; aclarubicin was most stable in sodium chloride injection, with a pH of 6.2, and any increase or decrease in pH appeared to affect stability adversely.[1]

1. Poochikian GK, *et al.* Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; 38: 483–6.

Adverse effects. An early review[1] noted that a strikingly high incidence of ECG changes had been seen with aclarubicin, but that although acute cardiotoxicity occurred, the chronic cardiomyopathy classically associated with the anthracyclines (see p. 784.1) appeared to be rare. Alopecia was also rare, although gastrointestinal disturbances and mucositis were as common or more common than with doxorubicin.

1. Warrell RP. Adacinomycin A: clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Exp Clin Res* 1986; 12: 275–82.

Uses. An early review of studies in patients with relapsed acute myeloid leukaemia confirmed the activity of aclarubicin, with reported complete remission rates of the order of 12 to 24%.[1] Doses varied from 10 to 30 mg/m² daily to higher doses of 75 to 120 mg/m² for 2 to 4 days; in general a total dose of about 300 mg/m² appeared to be necessary to induce remission. Less information was available concerning activity in acute lymphoblastic leukaemia, but response rates were lower than those in acute myeloid leukaemia. Results in the malignant lymphomas were generally disappointing.

Longer-term follow-up has confirmed that remission rates and survival are similar for induction regimens in acute myeloid leukaemia using either aclarubicin or daunorubicin.[2,3] A regimen of aclarubicin with low-dose cytarabine and granulocyte colony-stimulating factor (CAG) has been used, including in elderly patients and those with refractory disease.[4-6]

1. Warrell RP. Adacinomycin A: clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Exp Clin Res* 1986; 12: 275–82.
2. de Nully Brown P, *et al.* Long-term survival and development of secondary malignancies in patients with acute myeloid leukemia treated with aclarubicin or daunorubicin plus cytosine arabinoside followed by intensive consolidation chemotherapy in a Danish national phase III trial. *Leukemia* 1997; 11: 37–41.
3. Öberg G, *et al.* Long-term follow-up of patients ≥60 yr old with acute myeloid leukaemia treated with intensive chemotherapy. *Eur J Haematol* 2002; 68: 376–81.
4. Li JM, *et al.* Aclarubicin and low-dose cytosine arabinoside in combination with granulocyte colony-stimulating factor in treating acute myeloid leukemia patients with relapsed or refractory disease and myelodysplastic syndrome: a multicenter study of 112 Chinese patients. *Int J Hematol* 2005; 82: 48–54.
5. Qian SX, *et al.* Effect of low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor priming (CAG regimen) on the outcome of elderly patients with acute myeloid leukemia. *Leuk Res* 2007; 31: 1383–8.
6. Xue SL, *et al.* CAG regimen enables relapsed or refractory T-cell acute lymphocytic leukemia patients to achieve complete remission: a report of six cases. *Am J Hematol* 2008; 83: 167–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Klasinomycin; *Jpn*: Aclacinon.

AE-941

CAS — 305838-77-1.

NOTE. The name Neovastat has been used as a trade mark for AE-941.

Profile

AE-941 is an angiogenesis inhibitor derived from shark cartilage extract. It has been investigated for the treatment of renal cell carcinoma, non-small cell lung cancer, and some other neoplasms.

References.
1. Sauder DN, *et al.* Neovastat (AE-941), an inhibitor of angiogenesis: randomized phase I/II clinical trial results in patients with plaque psoriasis. *J Am Acad Dermatol* 2002; 47: 535–41.
2. Gingras D, *et al.* Neovastat—a novel antiangiogenic drug for cancer therapy. *Anticancer Drugs* 2003; 14: 91–6.
3. Lu C, *et al.* Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. *J Natl Cancer Inst* 2010; 102: 859–65.

Afatinib *(USAN, rINN)*

Afatinibum; BIBW-2992; Афатиниб.
(2*E*)-*N*-[4-(3-Chloro-4-fluoroanilino)-7-[[(3*S*)-oxolan-3-yl]oxy]quinazolin-6-yl]-4-(dimethylamino)but-2-enamide.
$C_{24}H_{25}ClFN_5O_3$=485.9
CAS — 850140-72-6.
ATC — L01XE13.
ATC Vet — QL01XE13.
UNII — 41UD74L59M.

NOTE. The name Tomtovok has been used as a trade mark for afatinib.

Afatinib Maleate *(rINNM)*

Afatinib Dimaleate (USAN); Afatinib, Maléate de; Afatinibi Maleas; BIBW-2992 MA2; Maleato de afatinib; Афатиниба Малеат.
$C_{24}H_{25}ClFN_5O_3.2C_4H_4O_4$=718.1
CAS — 850140-73-7.
UNII — V1T5K7RZ0B.

Uses and Administration

Afatinib is a tyrosine kinase inhibitor directed against the epidermal growth factor receptor (EGFR) family; it is used in the treatment of metastatic non-small cell lung cancer (p. 711.1) that has EGFR exon 19 deletions or exon 21 (L858R) substitutions. It is given as the maleate but doses are expressed in terms of the base; 59.12 mg of afatinib maleate is equivalent to about 40 mg of afatinib. A usual oral dose of 40 mg once daily is taken on an empty stomach. A missed dose should not be taken within 12 hours of the next dose. Treatment may need to be modified if toxicity occurs, see Administration in Subsequent Cycles, below. Afatinib therapy is continued until disease progression or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

If afatinib is poorly tolerated when given with a P-glycoprotein inhibitor, the daily dose of afatinib should be reduced by 10 mg; afatinib may be increased back to the previous dose on stopping treatment with the inhibitor. If chronic treatment with a P-glycoprotein inducer is required, the daily dose of afatinib should be increased by 10 mg as tolerated; afatinib should be decreased back to the previous dose 2 to 3 days after stopping the inducer.

Afatinib is also under investigation in various other malignancies.

References.
1. Chen X, *et al.* Clinical perspective of afatinib in non-small cell lung cancer. *Lung Cancer* 2013; 81: 155–61.
2. Nelson V, *et al.* Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. *Onco Targets Ther* 2013; 6: 135–43.

Administration in subsequent cycles. Treatment with afatinib may need to be modified for toxicity. Doses should be withheld if any of the following adverse effects occur:
- grade 3 or worse adverse effects
- grade 2 or worse diarrhoea that persists for more than 2 consecutive days despite anti-diarrhoeal medication
- grade 2 cutaneous reactions that are intolerable or prolonged (lasting more than 7 days)
- grade 2 or worse renal dysfunction

When the adverse effect has resolved, returned to baseline, or improved to grade 1, afatinib can be restarted at a reduced oral dose of 10 mg less than that at which the effect occurred. Afatinib should be permanently stopped if severe adverse effects occur at a dose of 20 mg daily, or if any of the following reactions occur:
- life-threatening bullous, blistering, or exfoliative skin lesions
- interstitial lung disease
- severe drug-induced hepatic impairment
- persistent ulcerative keratitis
- symptomatic left ventricular dysfunction

Adverse Effects and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Commonly reported adverse effects with afatinib are diarrhoea, stomatitis, cheilitis, rash, pruritus, dry skin, conjunctivitis, epistaxis, rhinorrhoea, paronychia, cystitis, decreased appetite and body weight, and pyrexia. Skin reactions can be severe and include bullous, blistering, or exfoliating lesions. Pulmonary toxicity has been reported including interstitial lung disease. Hepatotoxicity with increased liver enzyme values, hypokalaemia, and ventricular dysfunction have also occurred. Treatment may need to be stopped or modified for severe toxicity, see Administration in Subsequent Cycles, above.

Based on its mechanism of action and data from *animal* studies, afatinib is not recommended during pregnancy. Women of reproductive potential should use effective contraception during and for at least 2 weeks after treatment.

References.
1. Lacouture ME, *et al.* Dermatologic adverse events associated with afatinib: an oral ErbB family blocker. *Expert Rev Anticancer Ther* 2013; 13: 721–8.

Interactions

Afatinib is a substrate of P-glycoprotein and use with P-glycoprotein inhibitors or inducers could affect exposure to afatinib; dose adjustments may be required, see Uses and Administration, above. *In vitro* data suggest that afatinib is also an inhibitor of P-glycoprotein, and a substrate and an inhibitor of the breast cancer resistance protein (BCRP) transporter.

Pharmacokinetics

Peak concentrations of afatinib occur 2 to 5 hours after oral dosing. Exposure is reduced when afatinib is taken with a high-fat meal. It is 95% bound to plasma proteins. Afatinib is excreted, mainly as unchanged drug, in the faeces (85%) with a small amount in the urine (4%). The elimination half-life is 37 hours after repeated dosing, and steady state concentrations occur within 8 days.

Exposure to afatinib is increased in patients with renal impairment.

References.
1. Wind S, *et al.* Pharmacokinetics of afatinib, a selective irreversible ErbB family blocker, in patients with advanced solid tumours. *Clin Pharmacokinet* 2013;.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Gilotrif.

Aflibercept *(USAN, rINN)*

Afliberceptum; AVE-0005; VEGF Trap; VEGF Trap-Eye; VEGF $Trap_{R1R2}$; Афлиберцепт.
Des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211′:214-214′)-bisdisulfide dimer.
CAS — 862111-32-8.
ATC — S01LA05.
ATC Vet — QS01LA05.
UNII — 15C2VL427D.

NOTE. There are significant differences in the processing and formulation of preparations containing the active ingredient aflibercept and consequently they are not therapeutically interchangeable.

To emphasise this in the USA, preparations are available as:
- *Eylea* (*Regeneron, USA*): described as containing aflibercept
- *Zaltrap* (*Regeneron, USA*): described as containing ziv-aflibercept

However, in Europe and other countries the preparations *Eylea* and *Zaltrap* are both described as containing aflibercept, and the name ziv-aflibercept is not used.

Uses and Administration

Aflibercept is a recombinant human fusion protein that acts as a soluble decoy receptor and binds to vascular endothelial growth factor-A (VEGF-A), factor-B (VEGF-B), and placental growth factor (PlGF); this inhibits the activation of receptor tyrosine kinases, VEGFR-1 and VEGFR-2. The inhibition of these growth factors reduces neovascularisation and angiogenesis.

Aflibercept (*Eylea*) is used to treat neovascular (wet) age-related macular degeneration (p. 880.2). The initial recommended dose is 2 mg by intravitreal injection once each month for 3 doses, followed by 2 mg every 2 months. After 12 months of treatment, doses may be given less frequently, according to response. Aflibercept is also used for the treatment of macular oedema following central retinal vein occlusion, in a dose of 2 mg by intravitreal injection once every month. When visual and anatomical measures are stable for 3 monthly assessments, the interval between doses may be gradually increased and treatment stopped. Monitoring should continue and therapy may be restarted if necessary. However, if there is no improvement from the first 3 doses, treatment should be stopped.

Aflibercept, or as ziv-aflibercept in the USA, (*Zaltrap*) is used with fluorouracil, folinic acid, and irinotecan in the treatment of metastatic colorectal cancer (p. 706.3) that is resistant to or has progressed after an oxaliplatin-containing regimen. A dose of aflibercept 4 mg/kg is given by intravenous infusion over 1 hour every 2 weeks, and it should be given before any other component of the regimen on that day of treatment. The dose should be diluted to a final concentration of 0.6 to 8 mg/mL in sodium chloride 0.9% or glucose 5% and infused through a 0.2 micrometre polyethersulfone filter; other filters made of polyvinylidene fluoride or nylon should not be used. Doses may need to be reduced or withheld if severe hypertension, proteinuria, or neutropenia develop (see Administration in Subsequent Cycles, below). Therapy should continue until there is disease progression or unacceptable toxicity.

References.
1. Boyer D, *et al.* Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology* 2012; 119: 1024–32.
2. Van Cutsem E, *et al.* Addition of aflibercept to fluorouracil, leucovorin and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012; 30: 3499–3506.
3. Frampton JE. Aflibercept for intravitreal injection: in neovascular age-related macular degeneration. *Drugs Aging* 2012; 29: 839–46.
4. Heier JS, *et al.* VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012; 119: 2537–48. Correction. *ibid.* 2013; 120: 209–10.
5. Brown DM, *et al.* Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. *Am J Ophthalmol* 2013; 155: 429–37.
6. Holz FG, *et al.* VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol* 2013; 97: 278–84.
7. Thomas M, *et al.* Comparative effectiveness of aflibercept for the treatment of patients with neovascular age-related macular degeneration. *Clin Ophthalmol* 2013; 7: 495–501.
8. Evoy KE, Abel SR. Aflibercept: newly approved for the treatment of macular edema following central retinal vein occlusion. *Ann Pharmacother* 2013; 47: 819–27.

Administration in subsequent cycles. In the treatment of metastatic colorectal cancer, aflibercept, or as ziv-aflibercept in the USA, (*Zaltrap*) should be withheld in patients who develop recurrent or severe hypertension. Treatment may be restarted when the blood pressure is under control, at a permanently reduced dose of 2 mg/kg by intravenous infusion every 2 weeks. Aflibercept should be withheld in patients who develop proteinuria, until it is less than 2 g per 24 hours. If the proteinuria is recurrent, treatment should be restarted at a permanently lower dose of 2 mg/kg by intravenous infusion every 2 weeks. Dose of aflibercept should also be delayed in patients who have a neutrophil count below 1500 cells/mm^3.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of aflibercept **intravitreal injection** are conjunctival haemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intra-ocular pressure. Other adverse effects include endophthalmitis, retinal detachment, and retinal tear. Hypersensitivity reactions have been reported. There is a potential risk of thromboembolic events such as stroke, myocardial infarction, or vascular death following intravitreal use of vascular endothelial growth factor (VEGF) inhibitors.

Common adverse effects that occur in patients given **intravenous** aflibercept, or as ziv-aflibercept in the USA, include bleeding, hypertension, proteinuria, leucopenia, neutropenia, thrombocytopenia, decreases in body-weight and appetite, diarrhoea, abdominal pain, stomatitis, dysphonia, increases in liver function tests and serum-creatinine, fatigue, and headache. Arterial and venous thromboembolic events and severe hypersensitivity reactions have occurred. Reversible posterior leukoencephalopathy syndrome has been reported in patients given aflibercept.

Severe and sometimes fatal haemorrhage and gastrointestinal perforation have been associated with the use of intravenous aflibercept. Fistula formation can occur and wound healing may be compromised. Aflibercept should be stopped at least 4 weeks before elective surgery. After major surgery it should not be restarted for at least 4 weeks and not

until the surgical wound is fully healed; after minor surgery it may be restarted when the wound is fully healed.

Severe hypertension, including cases of hypertensive crisis, has been reported. Blood pressure should be monitored every 2 weeks and antihypertensive therapy started when necessary. Aflibercept may need to be withheld and the dose reduced after severe or recurrent hypertension is under control; it should be stopped in patients with hypertensive crisis or hypertensive encephalopathy. Patients should also be monitored for proteinuria during aflibercept therapy, which may need to be withheld or the dose reduced; it should be stopped in those who develop nephrotic syndrome or thrombotic microangiopathy.

A complete blood count with differential count should be made before each dose of intravenous aflibercept; treatment should be delayed if the neutrophil count is below 1500 cells/mm³.

Pharmacokinetics

Systemic absorption occurs after intravitreal administration of aflibercept; peak plasma concentrations are low and occur within 3 days, and free plasma-aflibercept concentrations are undetectable 2 weeks following administration. The terminal half-life of free aflibercept in plasma is about 6 days following intravenous administration of doses of 2 to 4 mg/kg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Eylea; *Jpn*: Eylea; *Neth.*: Zaltrap; *Switz.*: Eylea; Zaltrap; *UK*: Eylea; Zaltrap; *USA*: Eylea; Zaltrap.

Alemtuzumab *(BAN, rINN)*

Alemtutsumabi; Alemtuzumabum; Campath-1; Campath-1H; Алемтузумаб.

Immunoglobulin G 1 (human-rat monoclonal CAMPATH-1H γ1-chain antihuman antigen CD52), disulfide with human-rat monoclonal CAMPATH-1H light chain, dimer.

CAS — 216503-57-0.
ATC — L01XC04.
ATC Vet — QL01XC04.
UNII — 3A189DH42V.

NOTE. The name FluCam has been used for a regimen of alemtuzumab with fludarabine. Distinguish from Flucam, which is a proprietary name for ampiroxicam (p. 21.1).

Uses and Administration

Alemtuzumab is a humanised derivative of campath-1G, a rat monoclonal antibody to the CD52 antigen found on lymphocytes. It is used in the treatment of B-cell chronic lymphocytic leukaemia (p. 693.3) and is also licensed in the EU (under the trade name of *Lemtrada*) for use in relapsing-remitting multiple sclerosis (below).

For the treatment of **chronic lymphocytic leukaemia** the dose of alemtuzumab must be increased gradually to avoid infusion-related reactions (see Adverse Effects, below). Alemtuzumab should be diluted in 100 mL sodium chloride 0.9% or glucose 5%. The initial dose is 3 mg daily, given as an intravenous infusion over 2 hours (it may be increased up to 8 hours in some patients, see Adverse Effects, below). This dose should be repeated daily until it is tolerated; the dose should then be increased to 10 mg daily. When this dose is tolerated, the maintenance dose of 30 mg can be started; this dose escalation usually takes 3 to 7 days. The maintenance dose of 30 mg is given three times weekly on alternate days. The total duration of therapy, including dose escalation, is 12 weeks. Doses should be modified according to haematological toxicity (see Administration in Subsequent Cycles, below).

For the treatment of **multiple sclerosis** alemtuzumab has been given by intravenous infusion over 4 hours for 2 treatment courses, as follows:

- initial treatment course: 12 mg daily for 5 consecutive days, to a total dose of 60 mg
- second treatment course given 12 months after the initial course: 12 mg daily for 3 consecutive days, to a total dose of 36 mg

Missed doses within a treatment course should not be given on the same day as a scheduled dose. Patients should be pretreated with a corticosteroid on each of the first 3 days of any course. Oral prophylaxis with 200 mg twice daily of aciclovir (or similar) for herpes infection should also be started on the first day of each course and continued for a minimum of 1 month following treatment.

Alemtuzumab is under investigation for induction therapy in transplantation (see Organ and Tissue Transplantation, p. 1936.2, *et seq*).

References.
1. Hale G, *et al.* Alemtuzumab (Campath-1H) for treatment of lymphoid malignancies in the age of nonmyeloablative conditioning? *Bone Marrow Transplant* 2002; 30: 797–804.
2. Frampton JE, Wagstaff AJ. Alemtuzumab. *Drugs* 2003; 63: 1229–43.
3. Keating M, *et al.* Management guidelines for use of alemtuzumab in B-cell chronic lymphocytic leukemia. *Clin Lymphoma* 2004; 4: 220–7.
4. Faderl S, *et al.* The evolving role of alemtuzumab in management of patients with CLL. *Leukemia* 2005; 19: 2147–52.
5. Morris PJ, Russell NK. Alemtuzumab (Campath-1H): a systematic review in organ transplantation. *Transplantation* 2006; 81: 1361–7.
6. Magliocca JF, Knechtle SJ. The evolving role of alemtuzumab (Campath-1H) for immunosuppressive therapy in organ transplantation. *Transpl Int* 2006; 19: 705–14.
7. Ravandi F, O'Brien S. Alemtuzumab in CLL and other lymphoid neoplasms. *Cancer Invest* 2006; 24: 718–25.
8. Boyd K, Dearden CE. Alemtuzumab in the treatment of chronic lymphocytic lymphoma. *Expert Rev Anticancer Ther* 2008; 8: 525–33.
9. Robak T. Alemtuzumab for B-cell chronic lymphocytic leukemia. *Expert Rev Anticancer Ther* 2008; 8: 1033–51.
10. Ciancio G, Burke GW. Alemtuzumab (Campath-1H) in kidney transplantation. *Am J Transplant* 2008; 8: 15–20.
11. Dhesi S, *et al.* Alemtuzumab and liver transplantation: a review. *Curr Opin Organ Transplant* 2009; 14: 245–9.
12. Gribben JG, Hallek M. Rediscovering alemtuzumab: current and emerging therapeutic roles. *Br J Haematol* 2009; 144: 818–31.
13. Österborg A, *et al.* Management guidelines for the use of alemtuzumab in chronic lymphocytic leukemia. *Leukemia* 2009; 23: 1980–8.

Administration. Subcutaneous use of alemtuzumab has been investigated as a means of reducing adverse infusion reactions associated with intravenous dosage. Studies have found it to be safe and effective.[1,2] Similar blood concentrations are achieved to those after intravenous use, although accumulation in the blood took longer to achieve with subcutaneous use, and higher cumulative doses were required.[3] A dose of 30 mg subcutaneously three times weekly has been widely used; given for 4 to 12 weeks it has been shown to be as effective and safe as intravenous alemtuzumab in patients with fludarabine-refractory disease, and it has been suggested that the convenience of subcutaneous injection, which can be given on an outpatient basis, makes it the preferred route for this indication.[4] Although treatment has normally been started with lower doses and gradually increased (e.g. 3 mg on day 1, 10 mg on day 2, 30 mg on day 3, and then 30 mg three times weekly), use with the higher dose from the outset has been investigated.[5] Prolonged treatment with subcutaneous low-dose alemtuzumab (10 mg three times weekly for 18 weeks) has also been tried and was reported to be as effective as intravenous infusion in patients with chronic lymphocytic leukaemia and a poor prognosis.[6]

1. Montillo M, *et al.* Safety and efficacy of subcutaneous Campath-1H for treating residual disease with chronic lymphocytic leukemia responding to fludarabine. *Haematologica* 2002; 87: 695–700.
2. Lundin J, *et al.* Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). *Blood* 2002; 100: 768–73.
3. Hale G, *et al.* Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukemia following intravenous or subcutaneous routes of administration. *Blood* 2004; 104: 948–55.
4. Stilgenbauer S, *et al.* Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol* 2009; 27: 3994–4001.
5. Karlsson C, *et al.* Phase II study of subcutaneous alemtuzumab without dose escalation in patients with advanced-stage, relapsed chronic lymphocytic leukaemia. *Br J Haematol* 2009; 144: 78–85.
6. Cortelezzi A, *et al.* A pilot study of low-dose subcutaneous alemtuzumab therapy for patients with hemotherapy-refractory [sic] chronic lymphocytic leukemia. *Haematologica* 2005; 90: 410–12.

Administration in subsequent cycles. The dose of alemtuzumab may be modified from the usual intravenous maintenance dose (see Uses and Administration, above) for neutropenia and thrombocytopenia in those being treated for chronic lymphocytic leukaemia as follows:

In patients with higher baseline values whose absolute neutrophil count (ANC) falls to < 250 cells/mm³ and/or whose platelet count falls to $\leq 25\,000$ cells/mm³:

- for first occurrence: withhold alemtuzumab. Resume at 30 mg when ANC ≥ 500 cells/mm³ and platelet count $\geq 50\,000$ cells/mm³
- for second occurrence: withhold alemtuzumab. Resume at 10 mg when ANC ≥ 500 cells/mm³ and platelet count $\geq 50\,000$ cells/mm³
- for third occurrence: stop alemtuzumab

In patients who are started on alemtuzumab with a baseline ANC already ≤ 250 cells/mm³ and/or a baseline platelet count $\leq 25\,000$ cells/mm³, and who have a $\geq 50\%$ decrease from baseline:

- for first occurrence: withhold alemtuzumab. Resume at 30 mg upon return to baseline value
- for second occurrence: withhold alemtuzumab. Resume at 10 mg upon return to baseline value
- for third occurrence: stop alemtuzumab

If alemtuzumab is withheld, and the time to recovery is ≥ 7 days, then alemtuzumab should be restarted at the usual initial dose and increased gradually (see Uses and Administration, above).

Multiple sclerosis. Alemtuzumab has been licensed in the EU for the treatment of multiple sclerosis (p. 996.3). However, an FDA committee has raised concerns about its adverse effects such as auto-immune cytopenias and autoimmune thyroid disease which can be fatal and may outweigh its benefits. For further information on the adverse effects of alemtuzumab, see under Adverse Effects, Treatment, and Precautions, below.

It has been proposed that the secondary progressive phase of the disease might be due to post-inflammatory neurodegeneration and that immunotherapy would influence long-term disability only if given early in the disease course. A phase 2 randomised study assigned treatment-naive patients with early, relapsing-remitting multiple sclerosis to either alemtuzumab or interferon beta. Alemtuzumab (at a dose of either 12 mg daily or 24 mg daily) was given by intravenous infusion on 5 consecutive days during the first month, and on 3 consecutive days at months 12 and 24; interferon beta-1a at a dose of 44 micrograms was given subcutaneously 3 times weekly after dose escalation. All patients received intravenous methylprednisolone at the time of infusion. There were no significant differences between the groups receiving either dose of alemtuzumab on any outcome measure or adverse event. However, 6 cases of immune thrombocytopenic purpura occurred with alemtuzumab treatment, including one fatality, prompting suspension of therapy with alemtuzumab. Nonetheless, compared with interferon beta, alemtuzumab significantly improved mean disability scores and reduced the rate of relapse; efficacy was maintained over 36 months, even though some 70% of alemtuzumab-treated patients were not given the planned third cycle due to safety concerns. Alemtuzumab also increased brain volume on magnetic resonance imaging, whereas brain atrophy advanced among patients receiving interferon beta. The authors of the study noted that, while alemtuzumab appears to be more effective than interferon beta when given in the earliest stages of multiple sclerosis, there is a dilemma as to whether to expose young adults with little disability to the potentially serious adverse effects of alemtuzumab.[1]

Extended follow-up of patients in this study group, for up to 5 years from the start of therapy, found that alemtuzumab remained significantly more effective than interferon beta-1a.[2] The superiority of alemtuzumab compared with interferon beta-1a was further confirmed in a phase 3 study of previously untreated patients with early, relapsing-remitting multiple sclerosis[3] and also in those with at least one relapse after disease-modifying therapy with either interferon beta or glatiramer.[4]

1. Coles AJ, *et al.* CAMMS223 Trial Investigators. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008; 359: 1786–1801.
2. Coles AJ, *et al.* Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012; 78: 1069–78.
3. Cohen JA, *et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; 380: 1819–28.
4. Coles AJ, *et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; 380: 1829–39.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Alemtuzumab commonly causes bone marrow depression, which may be severe and prolonged; fatalities have occurred. Auto-immune anaemia and auto-immune thrombocytopenia and haemolytic anaemia have been reported less commonly; however, fatalities have been reported. Single doses greater than 30 mg, or cumulative weekly doses greater than 90 mg should not be used, because of the increased incidence of pancytopenia. Complete blood and platelet counts should be measured weekly during alemtuzumab therapy, and more frequently if anaemia, neutropenia, or thrombocytopenia occur. Treatment should be interrupted if severe myelosuppression or evidence of haematological toxicity are seen and stopped permanently if auto-immune anaemia or auto-immune thrombocytopenia develops. Lymphopenia may be profound with alemtuzumab therapy, and opportunistic infections are common, and occasionally life-threatening. Antimicrobial prophylaxis is recommended from the start of therapy until after completion; if serious infection occurs, treatment should be interrupted. Recovery of lymphocyte counts may take 6 months or longer after stopping treatment.

Alemtuzumab commonly causes an acute cytokine release syndrome. The reaction usually includes rigors, fever, nausea and vomiting, hypotension, rash, urticaria, pruritus, shortness of breath, headache, and diarrhoea. Rarer, more serious reactions may include bronchospasm, syncope, pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest, myocardial infarction, and cardiac arrest. Cardiac adverse effects have been fatal in

some instances. These infusion-related reactions are most common at the start of therapy: the dose must be increased gradually when beginning treatment, or if it is interrupted for 7 days or more. Pre-medication with an oral or intravenous corticosteroid, oral antihistamine, and analgesic should also be used, particularly before the first dose, and with dose increases. If acute infusion reactions persist, the infusion time may be extended to 8 hours from the time of reconstitution.

Other adverse effects include fatigue, anorexia, asthenia, malaise, arthralgia, myalgia, bone pain, back pain, chest pain, hypertension, cyanosis, and bradycardia or tachycardia. Localised oedema, stomatitis, mucositis, and abdominal pain have been reported, as have dizziness, paraesthesia, tremor, and taste loss. Confusion, insomnia or somnolence, depression, or anxiety may occur. Electrolyte disturbances include hyponatraemia and hypocalcaemia. Coughing, haemoptysis, sinusitis, bronchitis, and pharyngitis have been reported.

Alemtuzumab is contra-indicated for patients with active systemic infection, or underlying immunodeficiency.

Auto-immune disorders. Aside from auto-immune cytopenias, alemtuzumab has been associated with the development of auto-immune thyroid disease in 20 to 30% of patients, occurring months to years after treatment.[1] Anti-glomerular basement membrane disease has also been reported after alemtuzumab,[2] as has Guillain-Barré syndrome.[3] It has been commented[2] that B-cell recovery tends to precede T-cell recovery after alemtuzumab treatment, and that the auto-immune diseases seen after therapy are mainly antibody-mediated, and respond to B-cell depletion.

1. Jones JL, *et al.* IL-21 drives secondary autoimmunity in patients with multiple sclerosis, following therapeutic lymphocyte depletion with alemtuzumab (Campath-1H). *J Clin Invest* 2009; **119**: 2052–61.
2. Clatworthy MR, *et al.* Anti-glomerular basement membrane disease after alemtuzumab. *N Engl J Med* 2008; **359**: 768–9.
3. Abbi KKS, *et al.* Guillain-Barré syndrome after use of alemtuzumab (Campath) in a patient with T-cell prolymphocytic leukemia: a case report and review of the literature. *Leuk Res* 2010; **34**: e154–e156.

Effects on the lungs. Diffuse alveolar haemorrhage has been reported after a single dose of alemtuzumab was used during renal transplantation in a patient with X-linked Alport syndrome (an inherited disorder involving damage to the kidneys, haematuria, and hearing loss).[1]

1. Sachdeva A, Matuschak GM. Diffuse alveolar hemorrhage following alemtuzumab. *Chest* 2008; **133**: 1476–8.

Infection. Reactivation of hepatitis B,[1] hepatitis C,[2] and CMV[3] has been reported with the use of alemtuzumab. Patients who have been pretreated with purine analogues or those with advanced disease and not responding to alemtuzumab therapy appear to be at highest risk for infectious complications. Recommendations for screening and prophylaxis[4] and guidelines[5] and reviews[6] concerning management have been published. Six infection-related deaths have been reported[7] after previously untreated patients with B-cell chronic lymphocytic leukaemia were treated with fludarabine and rituximab, followed by alemtuzumab. These deaths may have resulted from a prolonged period of immunosuppression due to the sequencing of these drugs without sufficient recovery time. In the EU, alemtuzumab is licensed for use in patients for whom fludarabine combination chemotherapy is not appropriate.

1. Iannitto E, *et al.* Hepatitis B virus reactivation and alemtuzumab therapy. *Eur J Haematol* 2005; **74**: 254–8.
2. Anoop P, *et al.* Severe liver dysfunction from hepatitis C virus reactivation following alemtuzumab treatment for chronic lymphocytic leukaemia. *Br J Haematol* 2010; **148**: 484–6.
3. Laurenti L, *et al.* Cytomegalovirus reactivation during alemtuzumab therapy for chronic lymphocytic leukemia: incidence and treatment with oral ganciclovir. *Haematologica* 2004; **89**: 1248–52.
4. Thursky KA, *et al.* Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. *Br J Haematol* 2006; **132**: 3–12.
5. O'Brien SM, *et al.* Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Clin Lymphoma Myeloma* 2006; **7**: 125–30.
6. Elter T, *et al.* Management of infections in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Ann Hematol* 2009; **88**: 121–32.
7. Bayer, UK; Genzyme, UK. Important safety information: six infection-related deaths reported after treatment with MabCampath(alemtuzumab) following Fludarabine+Rituximab induction in patients with B-Cell Chronic Lymphocytic Leukemia (CLL) (issued 11th February 2008). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014104&RevisionSelectionMethod=Latest (accessed 12/05/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alemtuzumab 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 29/09/11)

Interactions

There are no formal interaction studies with alemtuzumab; however, it is recommended that it should not be given within 3 weeks of other chemotherapy drugs, and that patients should not receive live viral vaccines for at least 12 months after receiving alemtuzumab.

Pharmacokinetics

In patients with B-cell chronic lymphocytic leukaemia, distribution of alemtuzumab is mainly to the extracellular fluid and plasma. Over 12 weeks, clearance has been found to decrease with repeated dosing, with consequent accumulation in plasma, and the rate of elimination to approach zero-order kinetics. The half-life is reported to be 8 hours after a first dose of 30 mg, and 6 days after the last 30 mg dose. Steady-state concentrations are reached after about 6 weeks of therapy.

References.

1. Rebello P, *et al.* Pharmacokinetics of CAMPATH-1H in BMT patients. *Cytotherapy* 2001; **3**: 261–7.
2. Mould DR, *et al.* Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath™) in patients with chronic lymphocytic leukaemia and its link to treatment response. *Br J Clin Pharmacol* 2007; **64**: 278–91.
3. Elter T, *et al.* Pharmacokinetics of alemtuzumab and the relevance in clinical practice. *Leuk Lymphoma* 2008; **49**: 2256–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Campath; *Austral.*: MabCampath; *Austria*: MabCampath†; *Belg.*: MabCampath†; *Braz.*: Campath†; *Canad.*: MabCampath; *Cz.*: MabCampath†; *Denm.*: MabCampath†; *Fr.*: MabCampath†; *Ger.*: MabCampath†; *Gr.*: MabCampath†; *Hong Kong*: MabCampath; *Hung.*: MabCampath†; *Indon.*: MabCampath; *Irl.*: MabCampath†; *Israel*: MabCampath†; *Ital.*: MabCampath†; *Malaysia*: MabCampath; *Mex.*: MabCampath; *Neth.*: MabCampath†; *Norw.*: MabCampath†; *NZ*: MabCampath; *Pol.*: MabCampath†; *Port.*: MabCampath†; *Rus.*: Campath (Компас); *S.Afr.*: MabCampath; *Singapore*: MabCampath; *Spain*: MabCampath†; *Swed.*: MabCampath†; *Switz.*: MabCampath†; *Thai.*: MabCampath; *Turk.*: MabCampath; *UK*: MabCampath†; *Ukr.*: MabKampat (МабКампат); *USA*: Campath.

Alitretinoin *(BAN, USAN, rINN)*

Ácido 9-*cis*-retinoico; AGN-192013; Alitretinoiini; Alitretinoína; Alitrétinoïne; Alitretinoinum; ALRT-1057; BAL-4079; 9-*cis*-Retinoic Acid; LG-100057; LGD-1057; NSC-659772; Алитретиноин.

(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid.

$C_{20}H_{28}O_2$=300.4

CAS — 5300-03-8.

ATC — D11AH04; L01XX22.

ATC Vet — QD11AH04; QL01XX22.

UNII — 1UA8E65KDZ.

Uses and Administration

Alitretinoin is a retinoid related to isotretinoin (p. 1706.2). It is given orally for severe chronic hand eczema (p. 1684.1) that is unresponsive to treatment with potent topical corticosteroids. Patients with mainly hyperkeratotic eczema are more likely to respond to treatment with alitretinoin. It is also used topically, in the management of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma (p. 718.1).

The recommended starting dose of oral alitretinoin in adults is 30 mg once daily, with reduction to 10 mg once daily if adverse effects occur. The usual dose range is from 10 to 30 mg once daily, taken with meals. Treatment may be continued for 12 to 24 weeks depending on response. In the event of relapse, further treatment courses may be considered.

Topical treatment with a 0.1% alitretinoin gel is applied directly to the lesions twice daily, increasing to up to 4 times daily if tolerated. Doses should be increased at intervals of at least 2 weeks. If local toxicity occurs, application frequency should be reduced, or treatment temporarily stopped, until the symptoms subside. EU licensed product information states that if no response is seen after 12 weeks, therapy should be stopped; however, US licensed product information states that some patients have required over 14 weeks to respond. Treatment may be continued as long as the patient responds.

References.

1. Cheer SM, Foster RH. Alitretinoin. *Am J Clin Dermatol* 2000; **1**: 307–14.
2. Bodsworth NJ, *et al.* Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. *Am J Clin Dermatol* 2001; **2**: 77–87.
3. Miles SA, *et al.* Antitumor activity of oral 9-cis-retinoic acid in HIV-associated Kaposi's sarcoma. *AIDS* 2002; **16**: 421–9.
4. Kurie JM, *et al.* Treatment of former smokers with 9-cis-retinoic acid reverses loss of retinoic acid receptor-beta expression in the bronchial epithelium: results from a randomized placebo-controlled trial. *J Natl Cancer Inst* 2003; **95**: 206–14.
5. Aboulafia DM, *et al.* 9-cis-Retinoic acid capsules in the treatment of AIDS-related Kaposi sarcoma: results of a phase 2 multicenter clinical trial. *Arch Dermatol* 2003; **139**: 178–86.
6. Ruzicka T, *et al.* Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of randomized, double-blind, placebo-controlled, multicenter trial. *Arch Dermatol* 2004; **140**: 1453–9.
7. Ruzicka T, *et al.* Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo controlled, multicentre trial. *Br J Dermatol* 2008; **158**: 808–17.
8. Garnock-Jones KP, Perry CM. Alitretinoin: in severe chronic hand eczema. *Drugs* 2009; **69**: 1625–34.
9. NICE. Alitretinoin for the treatment of severe chronic hand eczema (technology appraisal guidance 177, issued August 2009). Available at: http://www.nice.org.uk/nicemedia/live/12219/45225/45225.pdf (accessed 28/06/10)

Adverse Effects

Oral doses of alitretinoin may produce similar adverse effects to those of isotretinoin (see p. 1707.2). Decreases in concentrations of thyroid stimulating hormone and free T_4 are also often reported with alitretinoin, as are increases in platelets and increases in blood concentrations of creatine phosphokinase. Ankylosing spondylitis is uncommon.

Local skin toxicity may occur on topical application of alitretinoin, in particular erythema and oedema, and in some patients this may be dose-limiting. Pain, paraesthesia, rashes, pruritus, exfoliative dermatitis, and other skin disorders may also occur locally. Lymphadenopathy, phlebitis, cellulitis, and bacterial infections have been reported. Alitretinoin may have a weak photosensitising effect, and patients should minimise exposure of treated areas to sunlight or other ultraviolet light during therapy.

Precautions

When alitretinoin is given orally, the precautions described under isotretinoin (see p. 1709.2) including contra-indication of use in pregnancy and during breast feeding, should be adopted. Although absorption does not seem to occur to any great extent with topical use licensed product information also contra-indicates such use in pregnancy and in breast-feeding mothers. Oral alitretinoin is further contra-indicated in patients with severe renal impairment and uncontrolled hypothyroidism. Topical treatment with alitretinoin should not be used on lesions in close proximity to other skin disorders.

Interactions

The interactions described under isotretinoin (see p. 1710.1) also apply to oral alitretinoin. Alitretinoin is metabolised by the hepatic cytochrome P450 isoenzyme system, particularly CYP3A4. Use with CYP3A4 inhibitors such as ketoconazole increases the plasma concentration of alitretinoin and dose reduction may be required. Use of products containing diethyltoluamide is not recommended during topical alitretinoin therapy, as *animal* studies indicate an increase in diethyltoluamide toxicity with concurrent use.

Pharmacokinetics

After oral doses alitretinoin is variably absorbed from the gastrointestinal tract. When alitretinoin is taken with food, absorption becomes less variable and the systemic exposure is enhanced by a factor of 4. Alitretinoin is highly bound to plasma proteins. It undergoes metabolism by oxidation in the liver by the cytochrome P450 isoenzyme system into the major metabolite 4-oxo-alitretinoin. Alitretinoin and its metabolites are excreted mainly in the urine, with about 30% excreted in the faeces. The elimination half-life of unchanged alitretinoin is about 2 to 10 hours. Alitretinoin and 4-oxo-alitretinoin do not accumulate in the body.

Systemic absorption of topical alitretinoin is not considered to be extensive.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Panretin; *Austria*: Panretin; Toctino; *Canad.*: Toctino; *Cz.*: Panretin; *Denm.*: Toctino; *Fin.*: Toctino; *Fr.*: Panretin; Toctino; *Ger.*: Panretin; Toctino; *Gr.*: Panretin; *Irl.*: Panretin; *Israel*: Toctino; *Neth.*: Panretin; Toctino; *Norw.*: Toctino; *Pol.*: Panretin; *Port.*: Panretin; *Spain*: Panretin; *Switz.*: Toctino; *UK*: Toctino; *USA*: Panretin.

Altretamine *(BAN, USAN, rINN)*

Altretamiini; Altretamin; Altretamina; Altrétamine; Altretaminum; Hexamethylmelamine; HMM; NSC-13875; WR-95704; Альтретамин.

2,4,6-Tris(dimethylamino)-1,3,5-triazine; N^2,N^2,N^4,N^4,N^6,N^6-Hexamethyl-1,3,5-triazine-2,4,6-triamine.

$C_9H_{18}N_6$=210.3
CAS — 645-05-6.
ATC — L01XX03.
ATC Vet — QL01XX03.
UNII — Q88IH59O7H.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Altretamine). A white crystalline powder. Insoluble in water; soluble in chloroform. Store in airtight containers.

Uses and Administration

Altretamine is an antineoplastic agent structurally similar to the alkylating agent tretamine (triethylenemelamine) although its mode of action may be different. It is given orally and is licensed for use as a single agent in the palliative treatment of ovarian carcinoma (p. 711.2). Altretamine has also been tried in lung cancer. ***Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.***

The usual dose as a single agent in ovarian cancer is 260 mg/m² daily in four divided doses, for 14 or 21 consecutive days out of a 28-day cycle. Up to 12 cycles may be given. Therapy should be interrupted for at least 14 days, and subsequently restarted at a lower dose of 200 mg/m² daily, if the white cell count falls below 2000 cells/mm³ or the platelet count below 75 000 cells/mm³ or if neurotoxic or intolerable gastrointestinal symptoms occur. Lower doses are also used in combination regimens.

Reviews.
1. Lee CR, Faulds D. Altretamine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cancer chemotherapy. *Drugs* 1995; 49: 932–53.
2. Manetta A, *et al.* Hexamethylmelamine as a single second-line agent in ovarian cancer: follow-up report and review of the literature. *Gynecol Oncol* 1997; 66: 20–6.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression is usually moderate, manifesting as leucopenia, thrombocytopenia, and anaemia, and may require dosage reduction; blood counts should be monitored regularly. Nausea and vomiting are common and usually moderate although they may be dose-limiting. Prolonged or high-dose therapy may be associated with neurotoxicity, both peripheral (neuropathies) and central (ataxia, depression, confusion, drowsiness, and hallucinations); neurological examination should be performed regularly and treatment interrupted or the dose reduced as appropriate. Renal toxicity may also be dose-limiting. Other rare adverse effects include rashes, alopecia, and hepatotoxicity.

Handling. Altretamine is irritant; avoid contact with skin and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies altretamine 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 28/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Pyridoxine appears to reduce the activity of altretamine.

Antidepressants. Severe and potentially life-threatening orthostatic hypotension developed in 3 patients who took *amitriptyline* or *imipramine* with altretamine and in a fourth patient who took *phenelzine* and altretamine.[1] One patient was able to tolerate the antineoplastic with *nortriptyline*.

1. Bruckner HW, Schleifer SJ. Orthostatic hypotension as a complication of hexamethylmelamine anddepressant interaction. *Cancer Treat Rep* 1983; 67: 516.

Pharmacokinetics

Altretamine is well absorbed from the gastrointestinal tract after oral doses, but is rapidly demethylated in the liver producing variation in plasma-altretamine concentrations. The principal metabolites are pentamethylmelamine and tetramethylmelamine, which are excreted in urine. The elimination half-life has been reported to be 4 to 10 hours.

References.
1. Damia G, D'Incalci M. Clinical pharmacokinetics of altretamine. *Clin Pharmacokinet* 1995; 28: 439–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Hexalen†; *Canad.*: Hexalen; *Fr.*: Hexastat; *India*: Cantret; *Neth.*: Hexalen†; *Rus.*: Hexalen (Гексален); *Thai.*: Hexalen†; *USA*: Hexalen.

Pharmacopoeial Preparations
USP 36: Altretamine Capsules.

Alvocidib *(BAN, USAN, rINN)*

Alvocidibum; Avodenib; Flavopiridol; HL-275; HMR-1275; L86-8275; MDL-107826A; NSC-649890; Альвоцидиб.
(-)-*cis*-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one.
$C_{21}H_{20}ClNO_5$=401.8
CAS — 146426-40-6.
UNII — 45AD6X575G.

Alvocidib Hydrochloride *(BANM, USAN, rINNM)*

Alvocidib, Chlorhydrate d'; Alvocidibi Hydrochloridum; Hidrocloruro de alvocidib; HL-275; HMR-1275; L-868275; MDL-107826A; NSC-649890; Альвоцидиба гидрохлорид.
(-)-*cis*-2-(2-Chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methylpiperidin-4-yl)-4*H*-1-benzopyran-4-one hydrochloride.
$C_{21}H_{20}ClNO_5$,HCl=438.3
CAS — 131740-09-5.
UNII — D48MS3A6N9.

Profile

Alvocidib is an inhibitor of cyclin-dependent kinase that is under investigation as an antineoplastic for the treatment of chronic lymphocytic leukaemia.

Amatuximab *(USAN, rINN)*

Amatuximabum; MORAb-009; Аматуксимаб.
Immunoglobulin G1, anti-(mesothelin) (human-mouse monoclonal MORAb-009 heavy chain), disulfide with human-mouse monoclonal MORAb-009 κ-chain, dimer.
CAS — 931402-35-6.

Profile

Amatuximab is a humanised immunoglobulin G1 monoclonal antibody that targets the cell surface glycoprotein mesothelin which is overexpressed in several malignancies. It is under investigation in the treatment of mesothelioma.

Aminoglutethimide *(BAN, rINN)* ⊗

Aminoglutethimid; Aminoglutéthimide; Aminoglutethimidum; Aminoglutetimid; Aminoglutetimida; Aminoglutetimidas; Aminoglutetimidi; Aminoglutetymid; Aminoglutethimide; Ammlnoglutetimide; Ba-16038; Аминоглутетимид.
2-(4-Aminophenyl)-2-ethylglutarimide; 3-(4-Aminophenyl)-3-ethylpiperidine-2,6-dione.
$C_{13}H_{16}N_2O_2$=232.3
CAS — 125-84-8.
ATC — L02BG01.
ATC Vet — QL02BG01.
UNII — 0O54ZQ14I9.

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

Ph. Eur. 8: (Aminoglutethimide). A white or slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol.

USP 36: (Aminoglutethimide). A white or creamy-white, fine, crystalline powder. Very slightly soluble in water; readily soluble in most organic solvents. It forms water-soluble salts with strong acids. The pH of a 0.1% solution in dilute methyl alcohol (1 in 20) is between 6.2 and 7.3.

Uses and Administration

Aminoglutethimide is an analogue of glutethimide and was formerly used for its weak anticonvulsant properties. Aminoglutethimide blocks the production of adrenal steroids and acts as an aromatase inhibitor to block the conversion of androgens to oestrogens (the major source of oestrogens in women without ovarian function). It was used in the treatment of metastatic breast cancer (p. 702.1) in postmenopausal or oophorectomised women and as palliative treatment in men with advanced prostatic cancer (p. 712.3) but has largely been superseded by other drugs.

Aminoglutethimide has also been used in the treatment of Cushing's syndrome (p. 2559.1). Usual oral doses range from 1 to 2 g daily, in divided doses.

The *dextro*-isomer of aminoglutethimide, dexaminoglutethimide has been investigated.

Adverse Effects

The most frequent adverse effects reported with aminoglutethimide include drowsiness, lethargy, and rash (sometimes with fever); these generally diminish after the first 6 weeks of therapy. Dizziness and nausea occasionally occur. Leucopenia, thrombocytopenia, agranulocytosis, or severe pancytopenia have occurred rarely. Adrenal insufficiency may rarely occur, and there have been reports of other endocrine disturbances including hypothyroidism, and virilisation. Other rare effects include ataxia, headache, depression, gastrointestinal disturbances, hypercholesterolaemia, and orthostatic hypotension.

Overdosage may lead to CNS depression and impairment of consciousness, electrolyte disturbances, and respiratory depression.

Effects on the liver. Aminoglutethimide has been associated with reports of cholestatic jaundice, accompanied by rash[1,2] and fever,[2] and probably due to an idiosyncratic hypersensitivity reaction.[1] It has been suggested that liver function tests should be carried out in patients receiving aminoglutethimide who develop fever and eruptions.[2]

1. Gerber SB, Miller KB. Cholestatic jaundice and aminoglutethimide. *Ann Intern Med* 1982; 97: 138.
2. Perrault DJ, Domovitch E. Aminoglutethimide and cholestasis. *Ann Intern Med* 1984; 100: 160.

Effects on the lungs. Pulmonary infiltrates in a patient who developed progressive dyspnoea on starting therapy with aminoglutethimide were found to be due to diffuse alveolar damage and haemorrhage; thrombocytopenia was present but prothrombin and bleeding times were normal. The patient's gas exchange and chest radiographs improved on stopping aminoglutethimide and giving corticosteroids.[1] Blood and pulmonary eosinophilia, which resolved on stopping aminoglutethimide therapy, has also been reported.[2]

1. Rodman DM, *et al.* Aminoglutethimide, alveolar damage, and hemorrhage. *Ann Intern Med* 1986; 105: 633.
2. Bell SC, Anderson EG. Pulmonary eosinophilia associated with aminoglutethimide. *Aust N Z J Med* 1998; 28: 670–1.

Lupus. SLE occurred in a patient who received aminoglutethimide, and resolved when the drug was withdrawn.[1] In another report, however, a patient with a lupus-like syndrome had a reduction in disease activity when tamoxifen therapy was changed to aminoglutethimide.[2]

1. McCraken M, *et al.* Systemic lupus erythematosus induced by aminoglutethimide. *BMJ* 1980; 281: 1254.
2. Etherington J, *et al.* Effect of aminoglutethimide on the activity of a case of a connective tissue disorder with features of systemic lupus erythematosus. *Lupus* 1993; 2: 387.

Precautions

Aminoglutethimide inhibits adrenal steroid production so supplementary glucocorticoid therapy with hydrocortisone must normally be given, although supplementation may not be necessary in patients with Cushing's syndrome. Some patients also require a mineralocorticoid. It has been suggested that aminoglutethimide should be temporarily withdrawn in patients who undergo shock or trauma, or develop intercurrent infection.

Blood pressure, blood counts, and serum electrolytes should be regularly monitored during aminoglutethimide therapy and periodic monitoring of liver and thyroid function is recommended.

Aminoglutethimide should not be given during pregnancy as pseudohermaphroditism may occur in the fetus.

Aminoglutethimide frequently causes drowsiness: patients so affected should not drive or operate machinery.

Interactions

The rate of metabolism of some drugs is increased by aminoglutethimide; patients also taking warfarin or other coumarin anticoagulants, theophylline, tamoxifen, medroxyprogesterone, or oral hypoglycaemics, may require increased dosages of these drugs. The metabolism of dexamethasone is also accelerated, which limits its value for corticosteroid supplementation in patients receiving aminoglutethimide. Use with diuretics may lead to hyponatraemia, while alcohol may potentiate the central effects of aminoglutethimide.

For reference to aminoglutethimide's interactions with *digitoxin* (see p. 1353.2), *theophylline* (see p. 1235.2), *progestogens* (see p. 2302.2), *tamoxifen* (see Antineoplastics, p. 863.3), and *anticoagulants* (under Warfarin, p. 1532.2).

Pharmacokinetics

Aminoglutethimide is well absorbed after oral doses and peak plasma concentrations occur after 1 to 4 hours. It is metabolised in the liver, mainly to *N*-hydroxylaminoglutethimide and *N*-acetylaminoglutethimide, and appears to induce its own metabolism. The half-life, which is reported to be about 13 hours after a single dose, is decreased to around 9 hours after about 2 weeks of continuous therapy. Aminoglutethimide is excreted in urine, about half a dose being excreted unchanged and the remainder as metabolites. Only about 20 to 25% of a dose is bound to plasma protein.

Half-life. A study in 17 patients showed that the plasma half-life of aminoglutethimide had a mean value of 15.5 hours after single doses but fell to 8.9 hours during multiple-dose therapy.[1] This marked reduction could largely be attributed to a decrease in the volume of distribution; auto-induction of metabolism might be of less importance in decreasing half-life than had been previously suggested.

1. Lønning PE, *et al.* Single-dose and steady-state pharmacokinetics of aminoglutethimide. *Clin Pharmacokinet* 1985; 10: 353–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cytadren†; *Gr.*: Orimetene; *Hong Kong*: Orimetene†; *Rus.*: Mamomit (Мамомит).

Pharmacopoeial Preparations
BP 2014: Aminoglutethimide Tablets;
USP 36: Aminoglutethimide Tablets.

5-Aminolevulinic Acid

5-ALA; ALA; 5-Aminolaevulinic Acid; 5-Aminolevulínico, ácido; 5-Amino-4-oxovaleric Acid; δ-Aminolaevulinic Acid.
5-Amino-4-oxopentanoic acid.
$C_5H_9NO_3$=131.1.
CAS — 106-60-5.
ATC — L01XD04.
ATC Vet — QL01XD04.
UNII — 88755TAZ87.

Aminolevulinic Acid Hydrochloride *(USAN)*

Aminolaevulinic Acid Hydrochloride; Aminolevulínico, hidrocloruro ácido.
5-Aminolevulinic acid hydrochloride.
$C_5H_9NO_3$,HCl=167.6.
CAS — 5451-09-2.
ATC — L01XD04.
ATC Vet — QL01XD04.
UNII — V35KBM8JGR.

Hexaminolevulinate Hydrochloride *(USAN)*

P-1026.
Hexyl 5-amino-4-oxopentanoate hydrochloride.
$C_{11}H_{21}NO_3$,HCl=251.8.
CAS — 140898-91-5.
UNII — D4F329SL1O.

Methyl Aminolevulinate Hydrochloride *(USAN)*

Methyl Aminolaevulinate Hydrochloride; Metilaminolevulinato, hidrocloruro de; P-1202.
Methyl 5-amino-4-oxopentanoate hydrochloride.
$C_6H_{11}NO_3$,HCl=181.6.
CAS — 79416-27-6.
ATC — L01XD03.
ATC Vet — QL01XD03.
UNII — 7S736060IA.

Uses and Administration

5-Aminolevulinic acid is a naturally occurring haem precursor that is metabolised in the body to protoporphyrin IX, a photosensitiser that accumulates in malignant cells, and then to haem. 5-Aminolevulinic acid and its derivatives are used in photodynamic diagnosis and therapy (see under Porfimer Sodium, p. 849.1). They may be used to treat actinic keratoses, Bowen's disease, and basal cell carcinoma. Some are used in the diagnosis of bladder cancer or for visualisation of malignant tissue during surgery for glioma (see Malignant Neoplasms, below).

Aminolevulinic acid hydrochloride is used to treat actinic keratoses. It is applied topically as a 20% solution in the treatment of mild to moderate non-hyperkeratotic actinic keratoses of the face or scalp. The solution is applied to the surface of the lesions, allowed to dry, and then applied again. This is followed, 14 to 18 hours later, by illumination with blue wavelength light sufficient to supply a dose of 10 J/cm². Treatment may be repeated once after 8 weeks if necessary. Alternatively, a gel containing aminolevulinic acid hydrochloride equivalent to aminolevulinic acid 7.8% may be used. It is applied to the roughened surface of the lesions and about 5 mm of the surrounding skin, allowed to dry, then covered with an occlusive light-tight dressing for 3 hours. After removal of the dressing and any gel, the area is illuminated with red light, from either a narrow spectrum source supplying a dose of 37 J/cm² or a broader and continuous spectrum supplying a dose of 75 to 200 J/cm². Residual lesions may be re-treated after 3 months.

Aminolevulinic acid hydrochloride is given orally for the visualisation of malignant tissue during surgery for glioma. A dose of 20 mg/kg is given 3 hours before anaesthesia, and blue light illumination is used during surgery.

Methyl aminolevulinate hydrochloride is a derivative of 5-aminolevulinic acid that is applied topically for the treatment of non-hyperkeratotic, non-pigmented actinic keratoses of the face or scalp when other therapies are considered inappropriate. In some countries, it is also used for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for other therapies or for the treatment of Bowen's disease (squamous cell carcinoma *in situ*) when surgical excision is inappropriate. A cream containing the equivalent of 16% methyl aminolevulinate is applied to the lesions and covered with an occlusive dressing. After 3 hours the cream is removed and the lesions are exposed to red wavelength light; in the UK a dose of 75 J/cm² is used, whereas 37 J/cm² has been used in the USA. Exposure to the cream for more than 4 hours should be avoided. In the USA, two sessions of photodynamic therapy are given for actinic keratoses, a week apart. In the UK, one session is given for actinic keratoses, repeated after 3 months if necessary; for basal cell carcinoma or Bowen's disease two sessions are given a week apart.

Patients should avoid sunlight or bright light sources for about 2 days after topical application, and for 24 hours after oral administration.

Hexaminolevulinate hydrochloride is used for the detection of bladder cancer. A 50 mL solution containing hexaminolevulinate hydrochloride 100 mg (equivalent to about 85 mg of hexaminolevulinate) is instilled into the bladder and retained for 1 hour. After subsequent evacuation of the bladder, fluorescence cystoscopy using blue light should be started within 30 to 60 minutes.

Malignant neoplasms. The use of *topical* aminolevulinic acid or methyl aminolevulinate in the photodynamic therapy (PDT) of **actinic keratosis** and **basal cell carcinoma** (p. 714.2) has been reviewed.[1-6] Both aminolevulinic acid and methyl aminolevulinate are considered to be effective in clearing non-hyperkeratotic actinic keratoses of the face and scalp, with superior response rates and cosmetic outcome compared with cryotherapy.[7] More than 80% of lesions cleared completely after 2 treatments with aminolevulinic acid PDT; a recurrence rate of 19% was reported over 12 months.[8] Single treatment with methyl aminolevulinate is effective for thin lesions but thicker, non-responsive lesions may benefit from repeated treatment.[9] No significant differences in efficacy were seen between PDT with aminolevulinic acid or methyl aminolevulinate in the treatment of scalp actinic keratosis.[10] Topical PDT is less effective for acral lesions, although some consider that it may still offer therapeutic benefit.[7] Topical PDT with aminolevulinic acid was also found to prevent the development of new malignant lesions in patients with recurrent non-melanoma skin cancer.[11] A self-adhesive patch containing aminolevulinic acid (PD P 506 A) has been developed for easier application before therapy;[12] the patch also provides light protection. In one study, the majority of actinic keratosis lesions remained clear 12 months after a single patch-PDT treatment, and recurrence rates were superior to those of cryosurgery.[13] *Topical* PDT is considered effective for superficial basal cell carcinoma; it is less effective for nodular disease.[7] *Intralesional* use has been investigated to improve penetration of the photosensitiser, with good preliminary results.[14] Methyl aminolevulinate topical PDT may be preferable for difficult-to-treat basal cell carcinoma.[15,16]

Topical PDT is effective in **Bowen's disease** (squamous cell carcinoma *in situ*), with equivalence to cryotherapy, and equivalence or superiority to topical fluorouracil; cosmetic outcome is superior to standard therapy.[7] Topical PDT is not recommended for the treatment of invasive squamous cell carcinoma.[7] Topical methyl aminolevulinate PDT was more effective and cosmetically acceptable compared with topical 5-fluorouracil for pre-malignant skin disease in a small study in organ transplant recipients.[17]

PDT using *oral* 5-aminolevulinic acid as the photosensitiser, at doses of 30 or 60 mg/kg, has been used to treat **Barrett's oesophagus**, which is a major risk factor for oesophageal adenocarcinoma (p. 705.3).[18,19] A small study found similar clinical responses with low-dose (30 mg/kg) and high-dose (60 mg/kg) oral aminolevulinic acid protocols.[20] Good long-term results have been reported with aminolevulinic acid PDT in patients with early neoplasia or high-grade intraepithelial neoplasia.[21]

Aminolevulinic acid is given *orally* for the photodynamic detection of malignant tissue during **glioma** resection (see Malignant Neoplasms of the Brain, p. 701.2).[22,23] It has also been used for the fluorescence detection of **pleural malignancies**.[24]

An *intravesical* solution of hexaminolevulinate is used in the cystoscopic detection of non-muscle invasive **bladder cancer** (p. 700.2). Detection rates are higher compared with the use of standard white light cystoscopy,[25,26] although it may be less effective in patients previously treated with intravesical chemotherapy or immunotherapy.[26] Improvements in detection and associated complete resection are also thought to be related to lower recurrence rates.[25] Intravesical solutions of aminolevulinic acid have been studied as whole-bladder photodynamic therapy in the treatment of bladder tumours[27,28] and hexaminolevulinate is under investigation.

A *topical* application of 5-aminolevulinic acid 3% has been tried in the treatment of **cervical intraepithelial neoplasia**, with poor response.[29]

Skin disorders. 5-Aminolevulinic acid has been used topically in the photodynamic therapy (PDT) of skin condi-

1. Ormrod D, Jarvis B. Topical aminolevulinic acid HCl photodynamic therapy. *Am J Clin Dermatol* 2000; 1: 133–9.
2. Gupta AK, Ryder JE. Photodynamic therapy and topical aminolevulinic acid: an overview. *Am J Clin Dermatol* 2003; 4: 699–708.
3. Siddiqui MAA, *et al.* Topical methyl aminolevulinate. *Am J Clin Dermatol* 2004; 5: 127–37.
4. Marmur ES, *et al.* A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. *Dermatol Surg* 2004; 30: 264–71.
5. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. *Br J Dermatol* 2007; 156: 793–801.
6. Juzeniene A, *et al.* Application of 5-aminolevulinic acid and its derivatives for photodynamic therapy in vitro and in vivo. *Methods Mol Biol* 2010; 635: 97–106.
7. Morton CA, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; 159: 1245–66. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PDTguideline%20BJD%20Dec%202008.pdf (accessed 30/09/09)
8. Tschen EH, *et al.* Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol* 2006; 155: 1262–9.
9. Tarstedt M, *et al.* A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* 2005; 85: 424–8.
10. Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. *Br J Dermatol* 2007; 157: 87–91.
11. Apalla Z, *et al.* Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. *Br J Dermatol* 2010; 162: 171–5.
12. Hauschild A, *et al.* Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies. *Br J Dermatol* 2009; 160: 1066–74.
13. Szeimies R-M, *et al.* Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. *Br J Dermatol* 2010; 162: 410–14.
14. Cappugi P, *et al.* New proposal for the treatment of nodular basal cell carcinoma with intralesional 5-aminolevulinic acid. *J Chemother* 2004; 16: 491–3.
15. Horn M, *et al.* Topical methyl aminolevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. *Br J Dermatol* 2003; 149: 1242–9.
16. Vinciullo C, *et al.* Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol* 2005; 152: 765–72.
17. Perrett CM, *et al.* Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol* 2007; 156: 320–8.
18. Ackroyd R, *et al.* Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial. *Gut* 2000; 47: 612–17.
19. Barr H. Barrett's esophagus: treatment with 5-aminolevulinic acid photodynamic therapy. *Gastrointest Endosc Clin N Am* 2000; 10: 421–37.
20. Kelty CJ, *et al.* Comparison of high- vs low-dose 5-aminolevulinic acid for photodynamic therapy of Barrett's esophagus. *Surg Endosc* 2004; 18: 452–8.
21. Pech O, *et al.* Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. *Gastrointest Endosc* 2005; 62: 24–30.
22. Tonn J-C, Stummer W. Fluorescence-guided resection of malignant gliomas using 5-aminolevulinic acid: practical use, risks, and pitfalls. *Clin Neurosurg* 2008; 55: 20–6.
23. Colditz MJ, Jeffree RL. Aminolevulinic acid (ALA)-protoporphyrin IX fluorescence guided tumour resection. *J Clin Neurosci* 2012; 19: 1471–4.
24. Baas P, *et al.* Fluorescence detection of pleural malignancies using 5-aminolaevulinic acid. *Chest* 2006; 129: 718–24.
25. Malmström P-U, *et al.* Role of hexaminolevulinate-guided fluorescence cystoscopy in bladder cancer: critical analysis of the latest data and European guidance. *Scand J Urol Nephrol* 2012; 46: 108–16.
26. Lerner SP, *et al.* Fluorescence and white light cystoscopy for detection of carcinoma in situ of the urinary bladder. *Urol Oncol* 2012; 30: 285–9.
27. Waidelich R, *et al.* Whole bladder photodynamic therapy with 5-aminolevulinic acid using a white light source. *Urology* 2003; 61: 332–7.
28. Berger AP, *et al.* Photodynamic therapy with intravesical instillation of 5-aminolevulinic acid for patients with recurrent superficial bladder cancer: a single-center study. *Urology* 2003; 61: 338–41.
29. Barnett AA, *et al.* A randomised, double-blind, placebo-controlled trial of photodynamic therapy using 5-aminolaevulinic acid for the treatment of cervical intraepithelial neoplasia. *Int J Cancer* 2003; 103: 829–32.

tions such as psoriasis, recalcitrant viral warts, acne vulgaris, and cutaneous T-cell lymphoma.[1,2] Topical PDT is considered effective for clearing the lesions of cutaneous leishmaniasis, although further studies are needed. It also appears effective in the treatment of photoageing.[2] Variable results have been reported with this therapy in patients with plaque psoriasis. In one study therapy was generally well-tolerated,[3] but in another all patients reported stinging or burning during irradiation,[4] and topical PDT is not recommended for use in psoriasis.[2] PDT with 5-aminolevulinic acid has been reported to significantly improve an infected leg ulcer resistant to conventional therapies.[5] A topical 10% solution has been used with intraurethral PDT to treat condylomata acuminata.[6] Benefit has also been reported with topical PDT, using 5-aminolevulinic acid 20%, in 10 patients with actinic cheilitis, a common condition of the lower lip, which can progress to squamous cell carcinoma.[7] Topical PDT may potentially be beneficial in skin cancer prophylaxis, although further investigation is needed.[2]

PDT using topical aminolevulinic acid or methyl aminolevulinate can be effective in the treatment of inflammatory acne of the face and back.[2] However, the optimum regimen to achieve a sustained response with minimal adverse effect has not been established. A review[8] found that most studies reported on topical use of aminolevulinic acid 20% or methyl aminolevulinate 16%, but were small and of variable quality. The authors suggested that treatment for moderate to moderately severe inflammatory acne could consist of a short contact time of 15 to 60 minutes under occlusion, followed by broad spectrum yellow and/or red light. A course of therapy could consist of 2 to 4 treatments applied at intervals of 2 to 4 weeks.

1. Ibbotson SH. Topical 5-aminolaevulinic acid photodynamic therapy for the treatment of skin conditions other than non-melanoma skin cancer. *Br J Dermatol* 2002; 146: 178–88.
2. Morton CA, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; 159: 1245–66. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PDTguideline%20BJD%20Dec%202008.pdf (accessed 02/04/13)
3. Smits T, *et al.* A placebo-controlled randomized study on the clinical effectiveness, immunohistochemical changes and protoporphyrin IX accumulation in fractionated 5-aminolaevulinic acid-photodynamic therapy in patients with psoriasis. *Br J Dermatol* 2006; 155: 429–36.
4. Radakovic-Fijan S, *et al.* Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study. *Br J Dermatol* 2005; 152: 279–83.
5. Clayton TR, Harrison PV. Photodynamic therapy for infected leg ulcers. *Br J Dermatol* 2007; 156: 384–5.
6. Wang XL, *et al.* Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminata. *Br J Dermatol* 2004; 151: 880–5.
7. Sotiriou E, *et al.* Actinic cheilitis treated with one cycle of 5-aminolaevulinic acid-based photodynamic therapy: report of 10 cases. *Br J Dermatol* 2008; 159: 261–2.
8. Taylor MN, Gonzalez ML. The practicalities of photodynamic therapy in acne vulgaris. *Br J Dermatol* 2009; 160: 1140–8.

Adverse Effects and Precautions

The mechanism of action of topical 5-aminolevulinic acid or its derivatives generally results in local phototoxicity, manifest as a localised burning or stinging sensation, erythema, oedema, pruritus, scabbing, or pain. Symptoms are usually mild to moderate, and transient. During treatment, patients should be advised to avoid sunlight or prolonged exposure to bright light.

Other common adverse effects on the skin include scaling or crusting, ulceration, suppuration, blistering, bleeding, sensation of heat, erosion or exfoliation, and skin infection. Urticaria, rash, and changes in skin pigmentation may also occur. Application site discharge, eczema, and allergic contact dermatitis have been reported. Systemic effects may occur with topical use. Paraesthesia and headache have been reported commonly; nausea, fatigue, eye swelling or eye pain, and wound haemorrhage have also occurred.

Bladder pain, cystitis, dysuria, haematuria, and abnormal urinalysis may occur with intravesical use. Anaphylactic shock has been reported. Widespread bladder inflammation should be excluded before instillation because of the potential for increased porphyrin accumulation resulting in an increased risk of local toxicity and false fluorescence.

Adverse effects associated with oral use include nausea, hypotension, and photosensitivity. Other reported effects include anaemia, thrombocytopenia, leucocytosis, and increases in bilirubin, liver enzyme, and amylase values.

Handling. US licensed product information warns that nitrile gloves should be worn during application and removal of methyl aminolevulinate hydrochloride cream; vinyl or latex gloves do not provide adequate protection.

Hypersensitivity. Allergic reactions to aminolevulinic acid[1] and methyl aminolevulinate[2] have been reported.

1. Gniadzowska B, *et al.* Allergic contact dermatitis from 5 -aminolevulinic acid used for photodynamic therapy. *Contact Dermatitis* 1998; 38: 348–9.
2. Wulf HC, Philipsen P. Allergic contact dermatitis to 5-aminolaevulinic acid methylester but not to 5-aminolaevulinic acid after photodynamic therapy. *Br J Dermatol* 2004; 150: 143–5.

Porphyria. Licensed product information states that the use of 5-aminolevulinic acid and its derivatives is contra-indicated in patients with porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aminolevulinic acid given orally as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients. However, topical methyl aminolevulinate is classified as not porphyrinogenic because of insignificant systemic absorption; 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 28/03/13)

Interactions

Use with other known photosensitisers such as griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides, and tetracyclines might increase the photosensitivity reaction commonly seen with 5-aminolevulinic acid or its derivatives.

St John's wort. A patient taking St John's wort had a pronounced phototoxic reaction consisting of an erythematous rash and swelling of the face, neck, and hands, 6 hours after receiving oral aminolevulinic acid. Although both drugs have been associated with photosensitivity, the authors suggested a synergistic effect had occurred. Tests *in vitro* appeared to confirm this.[1]

1. Ladner DP, *et al.* Synergistic toxicity of 5 -aminolaevulinic acid-induced protoporphyrin IX used for photodiagnosis and hypericum extract, a herbal antidepressant. *Br J Dermatol* 2001; 144: 916–8.

Pharmacokinetics

After intravenous and oral doses of aminolevulinic acid hydrochloride equivalent to 100 mg of aminolevulinic acid, the mean half-life of aminolevulinic acid is stated to be about 0.83 hours and 0.7 hours, respectively; oral bioavailability is about 50 to 60%. *In-vitro* studies of dermal absorption found that the mean cumulative absorption of methyl aminolevulinate through healthy human skin after 24 hours was 0.26% of a dose and a skin depot containing 4.9% of the dose was formed.

References.

1. Juzeniene A, *et al.* Topical application of 5-aminolaevulinic acid, methyl 5-aminolaevulinate and hexyl 5-aminolaevulinate on normal human skin. *Br J Dermatol* 2006; 155: 791–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Metvix; ***Austral.***: Metvix; ***Austria***: Hexvix; Metvix; ***Belg.***: Gliolan; Hexvix; Metvix; ***Braz.***: Metvix; ***Canad.***: Levulan Kerastick; Metvix; ***Chile***: Levulan Kerastick; Metvix; ***China***: ALA (艾拉); ***Cz.***: Gliolan; Hexvix; MC 506†; Metvix; ***Denm.***: Ameluz; Gliolan; Hexvix; Metvix; ***Fin.***: Hexvix; Metvix; ***Fr.***: Gliolan; Hexvix; Metvixia; ***Ger.***: Gliolan; Hexvix; Metvix; ***Gr.***: Gliolan; Hexvix; Metvix; ***Irl.***: Alacare; Gliolan; Hexvix; Metvix; ***Ital.***: Hexvix; Metvix; ***Jpn***: Alabel; Alaglio; ***Neth.***: Ameluz; Gliolan; Hexvix; Metvix; ***Norw.***: Ameluz; Gliolan; Hexvix; Metvix; ***NZ***: Metvix; ***Pol.***: Gliolan; ***Port.***: Gliolan; Hexvix; Metvix; ***S.Afr.***: Metvix; ***Singapore***: Metvix; ***Spain***: Gliolan; Hexvix; Metvix; ***Swed.***: Gliolan; Hexvix; Metvix; ***Switz.***: Hexvix; Metvix; ***Thai.***: Levulan Kerastick; ***UK***: Ameluz; Gliolan; Hexvix; Metvix; Porphin; ***USA***: Cysview; Levulan Kerastick; Metvixia.

Amonafide (*USAN, rINN*)

Amonafida; Amonafidum; M-FA-142; Nafidimide; NSC-308847; Амонафид.

3-Amino-*N*-[2-(dimethylamino)ethyl]naphthalimide; 5-Amino-2-[2-(dimethylamino)ethyl]-1*H*-benz(de)isoquinoline-1,3(2*H*)-dione.

$C_{16}H_{17}N_3O_2$=283.3

CAS — 69408-81-7.

UNII — 1Q8D39N37L.

Amonafide Hydrochloride (*rINNM*)

Amonafide, Chlorhydrate de; Amonafide dihydrochloride; Amonafidi Hydrochloridum; Hidrocloruro de amonafida; Амонафида Гидрохлорид.

$C_{16}H_{17}N_3O_2$, 2HCl=356.2

CAS — 150091-68-2.

UNII — 2UAV344O66.

NOTE. The name Quinamed has been used as a trade mark for amonafide hydrochloride.

Amonafide Malate (*rINNM*)

Amonafide L-Malate (USAN); Amonafide, Malate d'; Amonafidi Malas; AS-1413; Malato de amonafida; XAN-02; Амонафида Малат.

$C_{16}H_{17}N_3O_2$, $C_4H_6O_5$=417.4

CAS — 618863-54-0.

UNII — U06Q37TEG.

NOTE. The name Xanafide has been used as a trade mark for amonafide malate

Profile

Amonafide is a topoisomerase inhibitor. Amonafide malate has been investigated for the treatment of acute myeloid leukaemia, but failed to improve the rate of complete remission. Amonafide hydrochloride has also been investigated, but some studies were stopped due to serious adverse effects.

Amrubicin (*USAN, rINN*)

Amrubicina; Amrubicine; Amrubicinum; SM-5887; Амрубицин.

(+)-(7*S*,9*S*)-9-Acetyl-9-amino-7-[(2-deoxy-β-D-*erythro*-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione.

$C_{25}H_{25}NO_9$=483.5

CAS — 110267-81-7 (amrubicin); 110311-30-3 (amrubicin hydrochloride).

ATC — L01DB10.

ATC Vet — QL01DB10.

UNII — 93N13LB4Z2.

Profile

Amrubicin is a synthetic anthracycline derivative related to compounds such as doxorubicin (p. 782.3). Amrubicin hydrochloride is a potent topoisomerase II inhibitor that is used as an antineoplastic in the treatment of lung cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Calsed.

Amsacrine (*BAN, USAN, pINN*)

Acridinyl Anisidide; *m*-AMSA; Amsacrina; Amsacrinum; Amsakriini; Amsakrin; CI-880; NSC-249992; Амсакрин.

4′-(Acridin-9-ylamino)methanesulphon-*m*-anisidide.

$C_{21}H_{19}N_3O_3S$=393.5

CAS — 51264-14-3.

ATC — L01XX01.

ATC Vet — QL01XX01.

UNII — 00DPD30SOY.

Incompatibility. Amsacrine is incompatible with sodium chloride 0.9% injection and with other chloride-containing solutions,[1,2] apparently because of the poor solubility of the hydrochloride salt in aqueous solution.[2] Amsacrine reacts with certain plastics.[1]

1. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; 17: 532–8.
2. Trissel LA, *et al.* Visual compatibility of amsacrine with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; 47: 2525–8.

Uses and Administration

Amsacrine is an antineoplastic agent that appears to act by intercalation with DNA and inhibition of nucleic acid synthesis. It may also exert an action on cell membranes. Cells in G_2 or S phases may be most sensitive to its actions.

It is used for the induction and maintenance of remission in adult acute leukaemias, particularly acute myeloid leukaemia.

Amsacrine is prepared as a solution in lactic acid and dimethylacetamide, and is given, diluted in glucose 5%, by intravenous infusion over 60 to 90 minutes.

For the induction of remission, amsacrine may be given at a dose of 90 mg/m² daily for 5 to 8 days, depending on clinical response. Courses may be repeated at 2- to 4-week intervals according to response, and the dose may be increased to 120 mg/m² daily in subsequent courses if tolerated. Maintenance doses of 150 mg/m² as a single dose or divided over 3 consecutive days have been given every 3 to 4 weeks, adjusted if necessary according to response.

Complete blood counts should be performed regularly, and cardiac, liver, kidney, and CNS function should be monitored.

Doses should be reduced in patients with hepatic or renal impairment (see p. 742.1).

References.
1. Ghaddar HM, *et al.* Amsacrine and continuous-infusion high-dose cytosine arabinoside as induction therapy for patients with newly-diagnosed acute myelogenous leukemia. *Leuk Lymphoma* 1996; 22: 71–6.
2. Reman O, *et al.* Groupe d'Étude et de Traitement de la Leucémie Aiguë Lymphoblastique de l'Adulte. Rescue therapy combining intermediate-dose cytarabine with amsacrine and etoposide in relapsed adult acute lymphoblastic leukemia. *Hematol J* 2004; 5: 123–9.
3. Sung WJ, *et al.* Phase II trial of amsacrine plus intermediate-dose Ara-C (IDAC) with or without etoposide as salvage therapy for refractory or relapsed acute leukemia. *Jpn J Clin Oncol* 2005; 35: 612–16.
4. Horstmann MA, *et al.* Amsacrine combined with etoposide and high-dose methylprednisolone as salvage therapy in acute lymphoblastic leukemia in children. *Haematologica* 2005; 90: 1701–3.
5. Kessler T, *et al.* Amsacrine containing induction therapy in elderly AML patients: comparison to standard induction regimens in a matched-pair analysis. *Leuk Res* 2008; 32: 491–4.

Administration in hepatic impairment. In moderate to severe hepatic impairment, dosage of amsacrine may need to be reduced by up to 50%. Some licensed product information recommends an initial reduction of 20 to 30%, to a dose between 60 and 75 mg/m² daily.

Administration in renal impairment. In moderate to severe renal impairment, dosage of amsacrine may need to be reduced by up to 50%. Some licensed product information recommends an initial reduction of 20 to 30%, to a dose between 60 and 75 mg/m² daily.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression is usually dose-limiting and may be severe. The nadir of the white cell count has been reported at about 12 days after treatment, with recovery usually by the 25th day. Pancytopenia and haemorrhage may develop. Nausea and vomiting (mild to moderate), stomatitis (mild to life-threatening), rashes, and alopecia may occur. Grand mal seizures, renal dysfunction, hepatotoxicity, and cardiotoxicity have also been reported. Amsacrine is irritant: there may be phlebitis and local tissue necrosis particularly when given in high concentrations.

Amsacrine should be given with caution to patients with liver or kidney disease, who may require dosage adjustments.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amsacrine 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 28/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Use with diuretics or nephrotoxic drugs such as the aminoglycosides may theoretically increase the risk of cardiotoxicity with amsacrine by precipitating hypokalaemia.

Pharmacokinetics

Amsacrine is poorly absorbed after oral doses. When given intravenously it has a reported terminal half-life of about 5 to 8 hours. It is metabolised in the liver and excreted mainly in the bile, mostly as metabolites. It is reported to be about 98% protein bound.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Amsidyl†; *Belg.*: Amsidine†; *Canad.*: Amsa PD; *Fr.*: Amsalyo; *Ger.*: Amsidyl; *Gr.*: Amsidine; Amsidyl; *Irl.*: Amsidine; *Neth.*: Amsidine; *Swed.*: Amekrin; *Switz.*: Amsidyl; *UK*: Amsidine†.

Anastrozole *(BAN, USAN, rINN)* ⊗

Anastrotsoli; Anastrozol; Anastrozolo; Anastrozolum; ICI-D1033; ZD-1033; Анастрозол.

2,2′-Dimethyl-2,2′-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(propiononitrile); α,α,α′,α′-Tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-*m*-benzenediacetonitrile.

$C_{17}H_{19}N_5$=293.4

CAS — 120511-73-1.

ATC — L02BG03.

ATC Vet — QL02BG03.

UNII — 2Z07MYW1AZ.

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

Ph. Eur. 8: (Anastrozole). A white or almost white powder. Very slightly soluble in water; freely soluble in dehydrated alcohol; practically insoluble in cyclohexane. It shows polymorphism.

USP 36: (Anastrozole). A white to off-white crystalline powder. Freely soluble in alcohol, in methyl alcohol, in acetone, and in tetrahydrofuran; very soluble in acetonitrile.

Uses and Administration

Anastrozole is a potent and selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, which converts adrenal androgens to oestrogens in peripheral tissue. It is used in the treatment of advanced or locally advanced breast cancer, and as adjuvant treatment in hormone receptor-positive early breast cancer (p. 702.1), in postmenopausal women in an oral dose of 1 mg once daily. Responses are unlikely in patients with oestrogen receptor-negative disease, unless they had a previous positive clinical response to tamoxifen. For patients with advanced breast cancer, therapy may be continued until tumour progression. Adjuvant therapy may be continued for up to 5 years, although the optimum duration is uncertain.

References.
1. Jonat W, *et al.* Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006; 7: 991–6. Correction. *ibid.* 2007; 8: 6.
2. Graham PH. Anastrozole for malignant and benign conditions: present applications and future therapeutic integrations. *Expert Opin Pharmacother* 2007; 8: 2347–57.
3. Sanford M, Plosker GL. Anastrozole: a review of its use in postmenopausal women with early-stage breast cancer. *Drugs* 2008; 68: 1319–40.
4. Needleman SJ, Tobias JS. Review of the ATAC study: tamoxifen versus anastrozole in early-stage breast cancer. *Expert Rev Anticancer Ther* 2008; 8: 1871–81.
5. Nabholtz JM, *et al.* Comparative review of anastrozole, letrozole and exemestane in the management of early breast cancer. *Expert Opin Pharmacother* 2009; 10: 1435–47.
6. Kelly CM, Buzdar AU. Anastrozole. *Expert Opin Drug Safety* 2010; 9: 995–1003.
7. Geisler J. Differences between the non-steroidal aromatase inhibitors anastrozole and letrozole—of clinical importance? *Br J Cancer* 2011; 104: 1059–66.

Administration in hepatic impairment. UK licensed product information states that no dosage adjustment of anastrozole is required for patients with mild hepatic impairment, but contra-indicates its use in those with moderate or severe hepatic disease. US licensed product information states that no change in dose is required for those with mild to moderate hepatic impairment and that anastrozole has not been studied in those with severe hepatic impairment; dosage adjustment in patients with stable hepatic cirrhosis is not considered to be necessary.

Administration in renal impairment. US licensed product information allows for unchanged doses of anastrozole in renal impairment. However, UK licensed product information contra-indicates its use in patients with severe renal impairment (those with a creatinine clearance less than 20 mL/min).

Endometriosis. In a small, open-label study,[1] *oral* anastrozole 1 mg, given daily with a low-strength oral contraceptive for 6 months, reduced pelvic pain scores in women with refractory endometriosis (p. 2264.1). Adverse effects were mild, although most patients had breakthrough bleeding, which exacerbated pain. The authors supposed that a higher dose of oral contraceptive should be considered in future studies. A randomised, controlled study to investigate the efficacy of oral anastrozole with subcutaneous goserelin after surgery for endometriosis found the combination increased the pain-free interval and decreased recurrence rates compared with goserelin alone.[2]

There are also reports of success with oral letrozole 2.5 mg daily, given with calcium and vitamin D,[3] and also with norethisterone in some cases.[4] However, use with desogestrel in a small study of women with refractory endometriosis caused the development of functional ovarian cysts, necessitating interruption of treatment.[5]

In a small pilot study of patients with rectovaginal endometriosis,[6] anastrozole 250 micrograms was given *vaginally* once daily for 6 months. Dysmenorrhoea improved significantly although chronic pelvic pain was unchanged. Adverse effects were mild.

A review[4] on the use of aromatase inhibitors for endometriosis noted that, while they may be useful in reducing pain, the long-term course of pain symptoms after interruption of therapy remains to be evaluated, and that their superiority over hormonal therapy has yet to be proven. Furthermore, permanent inhibition of aromatase activity is contra-indicated in women with endometriosis who wish to preserve their fertility, and they should only be offered to selected women who have severe pain despite previous surgical and hormonal therapy; further studies were considered necessary before routine use could be recommended.

1. Amsterdam LL, *et al.* Anastrazole [sic] and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril* 2005; 84: 300–4.
2. Soysal S, *et al.* The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. *Hum Reprod* 2004; 19: 160–7.
3. Razzi S, *et al.* Treatment of severe recurrent endometriosis with an aromatase inhibitor in a young ovariectomised woman. *BJOG* 2004; 11: 182–4.
4. Ferrero S, *et al.* Pharmacological treatment of endometriosis: experience with aromatase inhibitors. *Drugs* 2009; 69: 943–52.
5. Remorgida V, *et al.* Letrozole and desogestrel-only contraceptive pill for the treatment of stage IV endometriosis. *Aust N Z J Obstet Gynaecol* 2007; 47: 222–5.
6. Hefler LA, *et al.* Role of the vaginally administered aromatase inhibitor anastrozole in women with rectovaginal endometriosis: a pilot study. *Fertil Steril* 2005; 84: 1033–6.

Growth hormone deficiency. Up to 3 years of adjuvant treatment with anastrozole in adolescent boys with growth hormone deficiency (see Growth Retardation, p. 1921.3) resulted in significant gains in predicted adult height compared with placebo; the drug was well tolerated and normal pubertal progression was maintained.[1]

1. Mauras N, *et al.* Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years. *J Clin Endocrinol Metab* 2008; 93: 823–31.

Gynaecomastia. Anastrozole has been reported[1,2] to be under investigation for the treatment of gynaecomastia, but controlled studies suggest that it may be no better than placebo—see Gynaecomastia (p. 2264.3) and Gynaecomastia under Adverse Effects and Precautions of Flutamide (p. 799.1).

1. Grunmanis U, Braunstein GD. Treatment of gynecomastia. *Curr Opin Investig Drugs* 2001; 2: 643–9.
2. Mauras N, *et al.* Pharmacokinetics and pharmacodynamics of anastrozole in pubertal boys with recent-onset gynecomastia. *J Clin Endocrinol Metab* 2009; 94: 2975–8.

Infertility. Nonsteroidal aromatase inhibitors such as anastrozole and letrozole have been investigated for their ovulation-inducing effects, see Letrozole, p. 817.2.

Precocious puberty. For a report of the effective use of anastrozole with bicalutamide in the treatment of familial male precocious puberty (testotoxicosis), see Precocious Puberty, under Bicalutamide, p. 749.2.

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of anastrozole are gastrointestinal disturbances (including anorexia, nausea and vomiting, and diarrhoea), asthenia, hot flushes, dizziness, drowsiness, headache, and rash. Other commonly reported effects include hair thinning, vaginal dryness or bleeding, myalgia, arthralgia, carpal tunnel syndrome, and bone pain and/or fractures. Insomnia, depression, peripheral oedema, lymphoedema, increased cough, pharyngitis, dyspnoea, back pain, and hypertension are also common. An increased incidence of cardiovascular adverse events has been seen in women with pre-existing ischaemic heart disease and caution is advised in these patients. Abnormalities in liver enzyme values, hepatitis, thromboembolism, and hypercholesterolaemia can occur. Rare cases of erythema multiforme, Stevens-Johnson syndrome, and allergic reactions (including angioedema, urticaria, and anaphylaxis) have been reported. Other adverse reactions include thrombophlebitis, anaemia, leucopenia, anxiety, cataracts, and urinary-tract infections; bronchitis, rhinitis, and sinusitis have been reported.

Reductions in bone mineral density (BMD) can occur during use of anastrozole. Patients with or at risk of osteoporosis should therefore have their BMD assessed at the start of therapy and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be started as appropriate and carefully monitored.

The use of aromatase inhibitors such as anastrozole is generally contra-indicated in premenopausal women (particularly in pregnancy).

References.
1. Files JA, *et al.* Managing aromatase inhibitors in breast cancer survivors: not just for oncologists. *Mayo Clin Proc* 2010; 85: 560–6.
2. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol* 2006; 7: 633–43.

Breast feeding. Licensed product information states that it is unknown whether anastrozole is distributed into human milk; in the UK its use during breast feeding is contra-indicated while in the USA a decision to use may be made based on clinical judgement. It has been suggested[1] that if only a single dose is given, breast feeding should be withheld for 10 days.

1. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Effects on blood lipids. For a comparison of the effects of anastrozole, letrozole, and exemestane on blood lipids see under Exemestane, p. 792.3.

Effects on the liver. A case of acute hepatitis was attributed to anastrozole, 3 weeks after starting therapy.[1] In another case[2] there was some evidence of an auto-immune mechanism.

1. de la Cruz L, *et al.* Severe acute hepatitis in a patient treated with anastrozole. *Lancet* 2007; 369: 23–4.
2. Inno A, *et al.* Anastrozole-related acute hepatitis with autoimmune features: a case report. *BMC Gastroenterol* 2011; 11: 32.

Effects on the musculoskeletal system. In a series of 77 postmenopausal women treated with anastrozole for metastatic breast cancer, 12 complained of joint pains within 2 months of beginning therapy. Based on this experience and the incidence of arthralgia reported during clinical studies, the authors estimated that arthralgia occurs in 10 to 15% of patients treated with anastrozole, possibly as a result of the very low oestrogen concentrations achieved.[1] It has been suggested that there may be modest differences between ethnic groups in the incidences of joint symptoms and bone fractures,[2] which seem to be lower in Japanese patients.

Adjuvant anastrozole therapy for postmenopausal women with early breast cancer was associated with accelerated bone loss, but the risk appeared to be confined to those with osteopenia at baseline.[3] A retrospective review[4] including 316 patients treated with aromatase inhibitors (anastrozole, letrozole, or exemestane) found that there was a significant association between musculoskeletal symptoms and bone mineral density (BMD) results; those with severe symptoms had an increased likelihood of having an abnormal BMD. Patients who were also taking calcium and bisphosphonates had fewer symptoms and fewer fractures, and those who had taken tamoxifen before aromatase inhibitors were less likely to develop musculoskeletal symptoms. Those taking steroidal aromatase inhibitors had significantly more arthralgia, generalised bone pain or myalgia, and bone fractures than those taking nonsteroidal aromatase inhibitors. The need to assess the risk of osteoporosis before starting therapy has been stressed.[5]

1. Donnellan PP, *et al.* Aromatase inhibitors and arthralgia. *J Clin Oncol* 2001; 19: 2767.
2. Okishiro M, *et al.* Incidence of joint symptoms and bone fractures in Japanese postmenopausal breast cancer patients treated with adjuvant anastrozole. *J Cancer Res Clin Oncol* 2009; 135: 823–7.
3. Eastell R, *et al.* Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 2008; 26: 1051–8.
4. Muslimani AA, *et al.* Aromatase inhibitor-related musculoskeletal symptoms: is preventing osteoporosis the key to eliminating these symptoms? *Clin Breast Cancer* 2009; 9: 34–8.
5. Chien AJ, Goss PE. Aromatase inhibitors and bone health in women with breast cancer. *J Clin Oncol* 2006; 24: 5305–12.

CARPAL TUNNEL SYNDROME. Carpal tunnel syndrome has been reported in postmenopausal women given anastrozole; in one study,[1] more than 3 times as many women taking anastrozole developed carpal tunnel syndrome than those taking tamoxifen, although the incidence was still low (2.6%). Most cases were of mild or moderate intensity and short duration; risk factors were an age of 60 years or younger, or previous treatment with hormone replacement therapy or chemotherapy.

1. Sestak I, *et al.* Aromatase inhibitor-induced carpal tunnel syndrome: results from the ATAC trial. *J Clin Oncol* 2009; 27: 4961–5.

Effects on the skin. A cutaneous eruption, diagnosed as subacute cutaneous lupus erythematosus, appeared 1 month after starting anastrozole. The patient was also taking an ACE inhibitor. The condition improved slightly after stopping anastrozole and replacing the ACE inhibitor with atenolol, but reappeared with greater intensity when anastrozole was restarted. Anastrozole was stopped again and the patient was treated with hydroxychloroquine and corticosteroids; after 4 months, signs had resolved and no recurrence was seen after 1 year.[1]

1. Trancart M, *et al.* Anastrozole-induced subacute cutaneous lupus erythematosus. *Br J Dermatol* 2008; 158: 628–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies anastrozole 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 05/09/11)

Interactions

Tamoxifen. In a study of postmenopausal women with breast cancer, use of *daily* tamoxifen with anastrozole reduced anastrozole concentrations by 27% compared with daily anastrozole monotherapy; however, the effect of anastrozole on estradiol suppression was similar whether used alone or with tamoxifen.[1] In another study of daily anastrozole, *weekly* tamoxifen, or the combination thereof, there was no difference in anastrozole concentration in the combination arm compared with the anastrozole monotherapy arm in the first year.[2] The authors hypothesised that when given at a daily dose, tamoxifen has a mainly oestrogenic effect in an oestrogen-deprived environment, whereas a weekly dose still provides desirable oestrogenic properties when added to anastrozole, but without impairing anastrozole bioavailability.[2]

1. Dowsett M, *et al.* ATAC Trialists' Group. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex™ and tamoxifen alone or in combination' (ATAC) trial. *Br J Cancer* 2001; 85: 317–24.
2. Bonanni B, *et al.* Randomized biomarker trial of anastrozole or low-dose tamoxifen or their combination in subjects with breast intraepithelial neoplasia. *Clin Cancer Res* 2009; 15: 7053–60.

Pharmacokinetics

Anastrozole is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about 2 hours. Food decreases the rate of absorption, though this is not considered clinically significant. Anastrozole is 40% bound to plasma proteins. It is metabolised in the liver by *N*-dealkylation, hydroxylation, and glucuronidation; the main metabolite is triazole, which lacks pharmacological activity (but see also Metabolism, below). Anastrozole is excreted in the urine, chiefly as metabolites. The terminal plasma elimination half-life is about 40 to 50 hours, and steady-state concentrations occur after about 7 days in patients receiving once-daily doses.

Metabolism. Anastrozole is mainly cleared by hepatic metabolism (see Pharmacokinetics, above); it has been hypothesised[1] that differences in metabolism may contribute to the interindividual variability in the drug's effects. A study to characterise anastrozole metabolism concluded that hydroxylation and *N*-glucuronidation are the main metabolic pathways.[1] *In vitro* and *in vivo* data suggested that anastrozole is hydroxylated to hydroxyanastrozole, mainly by the cytochrome P450 isoenzyme CYP3A4; there may be some involvement of CYP3A5. Hydroxyanastrozole is then rapidly and extensively conjugated probably by uridine diphosphate glucuronosyltransferases (UGTs). *N*-Glucuronidation of anastrozole to anastrozole glucuronide occurs mainly by UGT1A4, although the precise contribution of the enzyme to *in vivo* metabolism is unknown. Triazole or any *N*-dealkylated metabolites could not be detected in *in vitro* studies; the role of *N*-dealkylation in anastrozole metabolism could not be confirmed.

1. Kamdem LK, *et al.* In vitro and in vivo oxidative metabolism and glucuronidation of anastrozole. *Br J Clin Pharmacol* 2010; 70: 854–69.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Anaskebir; Anastraze; Anebol; Arimidex; Aromenal; Cefer; Distalene; Gondonar; Leprofen; Pantestone; Puricap; Trozolite; ***Austral.***: Anastrol; Arimidex; ***Austria***: Anastrolan; Arimidex; ***Belg.***: Arimidex; ***Braz.***: Arimidex; ***Canad.***: Arimidex; ***Chile***: Anebol; Arimidex; Madelen; Trozolet; ***China***: Ai Da (艾达); Arimidex (瑞宁得); Rui Si Yi (瑞斯意); Rui Ting (瑞婷); *Cz.*: Acydex†; Alozex; Anabrest†; Anaprex; Anasolde†; Anastar; Anastrad; Anaya; Arimidex; Armotraz; Asnea; Betasolde†; Deltasolde; Ebezolid; Egistrozol; Epsisolde; Gammasolde; Mammozole; Mastoren; OncoFem; Trasolette†; Zelotrin†; Zenbrest; Zynzol; ***Denm.***: Anastelb; Arimidex; Mimastran; ***Fin.***: Anazol; Arimidex; ***Fr.***: Arimidex; ***Ger.***: Anablock; Anadex; Anastro; Anastromin; Arimidex; ***Gr.***: Anastrogen; Arimidex; Astrazol; Enastros; Londer; Oxeda; Strazal; Viastrol; Zolitrat; ***Hong Kong***: Arimidex; ***Hung.***: Anabrest; Anamataz; Anaromat; Arilla; Arimidex; Axastrol; Mammozole; Mastoren; Nobrec; Valmidex; Zynzol†; ***India***: Altraz; Altrol; Anabrez; Arimidex; Armotraz; ***Indon.***: Arimidex; ***Irl.***: Agerdex; Amidex; Anastarrow†; Arimidex; ***Israel***: Anastrol; Anastrose; Arimidex; ***Ital.***: Ankarma; Arimidex; Eristrol; Extroplex; Raoloz; Renazole; ***Malaysia***: Arimidex; ***Mex.***: Arimidex; ***Neth.***: Anoxidil; Arimidex; Barstra; Biostrol; Brestazol; Egistrozol; Genstra†; Kirana†; Mastrol; Regost; Renazole†; Strakir; Zolkir; Zolzyn; ***Norw.***: Arimidex; ***NZ***: Aremed; Arimidex; ***Philipp.***: Anzol; Arimidex; ***Pol.***: Anastralan; AnastroGen; AnastroLek; Ansyn; Apo-Nastrol; Arimidex; Arinel†; Atrozol; Egistrozol; Mamostrol; Symanastrol; Zolastrol; ***Port.***: Anacyne†; Arimidex; Astoz; Remidex†; ***Rus.***: Anastera (Анастера); Arimidex (Аримидекс); Egistrazol (Эгистразол); Mammosole (Маммозол); ***S.Afr.***: Arimidex; Stradexa; ***Singapore***: Aremed; Arimidex; ***Spain***: Amenur; Anabrest†; Arimidex; Curmyl†; ***Swed.***: Anastelb; Arimidex; ***Switz.***: Arimidex; ***Thai.***: Aremed; Arimidex; Femizet; ***Turk.***: Arimidex; ***UK***: Arimidex; ***Ukr.***: Arimidex (Аримидекс); Axastrol (Аксастрол); ***USA***: Arimidex; ***Venez.***: Arimidex; Trozolet.

Antineoplaston A10

3-Phenylacetylamino-2,6-piperidinedione.
$C_{13}H_{14}N_2O_3$=246.3

Profile

Antineoplaston A10, one of a group of peptide derivatives isolated from blood and urine, has been investigated for the treatment of breast cancer, brain stem glioma, and other malignant neoplasms although its value has been questioned (see below).

A critical review of the antineoplastons[1] noted that most work had been done with antineoplaston A10, which is insoluble in aqueous solutions, and its derivatives antineoplaston AS2.5 (phenylacetylglutamine), and antineoplaston AS2.1 (a 4:1 mixture of phenylacetic acid and phenylacetylglutamine), which had not been independently shown to be active against cancer. However, some interest in the antineoplastons subsequently continued.[2-4]

1. Green S. Antineoplastons: an unproved cancer therapy. *JAMA* 1992; 267: 2924–8.
2. Buckner JC, *et al.* Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma. *Mayo Clin Proc* 1999; 74: 137–45.
3. Badria F, *et al.* Immune modulatory potentials of antineoplaston A-10 in breast cancer patients. *Cancer Lett* 2000; 157: 57–63.
4. Burzynski SR, *et al.* Targeted therapy with antineoplastons A10 and AS2-1 of high-grade, recurrent, and progressive brainstem glioma. *Integr Cancer Ther* 2006; 5: 40–7.

AS-1411

AGRO-100.

Profile

AS-1411 is a selective oligonucleotide ligand (aptamer) that binds to the protein nucleolin, inducing apoptosis in cancer cells. It is under investigation for the treatment of renal cell carcinoma, pancreatic cancer, and acute myelogenous leukaemia.

References.

1. Bates PJ, *et al.* Discovery and development of the G-rich oligonucleotide AS1411 as a novel treatment for cancer. *Exp Mol Pathol* 2009; 86: 151–64.
2. Mongelard F, Bouvet P. AS-1411, a guanosine-rich oligonucleotide aptamer targeting nucleolin for the potential treatment of cancer, including acute myeloid leukemia. *Curr Opin Mol Ther* 2010; 12: 107–14.

Asparaginase *(USAN)*

L-Asparaginaasi; L-Asparaginas; Asparaginasa; L-Asparaginasa; L-Asparaginase; L-Asparaginasum; L-Asparaginaz; L-Asparagine Amidohydrolase; MK-965; NSC-109229; Re-82-TAD-15; Аспарагиназа.

CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.
UNII — G4FQ3CKY5R.

NOTE. Asparaginase (*USAN*) is an enzyme isolated from *Escherichia coli*, or obtained from other sources. See also Colaspase and Crisantaspase, below.

Incompatibility. Asparaginase is incompatible with rubber. Licensed product information recommends that it should not be mixed with other drugs.

Storage. Asparaginase should be stored at 2 degrees to 8 degrees (see also Stability, p. 744.1).

Colaspase *(BAN)*

CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Colaspase (*BAN*) is asparaginase obtained from selected strains of *Escherichia coli*, such as ATCC 9637.

Pharmacopoeias. *Chin.* includes Asparaginase obtained from *Escherichia coli* ASI 357.

Crisantaspase *(BAN, pINN)*

Asparaginase *Erwinia chrysanthemi* (USAN); Crisantaspasa; Crisantaspasum; Erwinia L-asparaginase; Krisantaspaasi; Krisantaspas; Крисантаспаза.

CAS — 9015-68-3; 1349719-22-7.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Crisantaspase (*BAN*) is asparaginase obtained from cultures of *Erwinia chrysanthemi* (*E. carotovora*).

Pegaspargase *(USAN, rINN)*

PEG-L-asparaginase; Pegaspargasa; Pégaspargase; Pegaspargasum; Пегаспаргаза.

A conjugate of colaspase with a polyethylene glycol of molecular weight 5000; Monomethoxypolyethylene glycol succinimidyl L-asparaginase.
CAS — 130167-69-0.
ATC — L01XX24.
ATC Vet — QL01XX24.
UNII — 7D96IR0PPM.

Stability. Although asparaginase was routinely kept under refrigeration,[1] information from a manufacturer (*Merck Sharp & Dohme*) indicated that it would remain stable for 48 hours at 15 degrees to 30 degrees. Licensed product information for pegaspargase states it should not be used if stored at room temperature for more than 48 hours.

1. Vogenberg FR, Souney PF. Stability guidelines for routinely refrigerated drug products. *Am J Hosp Pharm* 1983; **40:** 101–2.

Storage. Pegaspargase should be stored at 2 degrees to 8 degrees.

Units

One international unit of asparaginase splits 1 micromole of ammonia from L-asparagine in 1 minute under standard conditions.

Uses and Administration

Asparaginase is an enzyme that acts by breaking down the amino acid L-asparagine to aspartic acid and ammonia. It interferes with the growth of those malignant cells which, unlike most healthy cells, are unable to synthesise L-asparagine for their metabolism, but resistance to its action develops fairly rapidly. Its action is reportedly specific for the G_1 phase of the cell cycle.

Asparaginase and pegaspargase are used mainly in combination regimens for the induction of remissions in acute lymphoblastic leukaemia (p. 692.3). Pegaspargase may be used in patients who are hypersensitive to asparaginase (although hypersensitivity to pegaspargase can still occur, see Adverse Effects, below).

Crisantaspase may be given by intramuscular, intravenous, or subcutaneous injection. Colaspase may be given intramuscularly (maximum volume of 2 mL per injection), or intravenously over not less than 30 minutes into a running infusion of sodium chloride, or glucose 5%. Regimens vary, and dosage should follow local protocols, but a usual dose of asparaginase given as crisantaspase 6000 units/m² (200 units/kg) is given three times weekly for 3 weeks. Alternatively, pegaspargase may be given intramuscularly (maximum volume of 2 mL per injection) or intravenously diluted in 100 mL of sodium chloride, or glucose 5% and given over 1 to 2 hours into a running infusion, in a dose of 2500 units/m² no more frequently than every 14 days.

Asparaginase is not generally used alone as an induction agent but doses of 200 units/kg daily have been given intravenously as colaspase, for 28 days.

Many of the regimens using asparaginase or pegaspargase are for use in children; for further details see below.

Although not entirely reliable, an intradermal test dose of about 2 units has been recommended in the USA, to test for hypersensitivity before treatment with asparaginase or where more than a week has elapsed between doses. Desensitisation has been advocated in patients at increased risk of allergic reactions. The incidence of hypersensitivity is lower in patients given pegaspargase, and a test dose is not advocated.

References.
1. Muller HJ, Boos J. Use of L-asparaginase in childhood ALL. *Crit Rev Oncol Hematol* 1998; **28:** 97–113.
2. Asselin BL. The three asparaginases: comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol* 1999; **457:** 621–9.
3. Abshire TC, *et al.* Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 2000; **96:** 1709–15.
4. Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future. *Clin Pharmacokinet* 2005; **44:** 367–93.
5. Fu CH, Sakamoto KM. PEG-asparaginase. *Expert Opin Pharmacother* 2007; **8:** 1977–84.
6. Douer D. Is asparaginase a critical component in the treatment of acute lymphoblastic leukemia? *Best Pract Res Clin Haematol* 2008; **21:** 647–58.
7. Jaccard A, *et al.* L-asparaginase-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature. *Ann Oncol* 2009; **20:** 110–16. Correction. *ibid.*: 1612.
8. Zeidan A, *et al.* Pegasparaginase: where do we stand? *Expert Opin Biol Ther* 2009; **9:** 111–19.

Administration in children. Asparaginase and pegaspargase are used in children mainly in combination regimens for the induction of remission in acute lymphoblastic leukaemia. Pegaspargase may be used in children who are hypersensitive to asparaginase (although hypersensitivity to pegaspargase can still occur, see Adverse Effects, below). Regimens vary and dosage should follow local protocols, but doses are similar to those used in adults, see above. US licensed product information describes combination regimens using asparaginase with vincristine and prednisone for children with acute lymphoblastic leukaemia; typical asparaginase doses (given as colaspase) include:

- intravenous asparaginase 1000 units/kg daily for 10 days
- intramuscular asparaginase 6000 units/m² given every third day for 9 doses

Asparaginase toxicity is reported to affect children less than adults. A large study in children with acute lymphoblastic leukaemia also found that asparaginase derived from *Erwinia chrysanthemi* (crisantaspase) had a lower toxicity than that derived from *Escherichia coli* (colaspase); however, a lower survival rate was noted with crisantaspase over 5 years of treatment.[1]

1. Moghrabi A, *et al.* Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood* 2007; **109:** 896–904.

Adverse Effects

Asparaginase is a protein and may produce anaphylaxis and other hypersensitivity reactions including fever, rashes, bronchospasm, urticaria, hypotension, and laryngeal oedema. The risk of anaphylactic reactions increases with continued exposure to asparaginase, and may be increased on re-exposure to asparaginase after a drug-free interval. Patients who develop hypersensitivity to asparaginase derived from *Escherichia coli* may be able to continue treatment with that derived from *Erwinia chrysanthemi* as the enzymes are immunologically distinct. Hypersensitivity to pegaspargase is less common, but is still significant; about 30% of patients hypersensitive to asparaginase will be hypersensitive to pegaspargase too.

Liver function abnormalities occur in many patients, and there may be decreased blood concentrations of fibrinogen and clotting factors resulting in coagulopathy or thrombotic complications. There may also be alterations in blood lipids and cholesterol, and hypoalbuminaemia. Hyperammonaemia, due to the production of ammonia from asparagine, may occur. Uraemia, and occasionally renal failure, have been reported. Pancreatitis may occur and may be fatal: there may also be hyperglycaemia due to decreased insulin production, and death from ketoacidosis has occurred.

Gastrointestinal disturbances, including nausea and vomiting, and CNS disturbances, including drowsiness, depression, coma, hallucinations, seizures, and a Parkinson-like syndrome, have also been reported. Myalgia, reactive arthritis, and transient bone-marrow depression have occurred rarely, as has marked leucopenia. Fatal hyperthermia has been reported.

General references.
1. Earl M. Incidence and management of asparaginase-associated adverse events in patients with acute lymphoblastic leukemia. *Clin Adv Hematol Oncol* 2009; **7:** 600–6.

Effects on the blood. Central thrombosis or intracranial haemorrhage as well as peripheral thrombosis and haemorrhage have been reported after asparaginase therapy.[1–4] Although the precise mechanism for this effect remains unclear, asparaginase appears to deplete certain clotting factors as well as antithrombin III, plasminogen, and fibrinogen.[4] These decreases may be dependent on the formulation and resultant asparaginase activity of preparations,[5] and there is some suggestion that crisantaspase may affect coagulation factors less severely than colaspase.[6] A multicentre, retrospective survey[3] of paediatric patients with acute lymphoblastic leukaemia found that use of corticosteroids with colaspase may be an additional risk factor for thromboembolic events.

1. Priest JR, *et al.* A syndrome of thrombosis and hemorrhage complicating L-asparaginase therapy for childhood acute lymphoblastic leukemia. *J Pediatr* 1982; **100:** 984–9.
2. Ott N, *et al.* Sequelae of thrombotic or hemorrhagic complications following L-asparaginase therapy for childhood lymphoblastic leukemia. *Am J Pediatr Hematol Oncol* 1988; **10:** 191–5.
3. Sutor AH, *et al.* Bleeding and thrombosis in children with acute lymphoblastic leukaemia, treated according to the ALL-BFM-90 protocol. *Klin Padiatr* 1999; **211:** 201–4.
4. Alberts SR, *et al.* Thrombosis related to the use of L-asparaginase in adults with acute lymphoblastic leukemia: a need to consider coagulation monitoring and clotting factor replacement. *Leuk Lymphoma* 1999; **32:** 489–96.
5. Nowak-Göttl U, *et al.* Influence of two different Escherichia coli asparaginase preparations on fibrinolytic proteins in childhood ALL. *Haematologica* 1996; **81:** 127–31.
6. Carlsson H, *et al.* Effects of Erwinia-asparaginase on the coagulation system. *Eur J Haematol* 1995; **55:** 289–93.

Hypersensitivity. Reports of a low rate of cross-sensitivity to crisantaspase in patients hypersensitive to colaspase.[1,2]

1. Billett AL, *et al.* Allergic reactions to Erwinia asparaginase in children with acute lymphoblastic leukemia who had previous allergic reactions to Escherichia coli asparaginase. *Cancer* 1992; **70:** 201–6.
2. Vrooman LM, *et al.* Erwinia asparaginase after allergy to E. coli asparaginase in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2010; **54:** 199–205.

Precautions

Asparaginase is contra-indicated in patients with pancreatitis, and should be avoided in pregnancy. It should be given cautiously to patients with hepatic impairment; liver function should be measured regularly during treatment. Treatment should be stopped if an allergic reaction occurs and not restarted with the same type of asparaginase. Facilities for the management of anaphylaxis (see p. 1293.2) should be available during treatment. Some licensed product information recommends an intradermal test dose at the start of asparaginase treatment to check for hypersensitivity, as described under Uses, above, although such tests may not always be predictive. Careful observation is needed when re-treating with asparaginase after a break in therapy, as there may be an increased risk of allergic reactions. Desensitisation has been used in patients at increased risk of hypersensitivity, although it may itself be hazardous. Serum amylase and lipase concentrations should be monitored regularly as should blood glucose concentrations. Asparaginase has been reported to interfere with tests of thyroid function by transient reduction of concentrations of thyroxine-binding globulin. Routine screening of blood clotting factors should be carried out before starting treatment; if coagulopathy occurs, asparaginase should be withheld until recovery. Monitoring of blood count and bone marrow is also recommended. Measures to protect against the adverse effects of hyperuricaemia may be required (see p. 600.1).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies asparaginase 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 14/11/11)

Interactions

Use of asparaginase with other drugs that affect liver function may increase the risk of hepatotoxicity and concomitant corticosteroid therapy may increase the risk of coagulation abnormalities. If asparaginase is given with methotrexate the activity of the latter may be reduced (see below). Vincristine neurotoxicity may possibly be increased by use with asparaginase (see p. 884.1).

Methotrexate. Asparaginase inhibits protein synthesis and cell replication, and therefore may interfere with the action of drugs such as methotrexate that require cell replication for their antineoplastic effect.[1] Licensed product information for asparaginase states that this effect persists as long as plasma-asparagine concentrations are suppressed and recommends that methotrexate should not be given with, or after asparaginase, while asparagine concentrations are below normal. It has been suggested that giving methotrexate 24 hours *before* asparaginase permits at least an additive therapeutic effect.[2]

1. Jolivet J, *et al.* Prevention of methotrexate cytotoxicity by asparaginase inhibition of methotrexate polyglutamate formation. *Cancer Res* 1985; **45:** 217–20.
2. Capizzi RL. Asparaginase-methotrexate in combination chemotherapy: schedule-dependent differential effects on normal versus neoplastic cells. *Cancer Treat Rep* 1981; **65** (suppl 4): 115–21.

Pharmacokinetics

After intravenous injection the plasma half-life of the native enzyme has varied from about 8 to 30 hours; half-lives of up to 49 hours may be seen after intramuscular dosage. The mean half-life of pegaspargase is reported to be between 6 and 14 days. Asparaginase is found in the lymph at about 20% of the concentration in plasma. There is virtually no diffusion into the CSF. Little is excreted in the urine.

References.
1. Panetta JC, *et al.* Comparison of native *E. coli* and PEG asparaginase pharmacokinetics and pharmacodynamics in pediatric acute lymphoblastic leukemia. *Clin Pharmacol Ther* 2009; **86:** 651–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kidrolase; Oncaspar; ***Austral.***: Leunase; ***Austria***: Erwinase; ***Belg.***: Paronal; ***Braz.***: Elspar; ***Canad.***: Erwinase; Kidrolase; ***China***: Leunase (左旋门冬酰胺酶); ***Cz.***: Kidrolase; ***Fr.***: Kidrolase; ***Ger.***: Erwinase†; Oncaspar; ***Gr.***: Erwinase; Oncaspar; ***Hong Kong***: Leunase; ***India***: L-Aspase; Leucoginase; Leunase; Oncoginase; Onconase; ***Indon.***: Leunase; ***Irl.***: Erwinase; ***Israel***: Kidrolase; ***Jpn***: Leunase; ***Malaysia***: Leunase; ***Mex.***: Elspar; Leunase; ***Neth.***: Erwinase; Paronal; ***NZ***: Erwinase; Leunase; ***Philipp.***: Leunase; ***Pol.***: Oncaspar; ***Port.***: Erwinase; ***Rus.***: Oncaspar (Онкаспар); ***S.Afr.***: Laspar; ***Singapore***: Erwinase; Leunase; ***Thai.***: Erwinase; Leunase; ***Turk.***: Leunase; ***UK***: Erwinase; ***USA***: Elspar; Erwinaze; Oncaspar.

Atiprimod (rINN)

Atiprimodum; Атипримод.
2-[3-(Diethylamino)propyl]-8,8-dipropyl-2-azaspiro[4.5]decane.

$C_{22}H_{44}N_2$=336.6.
CAS — 123018-47-3 (atiprimod); 130065-61-1 (atiprimod hydrochloride); 183063-72-1 (atiprimod maleate).
UNII — MG7D3QD743.

Profile

Atiprimod is an antineoplastic that is under investigation for the treatment of carcinoid tumours and multiple myeloma.

Atrasentan Hydrochloride *(USAN, rINNM)*

A-147627.1; Abbott-147627; ABT-627; Atrasentan, Chlorhydrate d'; Atrasentani Hydrochloridum; Hidrocloruro de atrasentán; Атразентана Гидрохлорид.
(2*R*,3*R*,4*S*)-1-[(Dibutylcarbamoyl)methyl]-2-(*p*-methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-3-pyrrolidinecarboxylic acid hydrochloride.
$C_{29}H_{38}N_2O_6$,HCl=547.1
CAS — 173937-91-2 (atrasentan); 195733-43-8 (atrasentan hydrochloride).
UNII — E4G31X93ZA.

NOTE. The name Xinlay has been used as a trademark for atrasentan hydrochloride.

Profile

Atrasentan hydrochloride is a selective endothelin-A receptor antagonist that inhibits the effect of endothelin-1, a protein that may be involved in cancer progression. It is under investigation in the treatment of prostate cancer, and has been tried in other malignant neoplasms, as well as for complications of diabetes and the metabolic syndrome.

References.
1. Samara E, *et al.* Single-dose pharmacokinetics of atrasentan, an endothelin-A receptor antagonist. *J Clin Pharmacol* 2001; **41:** 397–403.
2. Carducci MA, *et al.* Atrasentan, an endothelin-receptor antagonist for refractory adenocarcinomas: safety and pharmacokinetics. *J Clin Oncol* 2002; **20:** 2171–80.
3. Carducci MA, *et al.* Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. *J Clin Oncol* 2003; **21:** 679–89.
4. Zonnenberg BA, *et al.* Phase I dose-escalation study of the safety and pharmacokinetics of atrasentan: an endothelin receptor antagonist for refractory prostate cancer. *Clin Cancer Res* 2003; **9:** 2965–72.
5. Ryan CW, *et al.* Dose-ranging study of the safety and pharmacokinetics of atrasentan in patients with refractory malignancies. *Clin Cancer Res* 2004; **10:** 4406–11.
6. Michaelson MD, *et al.* Randomized phase II study of atrasentan alone or in combination with zoledronic acid in men with metastatic prostate cancer. *Cancer* 2006; **107:** 530–5.
7. Carducci MA, *et al.* Atrasentan Phase III Study Group Institutions. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer* 2007; **110:** 1959–66.
8. Chiappori AA, *et al.* Phase I/II study of atrasentan, an endothelin A receptor antagonist, in combination with paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer. *Clin Cancer Res* 2008; **14:** 1464–9.
9. Phuphanich S, *et al.* New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. Phase I safety study of escalating doses of atrasentan in adults with recurrent malignant glioma. *Neuro-oncol* 2008; **10:** 617–623.
10. Nelson JB, *et al.* Atrasentan Phase 3 Study Group. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. *Cancer* 2008; **113:** 2478–87.
11. Raichlin E, *et al.* Efficacy and safety of atrasentan in patients with cardiovascular risk and early atherosclerosis. *Hypertension* 2008; **52:** 522–8.
12. Russo A, *et al.* Anti-endothelin drugs in solid tumors. *Expert Opin Emerg Drugs* 2010; **15:** 27–40.

Axitinib *(USAN, rINN)*

AG-013736; Axitinibum; Акситиниб.
N-Methyl-2-({3-[(1*E*)-2-(pyridin-2-yl)ethenyl]-1*H*-indazol-6-yl}sulfanyl)benzamide.
$C_{22}H_{18}N_4OS$=386.5
CAS — 319460-85-0.
UNII — C9LVQ0YUXG.

Uses and Administration

Axitinib is an inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases. It is given orally in the treatment of advanced renal cell carcinoma (p. 708.3). *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The recommended initial dose is 5 mg twice daily, given at 12-hourly intervals. The dose may be increased in patients who tolerate axitinib for at least 2 consecutive weeks with no adverse effects above grade 2, are normotensive, and are not receiving antihypertensive therapy; an increase to 7 mg twice daily, and then to 10 mg twice daily may be considered. If the dose must be decreased because of adverse effects, it is suggested that 5 mg twice daily is reduced to 3 mg twice daily, and then to 2 mg twice daily, if necessary.

The use of strong inhibitors of the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 should be avoided in patients given axitinib. If the combination must be used then the dose of axitinib should be halved, with further adjustments made according to patient response.

The dose of axitinib should be reduced in patients with hepatic impairment (see below).

Axitinib is also under investigation for the treatment of other cancers, including thyroid and liver cancers.

References.
1. Rini BI, *et al.* Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2009; **27:** 4462–8.
2. Kelly RJ, Rixe O. Axitinib (AG-013736). *Recent Results Cancer Res* 2010; **184:** 33–44.
3. Rini BI, *et al.* Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011; **378:** 1931–9.

Administration in hepatic impairment. The starting dose of axitinib should be reduced in patients with moderate hepatic impairment (Child-Pugh class B) to about half the usual starting dose (see Uses and Administration, above). Further dose adjustment should be made based on individual response. Specific information on its use in severe hepatic impairment (Child-Pugh class C) is lacking.

References.
1. Tortorici MA, *et al.* Influence of mild and moderate hepatic impairment on axitinib pharmacokinetics. *Invest New Drugs* 2011; **29:** 1370–80.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of axitinib include gastrointestinal disturbances, reduced appetite, weight loss, fatigue, asthenia, dysphonia, and palmar-plantar erythrodysesthesia.

Hypertension is also common and cases of hypertensive crisis have been reported. Blood pressure should be well-controlled before starting axitinib and monitored during therapy. Antihypertensive treatment may be needed but the dose of axitinib should be reduced if hypertension persists; axitinib should be stopped if hypertension is severe and persistent or there is evidence of hypertensive crisis. Arterial and venous thromboembolism have occurred in patients given axitinib. Reported haemorrhagic events have included cerebral haemorrhage, haematuria, and gastrointestinal bleeding. Gastrointestinal perforation and fistula formation have also been reported.

Other adverse effects include thyroid dysfunction, proteinuria, and elevations of liver enzymes values; patients should be assessed for these before starting axitinib and monitored during therapy. There have also been cases of reversible posterior leukoencephalopathy syndrome in patients given axitinib.

Axitinib should be stopped at least 24 hours before surgery, because of potential impairment of wound healing.

Interactions

Plasma concentrations of axitinib may be altered by the concomitant use of drugs that affect the cytochrome P450 isoenzymes CYP3A4 and CYP3A5. Strong inhibitors of these enzymes should be avoided, but if they must be used then the dose of axitinib should be reduced (see Uses and Administration, above). Grapefruit and grapefruit juice should also be avoided. Moderate and strong inducers of these enzymes can reduce axitinib concentrations and should therefore be avoided during axitinib therapy.

Pharmacokinetics

Axitinib is absorbed from the gastrointestinal tract. It has a bioavailability of about 58% and is highly bound to plasma proteins. Axitinib is metabolised mainly in the liver by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Most of the dose is excreted as metabolites in the urine and faeces; about 12% is excreted unchanged in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Denm.***: Inlyta; ***Jpn***: Inlyta; ***Neth.***: Inlyta; ***Norw.***: Inlyta; ***Switz.***: Inlyta; ***UK***: Inlyta; ***USA***: Inlyta.

Azacitidine *(BAN, USAN, rINN)*

5-Azacitidina; Azacitidina; Azacitidinum; 5-Azacytidine; Ladakamycin; NSC-102816; U-18496; Азацитидин.
4-Amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one.
$C_8H_{12}N_4O_5$=244.2
CAS — 320-67-2.
ATC — L01BC07.
ATC Vet — QL01BC07.
UNII — M801H13NRU.

Uses and Administration

Azacitidine is an antimetabolite antineoplastic with general properties similar to those of cytarabine (p. 774.1). It also inhibits cellular pyrimidine synthesis. Azacitidine is used in myelodysplastic syndromes (p. 694.3); it is also used in the treatment of acute myeloid leukaemia (p. 693.1) and chronic myelomonocytic leukaemia.

Azacitidine is given subcutaneously or intravenously in a dose of 75 mg/m² daily for 7 days, in 4-week cycles. For myelodysplastic syndromes, if there is no benefit after 2 cycles, and no toxicity other than nausea and vomiting has occurred, the dose may be increased to 100 mg/m² daily.

Treatment for at least 4 to 6 cycles is usually recommended; treatment is continued as long as the patient benefits, or until disease progression. Doses may need to be adjusted for haematological toxicity. Azacitidine should be used with caution in renal impairment and doses adjusted accordingly (see below).

References.
1. Siddiqui MAA, Scott LJ. Azacitidine: in myelodysplastic syndromes. *Drugs* 2005; **65:** 1781–9.
2. Kaminskas E, *et al.* FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist* 2005; **10:** 176–82.
3. Silverman LR, *et al.* Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol* 2006; **24:** 3895–3903.
4. Abdulhaq H, Rossetti JM. The role of azacitidine in the treatment of myelodysplastic syndromes. *Expert Opin Invest Drugs* 2007; **16:** 1967–75.
5. O'Dwyer K, Maslak P. Azacitidine and the beginnings of therapeutic epigenetic modulation. *Expert Opin Pharmacother* 2008; **9:** 1981–6.
6. Lyons RM, *et al.* Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *J Clin Oncol* 2009; **27:** 1850–6.
7. Fenaux P, *et al.* International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; **10:** 223–32.
8. Cataldo VD, *et al.* Azacitidine for the treatment of myelodysplastic syndrome. *Expert Rev Anticancer Ther* 2009; **9:** 875–84.
9. Keating GM. Azacitidine: a review of its use in higher-risk myelodysplastic syndromes/acute myeloid leukaemia. *Drugs* 2009; **69:** 2501–18.
10. Gurion R, *et al.* 5-azacitidine prolongs overall survival in patients with myelodysplastic syndrome—a systematic review and meta-analysis. *Haematologica* 2010; **95:** 303–10.

Administration in renal impairment. Adverse renal effects of azacitidine include abnormalities in renal-function tests, renal tubular acidosis, renal failure, and death. Licensed product information recommends that if serum-bicarbonate concentrations fall to below 20 mmol/litre, the dose of azacitidine should be halved for the next course. If there are rises in serum concentrations of urea or creatinine, the next cycle of azacitidine should be delayed until these return to normal or baseline, and the dose should be halved on the next treatment course.

Adverse Effects and Precautions

The adverse effects of azacitidine are generally similar to those seen with cytarabine (p. 775.1). Hypokalaemia, dyspnoea, and bruising are common.

Pharmacokinetics

Azacitidine is rapidly absorbed after subcutaneous use; the bioavailability relative to intravenous use is about 89%. The mean plasma half-life after subcutaneous injection is about 40 minutes. Azacitidine and its metabolites are excreted mainly in the urine; about 50% and 85% is recovered after subcutaneous and intravenous dosing, respectively. The mean elimination half-life is about 4 hours after subcutaneous or intravenous use.

References.
1. Marcucci G, *et al.* Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. *J Clin Pharmacol* 2005; **45:** 597–602.
2. Tsao CF, *et al.* Azacitidine pharmacokinetics in an adolescent patient with renal compromise. *J Pediatr Hematol Oncol* 2007; **29:** 330–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Vidaza; ***Austria***: Vidaza; ***Belg.***: Vidaza; ***Braz.***: Vidaza; ***Canad.***: Vidaza; ***Cz.***: Vidaza; ***Denm.***: Vidaza; ***Fr.***: Vidaza; ***Ger.***: Vidaza; ***Gr.***: Vidaza; ***Hong Kong***: Vidaza; ***Irl.***: Vidaza; ***Israel***: Vidaza; ***Ital.***: Vidaza; ***Jpn***: Vidaza; ***Malaysia***: Vidaza; ***Neth.***: Vidaza; ***Norw.***: Vidaza; ***NZ***: Vidaza; ***Philipp.***: Vidaza; ***Pol.***: Vidaza; ***Port.***: Vidaza; ***S.Afr.***: Vidaza; ***Singapore***: Vidaza; ***Spain***: Vidaza; ***Swed.***: Vidaza; ***Switz.***: Vidaza; ***Thai.***: Vidaza; ***Turk.***: Vidaza; ***UK***: Vidaza; ***USA***: Vidaza.

Bafetinib *(USAN, rINN)*

Bafétinib; Bafetinibum; INNO-406; NS-187; Бафетиниб.
N-(3-{[(4,5′-Bipyrimidin)-2-yl]amino}-4-methylphenyl)-4-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]methyl-3-(trifluoromethyl)benzamide.

$C_{30}H_{31}F_3N_8O$=576.6
CAS — 859212-16-1; 887650-05-7.
UNII — NWA4Z03I9B.

Profile

Bafetinib is an orally active tyrosine kinase inhibitor active against BCR-ABL and Lyn (part of the SRC family) kinases. It is under investigation for the treatment of malignant neoplasms such as chronic myeloid leukaemia, chronic lymphocytic leukaemia, brain cancer, and prostate cancer.

References.
1. Kantarjian H, *et al.* Phase 1 study of INNO-406, a dual Abl/Lyn kinase inhibitor, in Philadelphia chromosome-positive leukemias after imatinib resistance or intolerance. *Cancer* 2010; 116: 2665–72.
2. Santos FP, *et al.* Bafetinib, a dual Bcr-Abl/Lyn tyrosine kinase inhibitor for the potential treatment of leukemia. *Curr Opin Investig Drugs* 2010; 11: 1450–65.

Becatecarin *(USAN, rINN)*

Becatecarina; Bécatécarine; Becatecarinum; Betacatecarin; Betotecarin; BMS-181176; BMY-27557; DEAE-rebeccamycin; NSC-655649; XL-119; Бекатекарин.
1,11-Dichloro-6-[2-(diethylamino)ethyl]-12-(4-*O*-methyl-β-D-glucopyranosyl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione.
$C_{33}H_{34}Cl_2N_4O_7$=669.6
CAS — 119673-08-4.
UNII — A60X6MBU6G.

Profile

Becatecarin is a synthetic analogue of the antineoplastic antibiotic rebeccamycin. It is an inhibitor of the enzyme topoisomerase I, and is under investigation in the treatment of bile-duct and other tumours.

References.
1. Merchant J, *et al.* Phase I clinical and pharmacokinetic study of NSC 655649, a rebeccamycin analogue, given in both single-dose and multiple-dose formats. *Clin Cancer Res* 2002; 8: 2193–2201.
2. Goel S, *et al.* A phase II study of rebeccamycin analog NSC 655649 in patients with metastatic colorectal cancer. *Invest New Drugs* 2003; 21: 103–7.
3. Langevin AM, *et al.* Phase I trial of rebeccamycin analog (NSC #655649) in children with refractory solid tumors: a pediatric oncology group study. *J Pediatr Hematol Oncol* 2003; 25: 526–33.
4. Hussain M, *et al.* A phase II study of rebeccamycin analog (NSC-655649) in metastatic renal cell cancer. *Invest New Drugs* 2003; 21: 465–71.
5. Ricart AD, *et al.* Phase I and pharmacokinetic study of sequences of the rebeccamycin analogue NSC 655649 and cisplatin in patients with advanced solid tumors. *Clin Cancer Res* 2005; 11: 8728–36.
6. Langevin AM, *et al.* Children's Oncology Group. A phase II trial of rebeccamycin analogue (NSC #655649) in children with solid tumors: a Children's Oncology Group study. *Pediatr Blood Cancer* 2008; 50: 577–80.
7. Borthakur G, *et al.* Phase I study of XL119, a rebeccamycin analog, in patients with refractory hematologic malignancies. *Cancer* 2008; 113: 360–6.
8. Dowlati A, *et al.* Phase II and pharmacokinetic trial of rebeccamycin analog in advanced biliary cancers. *Cancer Chemother Pharmacol* 2009; 65: 73–8.

Belagenpumatucel-L *(USAN)*

NOTE. The name Lucanix has been used as a trade mark for belagenpumatucel-L.

Profile

Belagenpumatucel-L is an allogeneic cancer vaccine (p. 757.3) that is stated to produce improved antigen recognition because of its ability to block transforming growth factor β-2. It is under investigation for the treatment of non-small cell lung cancer.

Belinostat *(USAN, rINN)*

Belinostat; Belinostatum; PXD-101; Белиностат.
N-Hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide.
$C_{15}H_{14}N_2O_4S$=318.3
CAS — 414864-00-9.
UNII — F4HP6P17NZ.

Profile

Belinostat is a histone deacetylase inhibitor that is under investigation for the treatment of peripheral T-cell lymphomas and other malignant neoplasms.

References.
1. Steele NL, *et al.* Pharmacokinetic and pharmacodynamic properties of an oral formulation of the histone deacetylase inhibitor belinostat (PXD101). *Cancer Chemother Pharmacol* 2011; 67: 1273–9.
2. Giaccone G, *et al.* Phase II study of belinostat in patients with recurrent or refractory advanced thymic epithelial tumors. *J Clin Oncol* 2011; 29: 2052–9.

Belotecan *(rINN)*

Belotecán; Bélotécan; Belotecanum; CKD-602; Бельотекан.
(4*S*)-4-Ethyl-4-hydroxy-11-[2-(isopropylamino)ethyl]-1,12-dihydro-14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione.
$C_{25}H_{27}N_3O_4$=433.5
CAS — 256411-32-2.
UNII — 27Z82M2G1N.

NOTE. The name Camtobell has been used as a trade mark for belotecan.

Belotecan Hydrochloride *(USAN, pINNM)*

Bélotécan, Chlorhydrate de; Belotecani Hydrochloridum; CKD-602; Hidrocloruro de belotecán; Бельотекана Гидрохлорид.
(4*S*)-4-Ethyl-4-hydroxy-11-[2-[(1-methylethyl)amino]ethyl]-1,12-dihydro-14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione hydrochloride.
$C_{25}H_{27}N_3O_4$.HCl=470.0
CAS — 213819-48-8.
UNII — 01DZ4127G7.

Profile

Like irinotecan (p. 812.2), belotecan is a topoisomerase I inhibitor related to camptothecin. It is used for the treatment of ovarian cancer and small cell lung cancer. A liposomal formulation (S-CKD-602)is also under investigation.

References.
1. Lee DH, *et al.* A phase I and pharmacologic study of belotecan in combination with cisplatin in patients with previously untreated extensive-stage disease small cell lung cancer. *Clin Cancer Res* 2007; 13: 6182–6.
2. Lee DH, *et al.* Belotecan, new camptothecin analogue, is active in patients with small-cell lung cancer: results of a multicenter early phase II study. *Ann Oncol* 2008; 19: 123–7.
3. Kim SJ, *et al.* A multicenter phase II study of belotecan, new camptothecin analogue, in patients with previously untreated extensive stage disease small cell lung cancer. *Lung Cancer* 2010; 68: 446–9.
4. Kim YM, *et al.* The efficacy and toxicity of belotecan (CKD-602), a camptothecin analogue topoisomerase I inhibitor, in patients with recurrent or refractory epithelial ovarian cancer. *J Chemother* 2010; 22: 197–200.
5. Kim HS, *et al.* Comparison of the efficacy between topotecan- and belotecan-, a new camptothecin analog, based chemotherapies for recurrent epithelial ovarian cancer: a single institutional experience. *J Obstet Gynaecol Res* 2010; 36: 86–93.
6. Rhee CK, *et al.* A multicenter phase II study of belotecan, a new camptothecin analogue, as a second-line therapy in patients with small cell lung cancer. *Lung Cancer* 2011; 72: 64–7.

Bendamustine Hydrochloride

(BANM, USAN, rINNM)

Bendamustina, hidrocloruro de; Bendamustine, Chlorhydrate de; Bendamustinhydrochlorid; Bendamustini Hydrochloridum; Cytostasan; Hidrocloruro de bendamustina; IMET-3393; SDX-105; SyB-L-0501; Бендамустина Гидрохлорид.
5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolebutyric acid hydrochloride.
$C_{16}H_{21}Cl_2N_3O_2$.HCl=394.7
CAS — 16506-27-7 (bendamustine); 3543-75-7 (bendamustine hydrochloride).
ATC — L01AA09.
ATC Vet — QL01AA09.
UNII — 981Y8SX18M.

Stability. US licensed product information for bendamustine hydrochloride states that, once reconstituted as directed and further diluted with sodium chloride 0.9%, the final infusion solution is stable for 24 hours when refrigerated (2 degrees to 8 degrees) or for 3 hours when stored at room temperature (15 degrees to 30 degrees) and exposed to light.

Uses and Administration

Bendamustine is an antineoplastic alkylating agent used for the treatment of chronic lymphocytic leukaemia (p. 693.3) as well as for non-Hodgkin's lymphoma (p. 696.3) that has progressed during, or within 6 months of, treatment with rituximab. It may be given with prednisone for the treatment of multiple myeloma (p. 699.2) in patients older than 65 years of age who are not eligible for stem-cell transplantation and who cannot be treated with thalidomide or bortezomib. It may also be used for Hodgkin's disease and breast cancer.

Bendamustine is given intravenously as the hydrochloride. After reconstitution, it is usually diluted in 500 mL of sodium chloride 0.9%; the final concentration of bendamustine hydrochloride should be between 200 and 600 micrograms/mL. Doses should be modified or delayed in the event of toxicity until the patient has recovered, and until neutrophils and platelets have reached acceptable concentrations (see Bone-Marrow Depression, p. 730.3).

For the treatment of **chronic lymphocytic leukaemia**, bendamustine hydrochloride is given in a dose of 100 mg/m², infused over 30 to 60 minutes on days 1 and 2 of a 28-day cycle, for up to 6 cycles. For severe haematological or non-haematological toxicity, dose should be reduced to 50 mg/m² on days 1 and 2 of each cycle. If severe haematological toxicity recurs, the dose should be further reduced to 25 mg/m² on days 1 and 2 of each cycle. Dose re-escalation in subsequent cycles may be considered.

The recommended dose for **non-Hodgkin's lymphoma** is 120 mg/m², infused over 30 to 60 minutes on days 1 and 2 of a 21-day cycle, for up to 8 cycles. For severe haematological or non-haematological toxicity, dose should be reduced to 90 mg/m² on days 1 and 2 of each cycle. If severe toxicity recurs, the dose should be further reduced to 60 mg/m² on days 1 and 2 of each cycle.

For the treatment of **multiple myeloma**, bendamustine hydrochloride is given in a dose of 120 to 150 mg/m² infused over 30 to 60 minutes on days 1 and 2 of a 28-day cycle; intravenous or oral prednisone at a dose of 60 mg/m² is given on days 1 to 4 of the cycle.

References.
1. Knauf W. Bendamustine in the treatment of chronic lymphocytic leukemia. *Expert Rev Anticancer Ther* 2009; 9: 165–74.
2. Cheson BD, Rummel MJ. Bendamustine: rebirth of an old drug. *J Clin Oncol* 2009; 27: 1492–1501. Correction. *ibid.*; 2892.
3. Tageja N, Nagi J. Bendamustine: something old, something new. *Cancer Chemother Pharmacol* 2010; 66: 413–23.
4. Cheson BD, *et al.* Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel. *Clin Lymphoma Myeloma Leuk* 2010; 10: 21–7.
5. Elefante A, Czuczman MS. Bendamustine for the treatment of indolent non-Hodgkin's lymphoma and chronic lymphocytic leukemia. *Am J Health-Syst Pharm* 2010; 67: 713–23.
6. Garnock-Jones KP. Bendamustine: a review of its use in the management of indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *Drugs* 2010; 70: 1703–18.
7. NICE. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Technology Appraisal Guidance 216, issued February 2011). Available at: http://www.nice.org.uk/nicemedia/live/13343/53180/53180.pdf (accessed 22/09/11)
8. Hoy SM. Bendamustine: a review of its use in the management of chronic lymphocytic leukaemia, rituximab-refractory indolent non-Hodgkin's lymphoma and multiple myeloma. *Drugs* 2012; 72: 1929–50.

Administration in hepatic impairment. US licensed product information states that, although no meaningful effect on the pharmacokinetics of bendamustine was seen in mild hepatic impairment, data are limited, and therefore caution should be exercised when using bendamustine in these patients. Bendamustine should not be used in moderate or severe hepatic impairment due to a lack of data.

Administration in renal impairment. Although no meaningful effect on the pharmacokinetics of bendamustine was seen in renal impairment, US licensed product information states that data are limited, and that caution should be exercised in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with creatinine clearance less than 40 mL/minute, due to a lack of data.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bendamustine commonly causes myelosuppression and doses may need to be reduced (see Uses and Administration, above); patients are therefore susceptible to infection. Other common adverse effects include gastrointestinal disturbances, fever, asthenia, fatigue, malaise, dry mouth, somnolence, cough, headache, mucosal inflammation, and stomatitis. Infusion reactions are common; symptoms include fever, chills, pruritus, and rash. Anaphylactic reactions have been reported rarely, especially during the second and subsequent cycles of therapy. Prophylactic antihistamines, antipyretics, and corticosteroids should be considered. If severe infusion reactions occur, therapy should be stopped. Tumour lysis syndrome has been reported, usually within the first treatment cycle, and may lead to acute renal failure and death. Adequate volume status should be maintained and potassium and uric acid concentrations should be monitored; allopurinol may be used in patients at high risk. Skin reactions such as bullous exanthema can occur with bendamustine; therapy may need to be withheld or stopped. Worsening hypertension, including hypertensive crisis, has also occurred. Increases in creatinine concentrations and liver enzyme values have been reported; bendamustine should be used with caution in patients with renal or hepatic impairment.

Interactions

Bendamustine is extensively metabolised by cytochrome P450 isoenzyme CYP1A2. Inhibitors of CYP1A2, such as fluvoxamine and ciprofloxacin, may increase exposure to bendamustine. Conversely, CYP1A2 inducers, such as omeprazole, can reduce exposure to bendamustine; tobacco smoking also may increase exposure to bendamustine.

Pharmacokinetics

Bendamustine is about 95% bound to plasma proteins; data suggest it is not likely to displace nor to be displaced by highly protein-bound drugs. Bendamustine distributes freely into human red blood cells. It is mainly metabolised by hydrolysis via the cytochrome P450 isoenzyme CYP1A2. Little or no accumulation in plasma is anticipated for intravenous doses of bendamustine given on days 1 and 2 of a 28-day cycle. About 90% of the drug is eliminated, mainly via the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Levact; *Canad.*: Treanda; *Cz.*: Ribomustin; *Denm.*: Levact; *Fin.*: Levact; *Fr.*: Levact; *Ger.*: Levact; Ribomustin†; *Gr.*: Levact; Ribomustin; Treanda; *Hong Kong*: Treanda; *Irl.*: Levact; *Ital.*: Levact; *Jpn*: Treakisym; *Neth.*: Levact; *Norw.*: Levact; *Rus.*: Ribomustine (Рибомустин); *Singapore*: Symbenda; *Spain*: Levact; *Swed.*: Ribovact; *Switz.*: Ribomustin; *UK*: Levact; *Ukr.*: Ribomustine (Рибомустин); *USA*: Treanda.

Bevacizumab *(rINN)*

Bevacizumab; Bevacizumabum; R-435; rhuMAb-VEGF; Бевацизумаб.

Immunoglobulin G1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer.

CAS — 216974-75-3.
ATC — L01XC07.
ATC Vet — QL01XC07.
UNII — 2S9ZZM9Q9V.

Stability. UK licensed product information states that bevacizumab is chemically and physically stable for 48 hours at 2 degrees to 30 degrees in sodium chloride 0.9%, although immediate use is recommended from a microbiological point of view. If the solution is not used immediately, storage for longer than 24 hours at 2 degrees to 8 degrees cannot be recommended, unless dilution has taken place in controlled and validated aseptic conditions. In the USA, licensed product information states that bevacizumab solutions for infusion may be stored at 2 degrees to 8 degrees for up to 8 hours.

Bevacizumab should not be mixed with glucose.

A study tested the concentration change in bevacizumab when the drug was drawn up into 1-mL latex-free syringes, using a 20-gauge needle, and then capped with a 30-gauge needle, and stored at 4 degrees for varying times; 1 syringe was frozen at -10 degrees. Results were compared with an unopened vial of bevacizumab stored at 4 degrees and protected from light. Bevacizumab concentrations decreased by 1.6% at 1 week, 0% at 3 weeks, 8.8% at 3 months, and 15.9% at 6 months; the concentration in the frozen syringe decreased by 12% at 6 months.[1]

1. Bakri SJ, *et al.* Six-month stability of bevacizumab (Avastin) binding to vascular endothelial growth factor after withdrawal into a syringe and refrigeration or freezing. *Retina* 2006; **26**: 519–22.

Uses and Administration

Bevacizumab is a recombinant humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF), thereby inhibiting the angiogenesis that occurs during tumour growth. Bevacizumab is used with fluoropyrimidine-based chemotherapy in the treatment of metastatic colorectal cancer (p. 706.3). It has also been used with a taxane such as paclitaxel, for the first-line treatment of patients with metastatic breast cancer (p. 702.1). Bevacizumab may be used with platinum-based chemotherapy in the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer (p. 710.2). Bevacizumab is used with interferon alfa for the first-line treatment of advanced and/or metastatic renal cell cancer (p. 708.3). Bevacizumab is also used for the treatment of progressive glioblastoma (see Malignant Neoplasms of the Brain, p. 701.2).

Bevacizumab is usually given diluted in 100 mL of sodium chloride 0.9%; the final concentration should be kept within the range of 1.4 to 16.5 mg/mL. The first dose should be given as an intravenous infusion over 90 minutes; if this is well tolerated the second dose should be given over 60 minutes, and if this is well tolerated then subsequent doses may be given over 30 minutes.

In the treatment of **colorectal cancer**, bevacizumab is given in a dose of 5 or 10 mg/kg once every 2 weeks, or 7.5 or 15 mg/kg once every 3 weeks; doses depend on the combination of drugs used in the regimen.

For **breast cancer**, the recommended dose of bevacizumab is 10 mg/kg given once every 2 weeks, or 15 mg/kg given once every 3 weeks.

For **non-small cell lung cancer**, the recommended dose of bevacizumab is 7.5 or 15 mg/kg given once every 3 weeks. In the UK, combination therapy is given for up to 6 cycles, followed by bevacizumab monotherapy until disease progression.

For **renal cell carcinoma**, bevacizumab is given in a dose of 10 mg/kg once every 2 weeks.

For **glioblastoma**, the recommended dose of bevacizumab is 10 mg/kg once every 2 weeks.

There are no recommended dose reduction regimens should adverse effects occur with bevacizumab; therapy should either be permanently stopped or temporarily suspended.

Bevacizumab is under investigation for various other neoplasms, including gastric, ovarian, and prostate cancer. A related monoclonal antibody, ranibizumab (p. 2602.1) has been developed for the treatment of neovascular (wet) age-related macular degeneration, and it has been suggested that bevacizumab might also be of benefit.

A drug-eluting stent containing bevacizumab is under investigation.

References.

1. Hurwitz H, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335–42.
2. Johnson DH, *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non–small-cell lung cancer. *J Clin Oncol* 2004; **22**: 2184–91.
3. Zondor SD, Medina PJ. Bevacizumab: an angiogenesis inhibitor with efficacy in colorectal and other malignancies. *Ann Pharmacother* 2004; **38**: 1258–64.
4. Motl S. Bevacizumab in combination chemotherapy for colorectal and other cancers. *Am J Health-Syst Pharm* 2005; **62**: 1021–32. Correction. *ibid.*; 1241.
5. Kabbinavar FF, *et al.* Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005; **23**: 3706–12.
6. Midgley R, Kerr D. Bevacizumab—current status and future directions. *Ann Oncol* 2005; **16**: 999–1004.
7. Lyseng-Williamson KA, Robinson DM. Spotlight on bevacizumab in advanced colorectal cancer, breast cancer, and non-small cell lung cancer. *BioDrugs* 2006; **20**: 193–5.
8. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clin Ther* 2006; **28**: 1779–1802.
9. Pañares RL, Garcia AA. Bevacizumab in the management of solid tumors. *Expert Rev Anticancer Ther* 2007; **7**: 433–45.
10. Cilley JC, *et al.* Bevacizumab in the treatment of colorectal cancer. *Expert Opin Biol Ther* 2007; **7**: 739–49.
11. Burger RA. Experience with bevacizumab in the management of epithelial ovarian cancer. *J Clin Oncol* 2007; **25**: 2902–8.
12. Escudier B, *et al.* AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007; **370**: 2103–11.
13. Miller K, *et al.* Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; **357**: 2666–76.
14. Scott LJ. Bevacizumab: in first-line treatment of metastatic breast cancer. *Drugs* 2007; **67**: 1793–9.
15. McCormack PL, Keam SJ. Bevacizumab: a review of its use in metastatic colorectal cancer. *Drugs* 2008; **68**: 487–506.
16. Di Costanzo F, *et al.* Bevacizumab in non-small cell lung cancer. *Drugs* 2008; **68**: 737–46.
17. Norden AD, *et al.* Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology* 2008; **70**: 779–87.
18. Buie LW, Valgus J. Bevacizumab: a treatment option for recurrent glioblastoma multiforme. *Ann Pharmacother* 2008; **42**: 1486–90.
19. Moen MD. Bevacizumab: in previously treated glioblastoma. *Drugs* 2010; **70**: 181–9.
20. Koutras AK, *et al.* Bevacizumab in the treatment of breast cancer. *Cancer Treat Rev* 2010; **36**: 75–82.
21. McDermott DF, George DJ. Bevacizumab as a treatment option in advanced renal cell carcinoma: an analysis and interpretation of clinical trial data. *Cancer Treat Rev* 2010; **36**: 216–23.
22. Iwamoto FM, Fine HA. Bevacizumab for malignant gliomas. *Arch Neurol* 2010; **67**: 285–8.

Administration. It has been suggested that bevacizumab may be safely given at an infusion rate of 500 micrograms/kg per minute; this means a dose of 5 mg/kg could be given over 10 minutes.[1]

1. Reidy DL, *et al.* Bevacizumab 5 mg/kg can be infused safely over 10 minutes. *J Clin Oncol* 2007; **25**: 2691–5.

Eye disorders. In addition to the conditions discussed below, bevacizumab is being tried in many eye disorders, mostly those associated with choroidal or retinal neovascularisation, or with macular oedema, but the number of patients is mostly small, with evidence limited to case reports or small case series.[1]

1. Gunther JB, Altaweel MM. Bevacizumab (Avastin) for the treatment of ocular disease. *Surv Ophthalmol* 2009; **54**: 372–400.

AGE-RELATED MACULAR DEGENERATION. Promising short-term results with intravenous[1,2] or intravitreal[3-9] bevacizumab to treat age-related macular degeneration (p. 880.2) or its complications were reported, and a controlled study[10] found its intravitreal use to be superior to pegaptanib or to photodynamic therapy with verteporfin. However, bevacizumab is unlicensed for this use and has been associated with adverse effects (see Effects on the Eyes, p. 748.1). Ranibizumab (p. 2602.1) is a humanised antibody fragment derived from bevacizumab that is licensed for the treatment of this disease. A multicentre comparative study[11] found that ranibizumab and bevacizumab, both given according to the same intravitreal schedule, had equivalent effects on visual acuity during 1 year of follow-up. No significant differences were seen between the 2 drugs in rates of death or thrombotic events, although the rate of serious systemic adverse events (mainly hospitalisation) was higher with bevacizumab.

1. Michels S, *et al.* Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005; **112**: 1035–47.
2. Bolz M, *et al.* Effect of systemic bevacizumab therapy on retinal pigment epithelial detachment. *Br J Ophthalmol* 2007; **91**: 785–9.
3. Avery RL, *et al.* Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113**: 363–72.
4. Bashshur ZF, *et al.* Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2006; **142**: 1–9.
5. Spaide RF, *et al.* Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006; **26**: 383–90.
6. Pung AE, *et al.* The International Intravitreal Bevacizumab Safety Survey: using the Internet to assess drug safety worldwide. *Br J Ophthalmol* 2006; **90**: 1344–9.
7. Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. *Ann Pharmacother* 2007; **41**: 614–25.
8. Madhusudhana KC, *et al.* Intravitreal bevacizumab (Avastin) for the treatment of choroidal neovascularization in age-related macular degeneration: results from 118 cases. *Br J Ophthalmol* 2007; **91**: 1716–17.
9. Ávila MP, *et al.* Twelve-month short-term safety and visual-acuity results from a multicentre prospective study of epiretinal strontium-90 brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularisation secondary to age-related macular degeneration. *Br J Ophthalmol* 2009; **93**: 305–9.
10. Tufail A, *et al.* Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. *BMJ* 2010; **340**: c2459.
11. Martin DF, *et al.* CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011; **364**: 1897–908.

GLAUCOMA. Neovascular glaucoma is a severe complication in patients affected by proliferative diabetic retinopathy or central retinal vein occlusion, and can result in complete loss of vision; treatment is unsatisfactory, and early diagnosis with aggressive control of intra-ocular pressure is crucial. In a small study of patients who had already undergone standard retinal ablative treatment, a total of 3 intravitreal injections of bevacizumab were given, at intervals of 4 weeks. Regression of corneal oedema with significant pain reduction was seen after the first injection, without any notable improvement in visual acuity; however, after the third injection, regression of iris neovascularisation as well as significant improvement of visual acuity was seen in most cases.[1]

1. Costagliola C, *et al.* Intravitreal bevacizumab (Avastin) injection for neovascular glaucoma: a survey on 23 cases throughout 12-month follow-up. *Br J Clin Pharmacol* 2008; **66**: 667–73.

PTERYGIUM. Bevacizumab has been investigated in the management of pterygium.[1]

1. Mauro J, Foster CS. Pterygia: pathogenesis and the role of subconjunctival bevacizumab in treatment. *Semin Ophthalmol* 2009; **24**: 130–4.

RETINOPATHY OF PREMATURITY. For reference to the investigational use of bevacizumab in infants with retinopathy of prematurity see p. 2120.3.

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Bevacizumab has been reported to be effective.[1]

1. Stefanadis C, *et al.* Avastin-eluting stent: long-term angiographic and clinical follow up. *Hellenic J Cardiol* 2008; **49**: 188–90.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bevacizumab may impair wound healing; therapy should not be started for at least 28 days after major surgery or until the surgical incision is fully healed; it should also be withheld before elective surgery. Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation is more common in patients receiving bevacizumab; fatalities have been reported. Serious, and sometimes fatal, non-gastrointestinal fistulas can also occur, usually within the first 6 months of therapy. Bevacizumab should be stopped permanently in patients who develop gastrointestinal perforation, or fistulas, or wound dehiscence needing medical intervention. Very rare cases of nasal septum perforation have been reported.

Leucopenia, anaemia, neutropenia, thrombocytopenia, and febrile neutropenia have also occurred; severe neutropenia with infection has caused fatalities. Bevacizumab can cause two distinct patterns of bleeding. Minor

haemorrhage such as epistaxis may occur; severe or fatal bleeding including CNS haemorrhage and pulmonary haemorrhage presenting as haemoptysis has been reported. There is an increased risk of serious arterial and venous thromboembolic events associated with the use of bevacizumab including pulmonary embolism, stroke, transient ischaemic attacks, myocardial infarction, angina, and death. Bevacizumab may cause congestive heart failure; the risk is higher in those patients who have concurrent or previous treatment with anthracyclines. Hypertension, possibly dose-dependent, has occurred; blood pressure should be monitored, and therapy stopped in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria may develop; bevacizumab should be stopped in patients who develop nephrotic syndrome. Other adverse effects include asthenia, pain, abdominal pain, gastrointestinal disturbances, stomatitis, headache, taste alteration, dyspnoea, lachrymation disorder, and exfoliative dermatitis. Peripheral sensory neuropathy, syncope, somnolence, supraventricular tachycardia, palmar-plantar erythrodysesthesia syndrome, myalgia, arthralgia, and muscular weakness have been commonly reported. Mucosal inflammation, dry skin, and skin discoloration are also common. Laboratory abnormalities reported include hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, and increased INR. Infusion reactions, manifesting as hypertension, hypoxia, wheezing, chest pain, headaches, rigors, and diaphoresis may occur rarely with the first dose of bevacizumab; treatment should be interrupted.

There have been rare reports of reversible posterior leukoencephalopathy syndrome, a neurological disorder; this may present as seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Bevacizumab therapy should be stopped, and patients treated symptomatically.

References.
1. Hurwitz H, Saini S. Bevacizumab in the treatment of metastatic colorectal cancer: safety profile and management of adverse events. *Semin Oncol* 2006; 33 (suppl 10): S26–S34.
2. Saif MW, Mehra R. Incidence and management of bevacizumab-related toxicities in colorectal cancer. *Expert Opin Drug Safety* 2006; 5: 553–66.
3. Gressett SM, Shah SR. Intricacies of bevacizumab-induced toxicities and their management. *Ann Pharmacother* 2009; 43: 490–501.
4. Higa GM, Abraham J. Biological mechanisms of bevacizumab-associated adverse events. *Expert Rev Anticancer Ther* 2009; 9: 999–1007.
5. Shord SS, *et al.* Understanding and managing the possible adverse effects associated with bevacizumab. *Am J Health-Syst Pharm* 2009; 66: 999–1013.
6. Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. *Gynecol Oncol* 2010; 117: 497–504.

Effects on the cardiovascular system. For a discussion of the incidence of hypertension associated with use of bevacizumab, see Effects on the Kidneys, below.

Effects on the eyes. As of November 2008, the UK manufacturer of bevacizumab (*Roche, UK*) reported on 25 Canadian cases of adverse events after the unlicensed intravitreal use of the drug; symptoms included ocular irritation, photophobia, blurred vision, and floaters associated with mild to moderate anterior and posterior cellular inflammation.[1] The US manufacturer (*Genentech, USA*) reported that, as of December 2008, there had been 36 Canadian reports of intra-ocular adverse effects, of which 32 were serious intra-ocular inflammatory reactions, after intravitreal use of bevacizumab.[2] Other adverse reactions reported after intravitreal use include retinal pigment epithelial tear[3] and submacular haemorrhage[4] after use for age-related macular degeneration, and macular ischaemia[5] after use for central retinal vein occlusion in patients with diabetes and vascular disease; retinal detachment has occurred after use for proliferative diabetic retinopathy, when used as an adjunct to vitrectomy[6] and when used for neovascular glaucoma in one patient,[7] where it was associated with macular hole.

1. Roche, UK. Reports of severe eye inflammation and sterile endophthalmitis following off-label intravitreal use of AVASTIN (bevacizumab) in Canada (issued 9th February, 2009). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON041212&RevisionSelectionMethod=Latest (accessed 04/09/09)
2. Genetech, USA. Important Drug Notification: reports of intraocular inflammatory reactions after intravitreal injection with AVASTIN (issued 19th December, 2008). Available at: http://www.gene.com/gene/products/information/pdf/avastin_ocular_letter.pdf (accessed 04/09/09)
3. Hannan SR, *et al.* Retinal pigment epithelial tear following intravitreal bevacizumab for choroidal neovascular membrane due to age-related macular degeneration. *Br J Ophthalmol* 2007; 91: 977–8.
4. Goverdhan SV, Lochhead J. Submacular haemorrhages after intravitreal bevacizumab for large occult choroidal neovascularisation in age-related macular degeneration. *Br J Ophthalmol* 2008; 92: 210–12.
5. Shimura M, Yasuda K. Macular ischaemia after intravitreal bevacizumab injection in patients with central retinal vein occlusion and a history of diabetes and vascular disease. *Br J Ophthalmol* 2010; 94: 381–3.
6. Arevalo JF, *et al.* Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008; 92: 213–16.
7. Mitamura Y, *et al.* Retinal detachment with macular hole following intravitreal bevacizumab in patient with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008; 92: 717–18.

Effects on the kidneys. A systematic review and subsequent meta-analysis of 7 studies in 1850 patients with various cancers estimated the incidence and risk of developing hypertension and proteinuria with bevacizumab therapy.[1] The relative risk (RR) of developing proteinuria was 1.4 with low-dose bevacizumab (95% confidence interval 1.1 to 1.7) and even higher with high-dose therapy (RR 2.2; 95% confidence interval 1.6 to 2.9). For hypertension, the RR was 3.0 for low-dose bevacizumab (95% confidence interval 2.2 to 4.2) and 7.5 for high-dose therapy (95% confidence interval 4.2 to 13.4). US licensed product information states that hypertension can persist after stopping bevacizumab; therapy should be stopped permanently in those with hypertensive crisis or hypertensive encephalopathy. (For the suggestion that hypertension is a problem with angiogenesis inhibitors in general see Effects on the Cardiovascular System in Sorafenib, p. 858.2.) The safety of continued treatment in patients with moderate to severe proteinuria has not been evaluated; therapy should be interrupted if proteinuria is equal to or greater than 2 g per 24 hours, and may be resumed when it is less than this.

Nephrotic syndrome has also been reported with use of bevacizumab;[2,3] therapy should be stopped in these patients. In one case,[3] there was evidence of a haemolytic-uraemic syndrome; renal biopsy revealed a glomerular thrombotic microangiopathy. Bevacizumab was stopped, with favourable response; however, sunitinib therapy was started but had to be stopped due to a recurrence of severe haemolytic-uraemic syndrome.

A patient who received 3 doses of bevacizumab was diagnosed with acute renal failure secondary to interstitial nephritis. His renal function resolved slowly after stopping therapy; haemodialysis was required.[4]

1. Zhu X, *et al.* Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis* 2007; 49: 186–93.
2. George BA, *et al.* Nephrotic syndrome after bevacizumab: case report and literature review. *Am J Kidney Dis* 2007; 49: e23–e29.
3. Frangié C, *et al.* Renal thrombotic microangiopathy caused by anti-VEGF-antibody treatment for metastatic renal-cell carcinoma. *Lancet Oncol* 2007; 8: 177–8.
4. Barakat RK, *et al.* Interstitial nephritis secondary to bevacizumab treatment in metastatic leiomyosarcoma. *Ann Pharmacother* 2007; 41: 707–10.

Effects on the musculoskeletal system. Osteonecrosis of the jaw (similar to that seen with the bisphosphonates, see under Bisphosphonates, p. 1176.3) has been reported in 2 patients after bevacizumab therapy; neither patient had been treated with bisphosphonates.[1] Other cases have occurred when bevacizumab and bisphosphonates were given together; it has been postulated that anti-angiogenic agents such as bevacizumab and sunitinib (see also Effects on the Musculoskeletal System, under Sunitinib, p. 859.2) contribute to oral mucosal breakdown and subsequent development of osteonecrosis of the jaw.[2]

1. Estilo CL, *et al.* Osteonecrosis of the jaw related to bevacizumab. *J Clin Oncol* 2008; 26: 4037–8.
2. Ayllon J, *et al.* Osteonecrosis of the jaw under bisphosphonate and antiangiogenic therapies: cumulative toxicity profile? *Ann Oncol* 2009; 20: 600–1.

Effects on the nervous system. There are reports of reversible posterior leukoencephalopathy syndrome (RPLS) attributed to bevacizumab.[1,2] Presenting symptoms included lethargy, seizures, hypertension, acute bilateral loss of vision, headache, and confusion. Recovery was rapid after symptomatic treatment.

The symptoms of RPLS may be difficult to distinguish from those of uncontrolled hypertension, and patients presenting with the above signs and symptoms should be examined neurologically.[3]

1. Glusker P, *et al.* Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; 354: 980–1.
2. Ozcan C, *et al.* Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; 354: 981–2.
3. Health Canada. Association of AVASTIN(bevacizumab) with hypertensive encephalopathy and reversible posterior leukoencephalopathy syndrome (RPLS) (issued 24th October 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2006/avastin_pc-cp-eng.php (accessed 30/07/08)

Effects on the spleen. Splenic infarction has been reported in a patient given bevacizumab, fluorouracil, folinic acid, and irinotecan. Bevacizumab was stopped. Four further chemotherapy cycles were given. The splenic infarcts partially regressed, although the patient died from metastatic progression. The authors attributed the splenic infarction to bevacizumab, which has been associated with arterial thromboembolic events.[1]

1. Malka D, *et al.* Splenic infarction and bevacizumab. *Lancet Oncol* 2006; 7: 1038.

Fistula formation. US licensed product information for bevacizumab states that the incidence of gastrointestinal perforation, including fistula formation and/or intra-abdominal abscess, in bevacizumab-treated patients with colorectal cancer or non-small cell lung cancer was 2.4% and 0.9%, respectively. Reports of other types of fistulas such as bronchopleural, urogenital, and biliary fistulas, across various indications and mostly within the first 6 months of therapy, are less common; however, reports of tracheo-oesophageal fistula formation include some fatalities.[1,2] Therapy should be permanently stopped in patients with tracheo-oesophageal or gastrointestinal fistulas.

1. Roche, Canada. Health Canada endorsed Important safety information on AVASTIN (bevacizumab): association of AVASTIN (bevacizumab) with tracheo-esophageal fistula (issued June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/avastin_hpc-cps_2_e.pdf (accessed 13/06/07)
2. Genentech, USA. Important drug warning regarding AVASTIN (bevacizumab) (issued April 2007). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicinalProducts/ucm153953.pdf (accessed 21/07/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bevacizumab 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 29/09/11)

Interactions

The US manufacturer of bevacizumab has recommended that it should not be used with *sunitinib* after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1] UK licensed product information states that this was reversible upon stopping the 2 drugs.

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicinalProducts/ucm126434.pdf (accessed 21/07/10)

Pharmacokinetics

Bevacizumab has a half-life of about 20 days. The predicted time to steady state is about 100 days. Male patients and those with a higher tumour burden have higher clearances of bevacizumab than females and those with tumour burdens below the median, respectively; although no evidence of lesser efficacy has been seen due to this higher clearance, the relationship between exposure to bevacizumab and clinical outcome is not known.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avastin; *Austral.*: Avastin; *Austria*: Avastin; *Belg.*: Avastin; *Braz.*: Avastin; *Canad.*: Avastin; *Chile*: Avastin; *China*: Avastin (安维汀); *Cz.*: Avastin; *Denm.*: Avastin; *Fin.*: Avastin; *Fr.*: Avastin; *Ger.*: Avastin; *Gr.*: Avastin; *Hong Kong*: Avastin; *Hung.*: Avastin; *Indon.*: Avastin; *Irl.*: Avastin; *Israel*: Avastin; *Ital.*: Avastin; *Jpn*: Avastin; *Malaysia*: Avastin; *Mex.*: Avastin; *Neth.*: Avastin; *Norw.*: Avastin; *NZ*: Avastin; *Philipp.*: Avastin; *Pol.*: Avastin; *Port.*: Avastin; *Rus.*: Avastin (Авастин); *S.Afr.*: Avastin; *Singapore*: Avastin; *Spain*: Avastin; *Swed.*: Avastin; *Switz.*: Avastin; *Thai.*: Avastin; *Turk.*: Altuzan; *UK*: Avastin; *Ukr.*: Avastin (Авастин); *USA*: Avastin.

Bexarotene *(BAN, USAN, rINN)*

Beksaroteeni; Beksaroten; Bexaroten; Bexarotène; Bexaroteno; Bexarotenum; LG-100069; LGD-1069; Бексаротен.

p-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)vinyl]benzoic acid.

$C_{24}H_{28}O_2$=348.5

CAS — 153559-49-0.

ATC — L01XX25.

ATC Vet — QL01XX25.

UNII — A61RXM4375.

Uses and Administration

Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. It is used in the treatment of cutaneous T-cell lymphoma (see Mycosis Fungoides, p. 698.3), in a usual initial oral dose of 300 mg/m² daily as a single dose taken with a meal. Dosage is adjusted according to toxicity. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For the topical treatment of refractory disease a 1% gel may be applied on alternate days for the first week, gradually increased at weekly intervals to up to 4 times daily, depending on tolerance.

References.
1. Anonymous. Bexarotene (Targretin) for cutaneous T-cell lymphoma. *Med Lett Drugs Ther* 2000; 42: 31–2.
2. Lowe MN, Plosker GL. Bexarotene. *Am J Clin Dermatol* 2000; 1: 245–50.
3. Duvic M, *et al.* Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol* 2001; 19: 2456–71.
4. Wong S-F. Oral bexarotene in the treatment of cutaneous T-cell lymphoma. *Ann Pharmacother* 2001; 35: 1056–65.
5. Heald P, *et al.* Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol* 2003; 49: 801–15.
6. Hanifin JM, *et al.* Novel treatment of chronic severe hand dermatitis with bexarotene gel. *Br J Dermatol* 2004; 150: 545–53.
7. Farol LT, Hymes KB. Bexarotene: a clinical review. *Expert Rev Anticancer Ther* 2004; 4: 180–8.
8. Gniadecki R, *et al.* The optimal use of bexarotene in cutaneous T-cell lymphoma. *Br J Dermatol* 2007; 157: 433–40.
9. Lessin SR, *et al.* Treatment of parapsoriasis with bexarotene 1% gel. *Int J Dermatol* 2008; 47: 1325–7.
10. Abbott RA, *et al.* Bexarotene therapy for mycosis fungoides and Sézary syndrome. *Br J Dermatol* 2009; 160: 1299–1307.
11. Talpur R, *et al.* Phase I/II randomized bilateral head-head comparison of topical bexarotene 1% gel for alopecia areata. *J Am Acad Dermatol* 2009; 61: 592.e1–592.e9.
12. Qu L, Tang X. Bexarotene: a promising anticancer agent. *Cancer Chemother Pharmacol* 2010; 65: 201–5.

Adverse Effects and Precautions

The main adverse effects noted after oral therapy with bexarotene include hyperlipidaemia, hypothyroidism, leucopenia, headache, oedema, altered liver function, rash, and pruritus. Exfoliative dermatitis, alopecia, and skin disorders may occur. Other common adverse effects include anaemia, insomnia, dizziness, eye or ear disorders, gastrointestinal disturbances, arthralgia, and myalgia. Acute pancreatitis has been associated with hypertriglyceridaemia, and patients with risk factors for pancreatitis should generally not be given bexarotene. If triglyceride concentrations rise during therapy, dose reductions are recommended, and lipid-lowering therapy may be instituted (with the exception of gemfibrozil, see below). The most common adverse events associated with topical therapy are rash, pruritus, and pain. Bexarotene capsules and gel should not be used during pregnancy because of the risk of fetal malformation.

References.
1. Assaf C, *et al.* Minimizing adverse side-effects of oral bexarotene in cutaneous T-cell lymphoma: an expert opinion. *Br J Dermatol* 2006; 155: 261–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bexarotene 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 28/09/11)

Interactions

Gemfibrozil. Gemfibrozil inhibits clearance of bexarotene, resulting in extremely high triglyceride levels and pancreatitis.[1]

1. Talpur R, *et al.* Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2002; 47: 672–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Targretin; *Austria*: Targretin; *Belg.*: Targretin; *Chile*: Targretin; *Cz.*: Targretin; *Denm.*: Targretin; *Fr.*: Targretin; *Ger.*: Targretin; *Gr.*: Targretin; *Hung.*: Targretin; *Irl.*: Targretin; *Ital.*: Targretin; *Neth.*: Targretin; *Norw.*: Targretin; *Pol.*: Targretin; *Port.*: Targretin; *Spain*: Targretin; *Swed.*: Targretin; *UK*: Targretin; *USA*: Targretin.

Bicalutamide *(BAN, USAN, rINN)*

Bicalutamida; Bicalutamidum; Bikalutamid; Bikalutamidi; ICI-176334; Бикалутамид.

(RS)-4′-Cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-m-toluidide.

$C_{18}H_{14}F_4N_2O_4S$=430.4

CAS — 90357-06-5.

ATC — L02BB03.

ATC Vet — QL02BB03.

UNII — A0Z3NAU9DP.

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

Ph. Eur. 8: (Bicalutamide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol and in dichloromethane; freely soluble in acetone.

USP 36: (Bicalutamide). A fine, white to off-white powder. Sparingly to slightly soluble in alcohol; freely soluble in acetone and in tetrahydrofuran; soluble in acetonitrile. Store in airtight containers.

Uses and Administration

Bicalutamide is a nonsteroidal anti-androgen with actions and uses similar to those of flutamide (p. 798.2). It is used orally in the treatment of prostatic cancer (p. 712.3). When used with a gonadorelin analogue in the palliative treatment of advanced prostatic cancer the usual dose is 50 mg daily. In the UK treatment is started at least 3 days before starting the gonadorelin analogue to suppress any flare reaction, but in the USA treatment is started at the same time. A similar dose is used with surgical castration, starting on the same day as surgery.

Bicalutamide in a dose of 150 mg daily may be given as monotherapy or adjuvant therapy to surgery or radiotherapy in men with locally advanced disease at high risk for disease progression. It has been used as monotherapy in localised disease, but there is some evidence to suggest that in men without high risk of disease progression, who would otherwise be managed with watchful waiting, the immediate use of bicalutamide may increase the risk of death.

References.
1. Wirth M, *et al.* Bicalutamide (Casodex) 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression. *Urology* 2001; 58: 146–51.
2. Boccardo F, *et al.* Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: updated results of a multicentric trial. *Eur Urol* 2002; 42: 481–90.
3. See WA, *et al.* Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. *J Urol (Baltimore)* 2002; 168: 429–35.
4. See W, *et al.* Immediate treatment with bicalutamide 150 mg as adjuvant therapy significantly reduces the risk of PSA progression in early prostate cancer. *Eur Urol* 2003; 44: 512–17.
5. Fradet Y. Bicalutamide (Casodex) in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2004; 4: 37–48.
6. Schellhammer PF, Davis JW. An evaluation of bicalutamide in the treatment of prostate cancer. *Clin Prostate Cancer* 2004; 2: 213–19.
7. Wirth MP, *et al.* Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. *J Urol (Baltimore)* 2004; 172: 1865–70.
8. Iversen P, *et al.* Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. *J Urol (Baltimore)* 2004; 172: 1871–6.
9. Klotz L, Schellhammer P. Combined androgen blockade: the case for bicalutamide. *Clin Prostate Cancer* 2005; 3: 215–19.
10. Wirth M, *et al.* Bicalutamide ('Casodex') 150 mg in addition to standard care in patients with nonmetastatic prostate cancer: updated results from a randomised double-blind phase III study (median follow-up 5.1 y) in the early prostate cancer programme. *Prostate Cancer Prostatic Dis* 2005; 8: 194–200.
11. Tyrell CJ, *et al.* Bicalutamide ('Casodex') 150 mg as adjuvant to radiotherapy in patients with localised or locally advanced prostate cancer: results from the randomised Early Prostate Cancer Programme. *Radiother Oncol* 2005; 76: 4–10.
12. McLeod DG, *et al.* Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006; 97: 247–54.
13. Wellington K, Keam SJ. Bicalutamide 150mg: a review of its use in the treatment of locally advanced prostate cancer. *Drugs* 2006; 66: 837–50.
14. Iversen P, Roder MA. The Early Prostate Cancer program: bicalutamide in nonmetastatic prostate cancer. *Expert Rev Anticancer Ther* 2008; 8: 361–9.

Precocious puberty. Bicalutamide, with either anastrozole or letrozole, has been reported to be effective in the treatment of familial male precocious puberty (p. 2254.1); in 2 boys the combination therapy was well tolerated, stabilised bone-age advancement while allowing for continued normal linear growth, and prevented progression of virilisation.[1]

1. Lenz AM, *et al.* Bicalutamide and third-generation aromatase inhibitors in testotoxicosis. *Pediatrics* 2010; 126: e728–e733.

Adverse Effects and Precautions

As for Flutamide, p. 798.3. Pruritus, asthenia, alopecia, hair regrowth, and dry skin occur commonly with bicalutamide. Hypersensitivity reactions, including angioedema and urticaria, have been reported infrequently.

Cardiovascular effects including angina, heart failure, arrhythmias, and ECG changes have been reported rarely. Interstitial pneumonitis and pulmonary fibrosis have also been reported rarely.

Effects on the gastrointestinal tract. There is some evidence that bicalutamide is associated with a lower incidence of diarrhoea than flutamide.[1]

1. Schellhammer P, *et al.* A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. *Urology* 1995; 45: 745–52.

Effects on the liver. Fulminant hepatotoxicity has been reported with bicalutamide treatment. Despite stopping the drug the patient developed secondary multiorgan failure and died.[1]

1. O'Bryant CL, *et al.* Bicalutamide-associated fulminant hepatotoxicity. *Pharmacotherapy* 2008; 28: 1071–5.

Effects on the lungs. For a review of cases of pneumonitis associated with anti-androgens including bicalutamide, see under Flutamide, p. 798.3.

Gynaecomastia. For a discussion of gynaecomastia, a frequent adverse effect of anti-androgen therapy, and its management, see under Flutamide, p. 799.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bicalutamide 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 05/09/11)

Interactions

Bicalutamide inhibits various cytochrome P450 isoenzymes, particularly CYP3A4, *in vitro*, and licensed product information recommends that terfenadine, astemizole, and cisapride should not be given with bicalutamide, and that other drugs with a narrow therapeutic index that are metabolised by cytochrome P450 isoenzymes should be used with caution. *In vitro* studies have shown that bicalutamide can displace warfarin from its protein binding sites (see also Antineoplastics, p. 1532.2).

Pharmacokinetics

Bicalutamide is well absorbed after oral doses. It undergoes extensive metabolism in the liver, the active *R*-enantiomer mainly by oxidation, the inactive *S*-enantiomer mainly by glucuronidation. It is excreted as metabolites in urine and faeces. The half-life of the *R*-enantiomer is about 6 to 7 days, and may be prolonged still further in severe hepatic impairment. The *S*-enantiomer is cleared more rapidly. Bicalutamide is about 96% bound to plasma proteins.

References.
1. Cockshott ID. Bicalutamide: clinical pharmacokinetics and metabolism. *Clin Pharmacokinet* 2004; 43: 855–78.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bidrostat; Biolutam; Bitakebir; Bosconar; Casodex; Codebup; Dimalan; Finaband; Gepeprostin; Liberprost; Raffolutil; ***Austral.***: Calutex; Cosamide; Cosudex; ***Austria***: Androbloc; BicaluPel; Bicamed; Casodex; ***Belg.***: Casodex; ***Braz.***: Casodex; Gepeprostin; Lutamidal; ***Canad.***: Casodex; ***Chile***: Biolev; Casodex; Lutamidal; ***China***: Casodex (康士得); Yan Lie Shu (岩列舒); ***Cz.***: Atembin; Bicaluplex; Bicalutagen; Bicalutanorm; Bicalutatam; Bicamal; Bicasil; Bikalard; Bikauk; Binabic; Calumid†; Casodex; Glanuta; Lanbica; Ormandyl†; ***Denm.***: Bicalustad; Bicalutatam; Bictamid; Casodex; Nycolutamid; ***Fin.***: Alidex†; Bicadex†; Bicamid†; Bicavan; Bicusan; Bidanil†; Bikalex†; Casodex; Kandex†; Skylutamide; ***Fr.***: Casodex; Ormandyl; ***Ger.***: Androcal; Bicadex; Bicalutin; Bicamed; Casodex; ***Gr.***: Apex; Bicadex; Bicalut; Bicamide; Bicaprol; Bicatin; Bikalen; Bilumide; Casodex; Encalor; Ormandyl; Procure; Verodex; Zarmol; ***Hong Kong***: Casodex; ***Hung.***: Bication; Bicusan; Bilutamid; Binabic; Calumid; Capro; Casodex; Grommar; Lanbicamid†; Sanotamid; ***India***: Biprosta; Caludec; Caluran; Calutide; Casodex; ***Indon.***: Casodex; ***Irl.***: Bicalinn; Biluta; Casodex; Casomide; ***Israel***: Bicamide; Casodex; Medimide; ***Ital.***: Casodex; Lutamid; Praxis; Safedex; ***Malaysia***: Casodex; ***Mex.***: Advanpro; Bicalem; Calutol; Casdrogen; Casodex; ***Neth.***: Bicamedica†; Bilumide; Biluron; Casodex; ***Norw.***: Casodex; ***NZ***: Bicalaccord; Bicalox; Cosudex; ***Philipp.***: Bicadex; Casodex; ***Pol.***: Binabic; Calubloc; Casodex; Neoprost; Prostide; ***Port.***: Bicastad; Casodex; Ormandyl; ***Rus.***: Bilumid (Билумид); Calumid (Калумид); Casodex (Касодекс); ***S.Afr.***: Bicadex; Bicalox; Caloxa; Casodex; ***Singapore***: Casodex; ***Spain***: Bicamylan; Bicarbex; Biobica; Casodex; Ormandyl†; Pencial; Probic; Saveprost; Wibical; ***Swed.***: Baculamyl†; Bicalustad; Bictamid; Casodex; Nycolutamid†; ***Switz.***: Bicamed; Casodex; ***Thai.***: Bypro; Calumid; Casodex; ***Turk.***: Casodex; Procalut; ***UK***: Casodex; ***Ukr.***: Areclok (Ареклок); Calumid (Калумид); Casodex (Касодекс); ***USA***: Casodex; ***Venez.***: Calutol; Casodex.

Multi-ingredient Preparations. *Arg.*: Zolapack; ***Austral.***: ZolaCos CP; ***NZ***: ZolaCos CP.

Pharmacopoeial Preparations
BP 2014: Bicalutamide Tablets;
USP 36: Bicalutamide Tablets.

Bleomycin Sulfate *(BANM, USAN, pINNM)*

Bleomicina, sulfato de; Bleomicino sulfatas; Bleomicin-szulfát; Bleomycin Sulphate; Bleomycine, Sulfate de; Bleomycini Sulfas; Bleomycinsulfat; Bleomycin-sulfat; Bleomysinisulfaatti; Sulfato de bleomicina; Блеомицина Сульфат.

CAS — 11056-06-7 (bleomycin); 67763-87-5 (bleomycin hydrochloride); 9041-93-4 (bleomycin sulfate).

ATC — L01DC01.

The symbol † denotes a preparation no longer actively marketed

ATC Vet — QL01DC01
UNII — 7DP3NTV15T

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

Int. and *Jpn* also include Bleomycin Hydrochloride. *Chin.* includes Bleomycin A5 Hydrochloride for Injection.

Ph. Eur. 8: (Bleomycin Sulfate). The sulfate of a mixture of glycopeptides obtained by the growth of *Streptomyces verticillus* or by any other means; the two principal components of the mixture are *N*-[3-(dimethylsulphonio) propyl]bleomycinamide (bleomycin A_2) and *N*-[4-(carbamimidoylamino)butyl]bleomycinamide (bleomycin B_2). A white or yellowish-white, very hygroscopic powder. It loses not more than 3% of its weight when dried. Very soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.5 to 6.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

USP 36: (Bleomycin Sulfate). The sulfate salt of a mixture of basic cytotoxic glycopeptides, produced by the growth of *Streptomyces verticillus* or produced by other means. It has a potency of not less than 1.5 units and not more than 2.0 units/mg. It contains between 55 and 70% of bleomycin A_2 and between 25 and 32% of bleomycin B_2; the content of bleomycin B_4 is not more than 1%. The combined percentage of bleomycin A_2 and B_2 is not less than 90%. A cream-coloured, amorphous powder. It loses not more than 6% of its weight when dried. Very soluble in water. A solution in water containing 10 units/mL has a pH of 4.5 to 6.0. Store in airtight containers.

Incompatibility. A loss of bleomycin activity was reported when bleomycin sulfate solutions were mixed with solutions of carbenicillin, cefazolin or cefalotin sodium, nafcillin sodium, benzylpenicillin sodium, methotrexate, mitomycin, hydrocortisone sodium succinate, aminophylline, ascorbic acid, or terbutaline.[1] The interactions of bleomycin have been summarised as the chelation of divalent and trivalent cations (especially copper), inactivation by compounds containing sulfhydryl groups, and precipitation by hydrophobic anions; solutions of bleomycin should not be mixed with solutions of essential amino acids, riboflavin, dexamethasone, or furosemide.[2]

1. Dorr RT, *et al.* Bleomycin compatibility with selected intravenous medications. *J Med* 1982; 13: 121–30.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; 17: 532–8.

Stability. Bleomycin sulfate solutions appear to be equally stable in plastic or glass,[1,2] despite some earlier studies suggesting loss of potency in plastic.[3,4] There is some evidence[5] that bleomycin is more stable in sodium chloride 0.9% than glucose 5%, and sodium chloride 0.9% is the diluent recommended by the licensed product information. UK licensed product information states that bleomycin sulfate is chemically and physically stable, once reconstituted and diluted as directed, for 10 days when refrigerated at 2 degrees to 8 degrees and protected from light. From a microbiological point of view, solutions should be used immediately; storage for longer than 24 hours at 2 degrees to 8 degrees is not recommended, unless prepared under controlled and validated aseptic conditions.

1. De Vroe C, *et al.* A study on the stability of three antineoplastic drugs and on their sorption by iv delivery systems and end-line filters. *Int J Pharmaceutics* 1990; 65: 49–56.
2. Stajich GV, *et al.* In vitro evaluation of bleomycin-induced cell lethality from plastic and glass containers. *DICP Ann Pharmacother* 1991; 25: 14–16.
3. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; 38: 1914–18.
4. Adams J, *et al.* Instability of bleomycin in plastic containers. *Am J Hosp Pharm* 1982; 39: 1636.
5. Koberda M, *et al.* Stability of bleomycin sulfate reconstituted in 5% dextrose injection or 0.9% sodium chloride injection stored in glass vials or polyvinyl chloride containers. *Am J Hosp Pharm* 1990; 47: 2528–9.

Units

8910 units of bleomycin complex A_2/B_2 are contained in 5 mg of bleomycin complex in one ampoule of the first International Reference Preparation (1980). The Ph. Eur. 8 specifies a potency of not less than 1500 international units per mg, calculated with reference to the dried substance. These units differ from those used by the USP: Bleomycin Sulfate (USP 36) contains 1.5 to 2.0 units of bleomycin in each mg. A change in the labelling of preparations in the UK, from units equivalent to those of the USP to international units in line with the Ph. Eur., resulted in an apparent but artefactual increase in UK doses by a factor of 1000.

In some countries doses were *formerly* described in terms of mg-potency, where 1 mg-potency corresponded to 1 unit. In the original preparation 1 mg-potency was equivalent to 1 mg-weight but improvements in purification of the product led to a situation in which ampoules labelled as containing 15 mg (i.e. 15 units) contained far fewer mg-weight of bleomycin.

Uses and Administration

Bleomycin is an antineoplastic antibiotic that binds to DNA and causes strand scissions, and is probably most effective in the G_2 and M phases of the cell cycle. It is widely used to treat malignant disease; particularly squamous cell carcinomas, including those of the cervix and external genitalia, oesophagus, skin, and head and neck; Hodgkin's disease and other lymphomas; malignant neoplasms of the testis, and malignant effusions. It has also been tried in other malignancies, including carcinoma of the bladder, lung, and thyroid, and some sarcomas, including Kaposi's sarcoma.

Bleomycin is often used with other antineoplastics, notably with doxorubicin, vinblastine, and dacarbazine (ABVD) for Hodgkin's disease, and with etoposide and cisplatin (BEP) in testicular tumours. Bleomycin is given as the sulfate by either the intramuscular, intravenous, or subcutaneous route. It may also be given intra-arterially or instilled intrapleurally or intraperitoneally. If intramuscular injections are painful they may be given in a 1% solution of lidocaine.

Doses are calculated in terms of the base, and are given in units, but the units used for preparations in the UK, which were formerly equivalent to those of the USP, are now international units equivalent to those of the Ph. Eur. (see Units, above). Since 1000 international units is equivalent to 1 USP unit, UK doses now appear to be 1000 times greater than those previously in use, or than those in use in the USA, and care is recommended in evaluating the literature.

In the UK the licensed dose as a single agent for **squamous cell** or **testicular tumours** is 15 000 international units (15 USP units) three times a week, or 30 000 international units twice a week, by intramuscular or intravenous injection, although in practice treatment of malignancy will generally be with combination regimens. This may be repeated, at usual intervals of 3 to 4 weeks, up to a total cumulative dose of 500 000 international units. The dose and total cumulative dose should be reduced in those over 60 years of age (see below). Doses should be adjusted according to tolerance, and may need to be adjusted as part of combination chemotherapy. Continuous intravenous infusion at a rate of 15 000 international units per 24 hours for up to 10 days or 30 000 international units per 24 hours for up to 5 days may also be used. In patients with **lymphoma** a dose of 15 000 international units once or twice weekly by intramuscular injection has been suggested, to a total dose of 225 000 international units. Again, dosage should be reduced in older patients and in combination regimens if necessary. In the treatment of **malignant effusions** a solution of 60 000 international units in 100 mL of sodium chloride 0.9% may be instilled into the affected serous cavity. Treatment may be repeated as necessary up to a total cumulative dose of 500 000 international units depending on the patient's age. Local anaesthetics or analgesics are given concomitantly.

In the USA licensed doses for **lymphomas** as well as **squamous cell** and **testicular** neoplasms are 250 to 500 international units/kg (0.25 to 0.5 USP units/kg), or 10 000 to 20 000 international units/m^2 (10 to 20 USP units/m^2), given once or twice weekly by slow intravenous, intramuscular, or subcutaneous injection. In view of the risk of an anaphylactoid reaction it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially (but see Administration, below). In patients with Hodgkin's disease, once a 50% response has been achieved it may be maintained with 1000 international units (1 USP unit) of bleomycin daily, or 5000 international units (5 USP units) weekly by slow intravenous or intramuscular injection.

In the UK, licensed product information suggests that a **total dose** of 500 000 international units (500 USP units) should not be exceeded. Total cumulative dose should not exceed 300 000 international units in those aged 60 to 69 years, 200 000 international units in those 70 to 79, and 100 000 international units in those 80 and over; the weekly dose should be no more than 60 000, 30 000 and 15 000 international units respectively. In the USA the recommended maximum total dose is 400 000 international units (400 USP units); it is generally agreed that patients receiving 400 000 international units or more are at increased risk of pulmonary toxicity (see Adverse Effects, p. 751.1).

Dosage should be reduced in patients with renal impairment (see below).

Bleomycin hydrochloride has also been given parenterally for malignant neoplasms, and bleomycin sulfate has been applied topically for the local treatment of skin tumours.

Administration. Although test doses have been suggested as a way of avoiding anaphylactoid reactions in patients with lymphoma being treated with bleomycin, a review[1] of the literature concluded that the evidence did not support such a strategy, since the onset of the reaction was unpredictable, and not associated with any particular dose. It had also been suggested that reactions were less frequent with intramuscular rather than intravenous dosage, but evidence for this was conflicting.

There is some suggestion that giving bleomycin by intravenous infusion rather than bolus injection in combination regimens may result in reduced pulmonary toxicity.[2,3]

Intralesional bleomycin is generally well tolerated; its uses by this route, which include malignancies and non-malignant skin conditions such as warts (p. 751.1) have been reviewed.[4]

1. Lam MSH. The need for routine bleomycin test dosing in the 21st century. *Ann Pharmacother* 2005; 39: 1897–1902.
2. Chisholm RA, *et al.* Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992; 30: 158–60.
3. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; 120: 617–24.
4. Saitta P, *et al.* Bleomycin in dermatology: a review of intralesional applications. *Dermatol Surg* 2008; 34: 1299–1313.

Administration in renal impairment. A significant portion of a dose of bleomycin is excreted largely unchanged in the urine, and dose reduction should be considered in patients with renal impairment. UK licensed product information suggests a 50% dose reduction when the serum creatinine concentration is between 20 and 40 micrograms/mL and further reduction for serum creatinine above this. US licensed product information gives the following proposed percentages of the initial dose, based on creatinine clearance (CC):

- CC 5 to 10 mL/minute: 40%
- CC 10 to 20 mL/minute: 45%
- CC 20 to 30 mL/minute: 55%
- CC 30 to 40 mL/minute: 60%
- CC 40 to 50 mL/minute: 70%
- CC 50 mL/minute and above: 100%

Leucoplakia. Leucoplakia is used to describe a white patch or plaque in the mouth which cannot be otherwise characterised. Such lesions are of concern because they may be pre-malignant, and patients with evidence of dysplasia may be at higher risk of transformation (see also Malignant Neoplasms of the Head and Neck, p. 708.1). Leucoplakia must be distinguished from other conditions such as candidiasis, lichen planus, and oral hairy leucoplakia which is associated with HIV infection.[1]

Leucoplakia is often associated with tobacco smoking, and smoking cessation can result in regression.[1] Where active treatment is desirable, small and easily accessible lesions can be removed surgically or by laser therapy, although they may recur.[1] For extensive patches or those in which surgery would be difficult, the treatments described include topical bleomycin 1%, dissolved in dimethylsulfoxide and applied for 5 minutes daily for 14 consecutive days. In a group of 19 patients with dysplastic leucoplakia improvement in the appearance of lesions and histological evidence of remission of the dysplasia occurred in the majority of patients. Sustained effects were also found on long-term follow-up for up to 10 years.[2]

There have been reports of partial or complete remission of leucoplakia in studies of vitamin A or betacarotene given orally long-term,[3-5] but lesions have recurred when supplementation was stopped.[4] Topical treatment with retinoids such as tretinoin or isotretinoin has also been tried, with similar results to those of oral vitamin A and retinoid treatments.[6,7] A small open study has also suggested that topical calcipotriol may be effective.[8]

A systematic review of treatments for leucoplakia found that there were few controlled studies, and that although these treatments might be effective in the resolution of lesions, the rate of relapse was high, and there was no evidence that they prevent malignant transformation.[9]

1. Scully C, Porter S. ABC of oral health: swellings and red, white, and pigmented lesions. *BMJ* 2000; 321: 225–8.
2. Epstein JB, *et al.* Topical bleomycin for the treatment of dysplastic oral leukoplakia. *Cancer* 1998; 83: 629–34.
3. Issing WJ, *et al.* Long-term follow-up of larynx leukoplakia under treatment with retinyl palmitate. *Head Neck* 1996; 18: 560–5.
4. Sankaranarayanan R, *et al.* Chemoprevention of oral leukoplakia with vitamin A and beta carotene: an assessment. *Oral Oncol* 1997; 33: 231–6.
5. Garewal HS, *et al.* β-Carotene produces sustained remissions in patients with oral leukoplakia: results of a multicenter prospective trial. *Arch Otolaryngol Head Neck Surg* 1999; 125: 1305–10.
6. Epstein JB, Gorsky M. Topical application of vitamin A to oral leukoplakia: a clinical case series. *Cancer* 1999; 86: 921–7.
7. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. *Cancer* 2002; 95: 1258–64.
8. Femiano F, *et al.* Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg* 2001; 30: 402–6.
9. Lodi G, *et al.* Interventions for treating oral leukoplakia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 21/05/08).

Malignant effusions. Bleomycin is used for the sclerotherapy of malignant pleural and pericardial effusions (p. 700.1).

Malignant neoplasms. Bleomycin is used in regimens for the management of Hodgkin's disease (p. 696.1), non-Hodgkin's lymphomas such as AIDS-related lympho-

mas (see p. 697.2), and for germ-cell tumours of the ovary and testis (see p. 711.2, and p. 715.1), as well as for some other malignancies including those of the head and neck, (p. 708.1), and Kaposi's sarcoma (p. 718.1).

Pneumothorax. In a patient with AIDS and pneumocystis pneumonia who developed pneumothorax, instillation of bleomycin into each pleural cavity was successful in resolving the pneumothorax after tetracycline sclerotherapy failed to do so.[1]

1. Knatiuk OW, *et al.* Bleomycin sclerotherapy for bilateral pneumothoraces in a patient with AIDS. *Ann Intern Med* 1990; 113: 988–90.

Warts. Several studies have examined the local use of bleomycin sulfate to treat severe or resistant warts (p. 1689.3) of the common, plane, plantar, eponychial, and mosaic types, usually by intralesional injection.[1-4] At the doses used, adverse effects, other than pain at the injection site,[1-3] do not seem to be common; however, nail dystrophy and Raynaud's phenomenon have been reported (see under Effects on the Skin, Hair, and Nails and Effects on the Vascular System, under Adverse Effects, below). Bleomycin has also been applied as a pressure-sensitive adhesive tape,[5] and various techniques for better intralesional use have been investigated.[6-8]

1. Shumack PH, Haddock MJ. Bleomycin: an effective treatment for warts. *Australas J Dermatol* 1979; 20: 41–2.
2. Bunney MH, *et al.* The treatment of resistant warts with intralesional bleomycin: a controlled clinical trial. *Br J Dermatol* 1984; 111: 197–207.
3. Munkvad M, *et al.* Locally injected bleomycin in the treatment of warts. *Dermatologica* 1983; 167: 86–9.
4. Dhar SB, *et al.* Intralesional bleomycin in the treatment of cutaneous warts: a randomized clinical trial comparing it with cryotherapy. *Indian J Dermatol Venereol Leprol* 2009; 75: 262–7.
5. Takigawa M, *et al.* Treatment of viral warts with pressure-sensitive adhesive tape containing bleomycin sulfate. *Arch Dermatol* 1985; 121: 1108.
6. Munn SE, *et al.* A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. *Br J Dermatol* 1996; 135: 969–71.
7. van der Velden EM, *et al.* Dermatography with bleomycin as a new treatment for verrucae vulgaris. *Int J Dermatol* 1997; 36: 145–50.
8. Pollock B, Sheehan-Dare R. Pulsed dye laser and intralesional bleomycin for treatment of resistant viol [sic] hand warts. *Lasers Surg Med* 2002; 30: 135–40.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

The most frequent adverse effects with bleomycin involve the skin and mucous membranes and include rash, erythema, pruritus, vesiculation, hyperkeratosis, nail changes, alopecia, hyperpigmentation, striae, and stomatitis. Fever is also common, and acute anaphylactoid reactions with hyperpyrexia and cardiorespiratory collapse have been reported in about 1% of patients with lymphoma. There is little depression of the bone marrow. Local reactions and thrombophlebitis may occur at the site of parenteral dosage.

The most serious delayed effect is pulmonary toxicity; interstitial pneumonitis occurs in about 10% of patients and progresses to fibrosis and death in about 1% of patients treated with bleomycin. Pulmonary toxicity is more likely in elderly patients and those given total doses greater than 400 000 international units (400 USP units). It is also more likely in patients who have had previous radiotherapy to the chest.

Effects on the lungs. Pneumonitis induced by bleomycin can progress to fatal pulmonary fibrosis. The presentation is often delayed; clinical manifestations include non-productive cough, dyspnoea, and sometimes fever (see Effects on the Lungs, p. 729.1). Pneumomediastinum has also been reported as an initial manifestation of fatal pulmonary toxicity due to bleomycin.[1] Risk factors for toxicity include increased age,[2,3] deteriorating renal function,[2] and concurrent or previous radiotherapy. The reaction is dose-related, and maximum doses have been set (see Uses and Administration, p. 750.2). Other factors that may be implicated include the regimen used, concomitant oxygen supplementation, smoking history, underlying lung disease, and growth factor support.[2,3] For further details of some of these risk factors, see under Interactions, below. There is no standard treatment for bleomycin-induced pneumonitis. Bleomycin therapy is usually stopped, and corticosteroids may be given[3] although strong evidence to support their use is lacking.[2] There is some suggestion that giving bleomycin by intravenous infusion rather than bolus injection may reduce pulmonary toxicity.[2]

1. Keijzer A, Kuenen B. Fatal pulmonary toxicity in testis cancer with bleomycin-containing chemotherapy. *J Clin Oncol* 2007; 25: 3543–4.
2. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; 120: 617–24.
3. Martin WG, *et al.* Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; 23: 7614–20.

Effects on the skin, hair, and nails. Permanent nail loss and nail loss followed by regrowth with dystrophy have been reported after intralesional injection of bleomycin for periungual warts.[1-3] In 2 cases this was preceded by blistering and ulceration,[1] or swelling, severe pain, and a burning sensation.[2] All 3 patients had received injections on one or two previous occasions when 2 patients had reported only mild pain.[1,3] Other reported cutaneous adverse effects of bleomycin include flagellate erythema, Raynaud's phenomenon, gangrene, fibrotic or sclerotic skin changes, hyperpigmentation, and neutrophilic eccrine hidradenitis (an inflammatory dermatosis with erythematous plaques and nodules, neutrophilic infiltrates of eccrine glands, and degeneration of eccrine cells). Acute generalised exanthematous pustulosis and alopecia have also been reported.[4]

1. Czarnecki D. Bleomycin and periungual warts. *Med J Aust* 1984; 141: 40.
2. Miller RAW. Nail dystrophy following intralesional injections of bleomycin for a periungual wart. *Arch Dermatol* 1984; 120: 963–4.
3. Urbina González F, *et al.* Cutaneous toxicity of intralesional bleomycin administration in the treatment of periungual warts. *Arch Dermatol* 1986; 122: 974–5.
4. Yamamoto T. Bleomycin and the skin. *Br J Dermatol* 2006; 155: 869–75.

Effects on the vascular system. Although thromboembolic disorders and Raynaud's syndrome have been associated with use of bleomycin in combination regimens, particularly with cisplatin and the vinca alkaloids or etoposide (see Effects on the Cardiovascular System, p. 727.2) there is some evidence for an association of Raynaud's syndrome with the use of bleomycin alone.[1,2]

There have also been cases of Raynaud's phenomenon reported after intralesional injection of bleomycin for treatment of warts on the hands and feet.[3-6] See also Effects on the Skin, Hair, and Nails, above.

1. Sundstrup B. Raynaud's phenomenon after bleomycin treatment. *Med J Aust* 1978; 2: 266.
2. Adoue D, Arlet P. Bleomycin and Raynaud's phenomenon. *Ann Intern Med* 1984; 100: 770.
3. Epstein E. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1991; 24: 785–6.
4. Gregg LJ. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1992; 26: 279–80.
5. de Pablo P, *et al.* Raynaud's phenomenon and intralesional bleomycin. *Acta Derm Venereol (Stockh)* 1992; 72: 465.
6. Vanhooteghem O, *et al.* Raynaud phenomenon after treatment of verruca vulgaris of the sole with intralesional injection of bleomycin. *Pediatr Dermatol* 2001; 18: 249–51.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2.

Bleomycin should be used with caution in the elderly, in patients with renal impairment or pulmonary infection or pre-existing impairment of pulmonary function, and in those who have received radiotherapy, particularly to the thorax. Patients should undergo regular chest X-rays. If these show infiltrates, or if breathlessness occurs, bleomycin should be stopped.

In view of the risk of an anaphylactoid reaction it has been suggested that patients with lymphomas should receive two test doses of 2000 international units (2 USP units) or less initially (but see Administration, p. 750.2).

AIDS. Cutaneous adverse effects occurred in 12 of 50 patients being treated with bleomycin for AIDS-associated Kaposi's sarcoma and increased in severity until bleomycin was withdrawn.[1] Bleomycin should be stopped in people with AIDS if cutaneous adverse effects are seen, and rechallenge should be avoided. However, the incidence of adverse effects did not appear to be higher in these patients than in cancer patients, and patients with AIDS seem to be less sensitive to bleomycin than to antibacterials such as co-trimoxazole and penicillins.

1. Caumes E, *et al.* Cutaneous side-effects of bleomycin in AIDS patients with Kaposi's sarcoma. *Lancet* 1990; 336: 1593.

Diving. Since the partial pressure of oxygen in the inspired air of a scuba diver increases with increasing depth, a theoretical possibility exists of a toxic [pulmonary] reaction to oxygen in bleomycin-treated patients who subsequently go diving, and such a risk would increase with the depth and duration of each dive.[1] However, the risks associated with diving after uncomplicated bleomycin-based treatment have been questioned;[2] the authors considered that resuming diving was acceptable 6 to 12 months after completing treatment with BEP (bleomycin, etoposide, and cisplatin), and recommended caution only in those who developed pulmonary function impairment when given bleomycin.

1. Zanetti CL. Scuba diving and bleomycin therapy. *JAMA* 1990; 264: 2869.
2. de Wit R, *et al.* Bleomycin and scuba diving: where is the harm? *Lancet Oncol* 2007; 8: 954–5.

Handling and disposal. *Urine* produced for up to 72 hours after a dose of bleomycin should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bleomycin 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 29/09/11)

Pregnancy. For a report of use of a bleomycin-containing chemotherapy regimen in a pregnant woman and subsequent adverse effects on the infant, see Pregnancy, under Cisplatin, p. 768.2. No adverse effects were reported in another infant whose mother was treated with combination chemotherapy containing bleomycin, see Pregnancy, under Teniposide, p. 867.2.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. There may be an increased risk of pulmonary toxicity in patients given bleomycin who receive oxygen, for example as part of a general anaesthetic procedure; a reduction in inspired oxygen concentration has been recommended.

Antineoplastics. Enhanced pulmonary toxicity, in some cases fatal, has been reported in patients given bleomycin and *cisplatin*,[1-4] presumably because cisplatin-induced renal impairment led to a decrease in bleomycin elimination. It seems reasonable to assume that similar interactions might occur if bleomycin were given with other nephrotoxic agents. It has been suggested that apart from a decrease in bleomycin dosage if nephrotoxicity occurs with such a combination, giving bleomycin by constant infusion rather than intermittent bolus might be less toxic.[1,5]

A study to investigate whether substitution of etoposide with *gemcitabine* would lead to a less leukaemogenic BEACOPP regimen was stopped early because of unexpectedly common pulmonary toxicity; one patient died. This toxicity was considered to be due to the use of gemcitabine with bleomycin.[6]

1. Bennett WM, *et al.* Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. *Cancer Treat Rep* 1980; 64: 921–4.
2. van Barneveld PWC, *et al.* Influence of platinum-induced renal toxicity on bleomycin-induced pulmonary toxicity in patients with disseminated testicular carcinoma. *Oncology* 1984; 41: 4–7.
3. Brodsky A, *et al.* Stevens-Johnson syndrome, respiratory distress and acute renal failure due to synergic bleomycin-cisplatin toxicity. *J Clin Pharmacol* 1989; 29: 821–3.
4. Sleijfer S, *et al.* Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. *Eur J Cancer* 1996; 32A: 550–2.
5. Chisholm RA, *et al.* Bleomycin lung: the effect of different chemotherapeutic regimens. *Cancer Chemother Pharmacol* 1992; 30: 158–60.
6. Bredenfeld H, *et al.* Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2004; 22: 2424–9.

Colony-stimulating factors. An increased incidence of pulmonary toxicity has been reported in patients receiving bleomycin as part of the ABVD regimen (with doxorubicin, vinblastine, and dacarbazine) who were given granulocyte colony-stimulating factor to alleviate neutropenia.[1] Another case of rapidly developing and fatal pneumonitis in a patient given BEP (bleomycin, etoposide, and cisplatin) with granulocyte colony-stimulating factor has been reported.[2]

Analyses of study data failed to show increased pulmonary toxicity when granulocyte colony-stimulating factor was added to bleomycin-containing regimens in patients with germ cell tumours or non-Hodgkin's lymphomas.[3-5] In a retrospective review of patients with Hodgkin's lymphoma, however, use of bleomycin with granulocyte colony-stimulating factor was associated with a statistically significant increase of pulmonary toxicity.[6]

1. Matthews JH. Pulmonary toxicity of ABVD chemotherapy and G-CSF in Hodgkin's disease: possible synergy. *Lancet* 1993; 342: 988.
2. Dirix LY, *et al.* Pulmonary toxicity and bleomycin. *Lancet* 1994; 344: 56.
3. Bastion Y, *et al.* Possible toxicity with the association of G-CSF and bleomycin. *Lancet* 1994; 343: 1221–2.
4. Bastion Y, Coiffier B. Pulmonary toxicity of bleomycin: is G-CSF a risk factor? *Lancet* 1994; 344: 474.
5. Saxman SB, *et al.* Pulmonary toxicity in patients with advanced-stage germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. *Chest* 1997; 111: 657–60.
6. Martin WG, *et al.* Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; 23: 7614–20.

Oxygen. Because bleomycin is thought to cause pulmonary toxicity partly by induction of free radicals, use with high concentrations of oxygen could be hazardous,[1] and reductions in inspired oxygen concentration have been recommended by licensed product information where oxygen supplementation is unavoidable. *Animal* studies show an increased risk of mortality with use of bleomycin and oxygen, although data in humans are lacking. The

need for oxygen restriction in bleomycin-treated patients has, however, been questioned.[2]

1. Sleijfer S. Bleomycin-induced pneumonitis. *Chest* 2001; 120: 617–24.
2. Donat SM, Levy DA. Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? *J Urol (Baltimore)* 1998; 160: 1347–52.

Pharmacokinetics

Bleomycin is thought to be poorly absorbed from the gastrointestinal tract. Absorption is rapid after parenteral, intraperitoneal, or intrapleural use. Bioavailability is 100% and 70% after intramuscular and subcutaneous dosage, respectively. A bioavailability of 45% has been reported after intraperitoneal or intrapleural use. Plasma protein binding is low. Enzymic degradation by bleomycin hydrolase occurs, mainly in plasma, the liver and other organs, and to a much lesser extent in skin and lungs. Elimination is biphasic: mean initial and terminal half-lives of 0.5 and 4 hours respectively have been reported after an intravenous bolus. Elimination may be more prolonged after continuous intravenous infusion and mean half-lives of 1.3 and 9 hours respectively have been reported. About two-thirds of a dose is excreted unchanged in the urine; the rate of excretion is determined by renal function. Drug concentrations in the CSF are low. Bleomycin crosses the placenta.

References.

1. Broughton A, *et al.* Clinical pharmacology of bleomycin following intravenous infusion as determined by radioimmunoassay. *Cancer* 1977; 40: 2772–8.
2. Alberts DS, *et al.* Bleomycin pharmacokinetics in man I: intravenous administration. *Cancer Chemother Pharmacol* 1978; 1: 177–81.
3. Yee GC, *et al.* Bleomycin disposition in children with cancer. *Clin Pharmacol Ther* 1983; 33: 668–73.

Genetic factors. Bleomycin is inactivated by bleomycin hydrolase (BLMH). Since response to chemotherapy may be determined by gene polymorphisms involved in metabolism, a study investigated whether the single nucleotide polymorphism (SNP) A1450G of the BLMH gene was associated with survival in patients with testicular cancer treated with bleomycin-containing chemotherapy. The homozygous variant G/G of this SNP was found to be associated with reduced survival and a higher prevalence of early relapses. The authors cautioned that this finding was hypothesis-generating and not yet clinically applicable.[1]

1. de Haas EC, *et al.* Variation in bleomycin hydrolase gene is associated with reduced survival after chemotherapy for testicular germ cell cancer. *J Clin Oncol* 2008; 26: 1817–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Bileco; Bleocris; Blocamicina; CytoRich; ***Austral.***: Blenamax; Blenoxane†; ***Belg.***: Bleomin†; ***Braz.***: Blenoxane; Bonar; Cinaleo; Tecnomicina; Tevableo; ***Canad.***: Blenoxane†; ***Chile***: Blexit; Nikableomicina; Oncobleocin†; ***Cz.***: Bleocin†; Bleomedac; ***Ger.***: Bleo-cell; Bleomedac; ***Gr.***: Bleocin; ***Hong Kong***: Bleocin; ***Hung.***: Bleocin†; ***India***: Bledmax; Bleochem; Bleocin; Bleocip; Bleolem; Bleonco; Bleostar-S; Bleotex; Naprobleo; Oil Bleo; Oncobleo; ***Indon.***: Blenamax; Bleocin; ***Jpn***: Bleo; Bleocin†; ***Malaysia***: Blenamax; Bleocin; ***Mex.***: Blanoxan; Bleolem; Bleomax; ***Neth.***: Bleomedac; ***NZ***: Blenoxane; ***Philipp.***: Bemocin; Blenoxane†; Bloicin-S; ***Pol.***: Bleocin†; ***Port.***: Bleocin; ***Rus.***: Blenamax (Бленамакс); Bleocin (Блеоцин); ***S.Afr.***: Blenamax; Blenoxane; Bleolem; ***Singapore***: Blenamax; Bleocin; ***Thai.***: Bleo-S†; Bleocin; Bleolem; ***Turk.***: Bleocin; Bleolem; ***UK***: Bleo; ***USA***: Blenoxane†.

Pharmacopoeial Preparations
BP 2014: Bleomycin Injection;
USP 36: Bleomycin for Injection.

Bortezomib *(BAN, USAN, rINN)*

Bortezomib; Bortezomibum; LDP-341; MG-341; MLN-341; PS-341; Бортезомиб

N-((1*S*)-1-Benzyl-2-[[(1*R*)-1-(dihydroxyboranyl)-3-methylbutyl]amino]-2-oxoethyl)pyrazinecarboxamide; {(1*R*)-3-Methyl-1-[(2*S*)-3-phenyl-2-(pyrazin-2-carboxamido)propanamido]butyl}boronic acid

$C_{19}H_{25}BN_4O_4$ = 384.2

CAS — 179324-69-7

ATC — L01XG32

ATC Vet — QL01XG32

UNII — 69G8BD63PP

Uses and Administration

Bortezomib is a reversible inhibitor of the 26S proteasome, a large protein complex in cells that is responsible for breaking down regulatory proteins of the cell cycle. Such inhibition disrupts tumour cell turnover and induces apoptosis. Bortezomib is used for the treatment of multiple myeloma (p. 699.2), either in combination with melphalan and prednisone for previously untreated patients or as monotherapy in relapsed/refractory multiple myeloma. In the USA, it is also used for mantle cell lymphoma in patients given at least one previous therapy.

In previously untreated multiple myeloma, an initial dose of bortezomib 1.3 mg/m² is given intravenously on days 1, 4, 8, 11, 22, 25, 29, and 32 of a 42-day cycle for 4 cycles. For the next 5 cycles, bortezomib is given at the same dose on days 1, 8, 22, and 29. Melphalan (9 mg/m²) and prednisone (60 mg/m²) are given orally on days 1 to 4 of each cycle.

For relapsed/refractory multiple myeloma and mantle cell lymphoma, bortezomib is given in initial bolus doses of 1.3 mg/m² intravenously on days 1, 4, 8, and 11 of a 21-day cycle. At least 72 hours should elapse between consecutive doses of bortezomib. In the UK, licensed product information recommends that patients with a confirmed complete response should receive 2 additional cycles of bortezomib, and that those who respond but do not achieve complete remission receive a total of 8 cycles. In the USA, extended therapy of more than 8 cycles may be given, either on the standard schedule recommended above, or on a maintenance schedule of one dose weekly for 4 weeks (days 1, 8, 15, and 22 of a 35-day cycle).

Before combination treatment, the platelet count should be ≥70 000 cells/mm³ and the absolute neutrophil count should be ≥1000 cells/mm³. Whether used in combination or as monotherapy, the bortezomib dose should be withheld, reduced, or treatment withdrawn, according to toxicity, particularly when peripheral neuropathy, neuropathic pain, and haematological toxicity occur (see Administration in Subsequent Cycles, below).

See also below for use in patients with hepatic impairment.

Bortezomib is under investigation for the treatment of other malignancies including non-Hodgkin's lymphoma. A subcutaneous formulation is also under investigation.

References.

1. Orlowski RZ. Bortezomib and its role in the management of patients with multiple myeloma. *Expert Rev Anticancer Ther* 2004; 4: 171–9.
2. Jagannath S, *et al.* Bortezomib in recurrent and/or refractory multiple myeloma: initial clinical experience in patients with impaired renal function. *Cancer* 2005; 103: 1195–1200.
3. Richardson PG, *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005; 352: 2487–98.
4. O'Connor OA. Marked clinical activity of the proteasome inhibitor bortezomib in patients with follicular and mantle-cell lymphoma. *Clin Lymphoma Myeloma* 2005; 6: 191–9.
5. Wang M, *et al.* Use of bortezomib in B-cell non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2006; 6: 983–91.
6. NICE. Bortezomib monotherapy for relapsed multiple myeloma (Issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf (accessed 23/05/08)
7. Terpos E, *et al.* Myeloma bone disease and proteasome inhibition therapies. *Blood* 2007; 110: 1098–1104.
8. Richardson PG, *et al.* Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed multiple myeloma. *Br J Haematol* 2007; 137: 429–35.
9. Utecht KN, Kolesar J. Bortezomib: a novel chemotherapeutic agent for hematologic malignancies. *Am J Health-Syst Pharm* 2008; 65: 1221–31.
10. Curran MP, McKeage K. Bortezomib: a review of its use in patients with multiple myeloma. *Drugs* 2009; 69: 859–88.
11. Laubach JP, *et al.* Clinical challenges associated with bortezomib therapy in multiple myeloma and Waldenströms macroglobulinemia. *Leuk Lymphoma* 2009; 50: 694–702. Correction. *ibid.*; 1235.
12. Einsele H. Bortezomib. *Recent Results Cancer Res* 2010; 184: 173–87.

Administration. Although licensed product information recommends no dose reduction of bortezomib for the elderly on the basis of age alone, toxicity often limits its use and reduced-intensity regimens have been investigated.[1-3] In combination treatment for elderly patients with untreated multiple myeloma, use of a once-weekly bortezomib regimen was well-tolerated without apparent detriment to efficacy (compared with the conventional initial twice-weekly schedule, see Uses and Administration, above).[1,2] In a retrospective review of elderly patients with relapsed disease, a once-weekly regimen of bortezomib was given with dexamethasone to patients with a median age of 80 years; toxicity and efficacy were comparable to a control cohort (median age 61 years) who were given the standard initial twice-weekly regimen (see Uses and Administration, above).[3]

1. Mateos M-V, *et al.* Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol* 2010; 11: 934–41.
2. Bringhen S, *et al.* Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood* 2010; 116: 4745–53.
3. Parrish C, *et al.* Feasibility and efficacy of administration of bortezomib-containing regimens to patients over the age of 70 years. *Br J Haematol* 2011; 153: 273–5.

ROUTE. A randomised study in patients with relapsed multiple myeloma found that subcutaneous bortezomib had similar efficacy to intravenous use.[1] The subcutaneous route also seemed to have a better systemic safety profile than intravenous bortezomib; peripheral neuropathy (of all grades) was significantly less, and overall rates of gastrointestinal disorders, respiratory, and nervous system disorders were also lower with subcutaneous use. Systemic exposure was similar between routes; peak plasma concentrations were lower but more sustained with subcutaneous use.

1. Moreau P, *et al.* Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol* 2011; 12: 431–40.

Administration in hepatic impairment. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment and close monitoring is recommended. In the UK and USA, specific recommendations are made according to the severity of impairment, defined by bilirubin and aspartate aminotransferase (AST/SGOT) concentrations:

- mild impairment, bilirubin ≤ the upper limit of normal (ULN) with AST > the ULN, or bilirubin > the ULN up to 1.5 times the ULN with any AST concentration: no dose modification required.
- moderate and severe impairment, bilirubin > 1.5 times the ULN with any AST concentration: reduce dose in the first cycle to bortezomib 700 micrograms/m² intravenously; in subsequent cycles doses can be increased up to 1 mg/m² or reduced to 500 micrograms/m² depending on tolerance.

See Uses and Administration, above for further details of dosing regimens.

Administration in subsequent cycles. When intravenous bortezomib is used *with melphalan and prednisone* for previously untreated multiple myeloma patients:

- if prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is seen in one cycle: consider reduction of the *melphalan* dose by 25% in the next cycle
- if the platelet count ≤ 30 000 cells/mm³ or absolute neutrophil count ≤ 750 cells/mm³ on a bortezomib dosing day (other than day 1): withhold bortezomib
- if several bortezomib doses in a cycle (≥ 3 doses during twice weekly dosing, or ≥ 2 doses during weekly dosing) or consecutive cycles are withheld: the bortezomib dose should be reduced by 25% (1.3 mg/m² to 1 mg/m²; 1 mg/m² to 700 micrograms/m²)

For grade 3 or more severe non-haematological toxicity (excluding neuropathy), dose modifications are as for patients on monotherapy, below

When used as *monotherapy* in relapsed/refractory multiple myeloma and mantle cell lymphoma, bortezomib should be withheld at the onset of any grade 3 non-haematological (excluding neuropathy) or grade 4 haematological toxicities. Once the toxicity has resolved, bortezomib may be restarted at a dose reduced by 25% (1.3 mg/m² to 1 mg/m²; 1 mg/m² to 700 micrograms/m²)

For those who have neuropathic pain and/or peripheral (sensory or motor) neuropathy, *whether treated with bortezomib monotherapy or as part of a combination regimen* the following dose modifications are recommended:

- grade 1 with pain, or grade 2: reduce bortezomib dose to 1 mg/m²
- grade 2 with pain, or grade 3: withhold bortezomib until toxicity resolves; restart with a reduced dose of 700 micrograms/m² and change treatment schedule to once weekly
- grade 4 (disabling sensory neuropathy or life-threatening motor neuropathy or paralysis): stop bortezomib

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Very common adverse effects of bortezomib include haematological toxicities (especially transient thrombocytopenia, neutropenia, and anaemia), decreased appetite, gastrointestinal disturbances, peripheral neuropathy, fatigue, fever, headache, dyspnoea, and rash. Complete blood counts including platelet counts should be monitored and therapy withheld or given at reduced doses if necessary. Peripheral neuropathy may also be dose-limiting.

Other common adverse effects include hyperglycaemia, hypokalaemia, insomnia, anxiety, confusion, depression, dry mouth, blurred vision, eye pain, vertigo, dizziness, dysgeusia, tremor, epistaxis, cough, rhinorrhoea, pruritus, urticaria, erythema, and oedema. Orthostatic hypotension is also common and may require treatment; caution is advised in patients with a history of syncope, those who are dehydrated, or those who take antihypertensives. Dizziness, orthostatic hypotension, fatigue, or blurred vision can affect the performance of tasks such as driving. Hypertension is also common. Musculoskeletal adverse effects such as myalgia, arthralgia, bone pain, and cramps are often reported.

Tachycardia, arrhythmias, palpitations, angina pectoris, atrial fibrillation, and myocardial infarction have occurred. There have been isolated cases of QT-interval prolongation but causality has not been confirmed. Congestive heart failure may develop or be exacerbated and pulmonary oedema has been reported. There are rare reports of pericarditis. Pulmonary disease such as pneumonitis has

occurred, and there have been rare reports of acute respiratory distress syndrome, some of them fatal. Bortezomib should not be used in patients with acute diffuse pulmonary or pericardial disease. Renal impairment is common in patients with multiple myeloma and acute renal failure has developed in patients on bortezomib. Dysuria is also common; urinary frequency or incontinence, urinary retention, haematuria, proteinuria, and haemorrhagic cystitis have been reported. Hepatotoxicity, which may be reversible, has included increases in liver enzyme values, hyperbilirubinaemia, and acute liver failure; bortezomib should be used with caution in hepatic impairment.

Tumour lysis syndrome may occur during bortezomib treatment, and those with a high tumour burden should be monitored closely. Immune-mediated reactions such as anaphylaxis, angioedema, serum-sickness-type reactions, polyarthritis with rash, and proliferative glomerulonephritis have been reported; bortezomib should be stopped if serious reactions occur. Reversible posterior leukoencephalopathy syndrome has occurred rarely and therapy should again be stopped; symptoms include seizures, hypertension, headache, blindness, and confusion. Bacterial, viral, and fungal infections have been reported in patients on bortezomib. Reactivation of latent herpes zoster infection can occur and prophylaxis with antivirals is recommended.

Other adverse effects that have been reported include injection site reactions, electrolyte disturbances, paralysis, disseminated intravascular coagulation, hearing impairment, thrombotic or bleeding events, ischaemic colitis, paralytic ileus, acute pancreatitis, pulmonary hypertension, Sweet's syndrome (acute febrile neutrophilic dermatosis), Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity reactions, alopecia, and erectile dysfunction have also been reported.

Effects on the nervous system. Treatment with bortezomib is often associated with peripheral neuropathy, mainly sensory, although cases of motor neuropathy have been reported. A review[1] identified risk factors for bortezomib-induced peripheral neuropathy as pre-existing neuropathy and comorbidities that cause nerve damage such as diabetes. The incidence of neuropathy with bortezomib is also higher in patients with multiple myeloma compared with solid tumours. Furthermore, high rates of peripheral neuropathy have been reported in newly diagnosed multiple myeloma patients before treatment. Results from an analysis[2] in relapsed and/or refractory multiple myeloma patients also found that the peripheral neuropathy associated with bortezomib seemed to be cumulative and dose-related, and increased in prevalence through the first 5 treatment cycles. Prolonged bortezomib exposure beyond this time did not seem to increase the incidence or severity of neuropathy. Development of neuropathy appeared to be independent of previous neurotoxic therapy. In most patients, neuropathic pain resolved or improved after dose modification or upon completion of therapy. Recovery is reported to take a median of 3 months after stopping bortezomib,[1] although some cases have taken up to 2 years for neuropathic symptoms to resolve.

Analgesics may be given symptomatically (see Choice of Analgesic, p. 4.2). For reference to use of topical menthol to relieve bortezomib-induced neuropathic pain, see p. 2553.3.

1. Argyriou AA, *et al.* Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. *Blood* 2008; 112: 1593–9. Correction. *ibid.*; 113: 4478.
2. Richardson PG, *et al.* Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol* 2006; 24: 3113–20.

Effects on the skin. In 3 studies of bortezomib in patients with non-Hodgkin's lymphoma, 26 of 140 patients developed an erythematous maculopapular rash. Six patients underwent biopsy; all cases revealed a small vessel necrotising vasculitis. Although some patients had dosage reductions implemented or therapy interrupted upon development of the rash, others were treated continuously without dose reduction, with no apparent adverse clinical consequences. In fact, analysis of the data supported a strong relationship between bortezomib-associated cutaneous vasculitis and a positive clinical response in patient with non-Hodgkin's lymphoma.[1] A macular brown-red eruption developed in a patient at the site of bortezomib infusions; abundant venous flushing was given from the fourth infusion, and the eruption did not recur, although hyperpigmentation persisted for several months.[2]

1. Gerecitano J, *et al.* Drug-induced cutaneous vasculitis in patients with non-Hodgkin lymphoma treated with the novel proteasome inhibitor bortezomib: a possible surrogate marker of response? *Br J Haematol* 2006; 134: 391–8.
2. Matalx J, *et al.* Persistent supravenous eruption induced by intravenous bortezomib therapy. *Br J Dermatol* 2008; 158: 863–4.

Infection. A retrospective analysis[1] of data from a study in relapsed multiple myeloma revealed an increase in herpes zoster infections with bortezomib treatment compared with dexamethasone. An incidence of 13% was reported which was comparable with that reported by other studies in relapsed multiple myeloma. Similarly, a herpes zoster incidence of 13% was found in newly diagnosed multiple myeloma patients treated with bortezomib (plus melphalan and prednisone),[2] compared with 4% in the control group (melphalan and prednisone only). The incidence of herpes zoster was reduced to 3% in the bortezomib group when antiviral prophylaxis was used. A retrospective review[3] found that prophylactic use of antivirals resulted in no cases of herpes zoster in 125 multiple myeloma patients treated with bortezomib. Most patients were given aciclovir 400 mg daily, or a reduced dose of 200 mg daily in renal impairment; famciclovir 500 mg daily or valaciclovir 250 to 500 mg daily were also used.

1. Chanan-Khan A, *et al.* Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. *J Clin Oncol* 2008; 26: 4784–90.
2. San Miguel JF, *et al.* VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008; 359: 906–17.
3. Vickrey E, *et al.* Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. *Cancer* 2009; 115: 229–32.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bortezomib 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 28/09/11)

Interactions

Bortezomib is both metabolised by, and a weak inhibitor of, cytochrome P450 isoenzymes, see below. Ketoconazole (a potent CYP3A4 inhibitor) increased exposure to bortezomib, but omeprazole (a potent CYP2C19 inhibitor) did not increase exposure to bortezomib. Patients should be closely monitored for toxicities or reduced efficacy when bortezomib is given with inhibitors or inducers of CYP3A4. Although melphalan plus prednisone increased exposure to bortezomib, the increase is not thought to be clinically relevant. Hypoglycaemia and hyperglycaemia have occurred in diabetic patients receiving oral antidiabetics who were given bortezomib.

Pharmacokinetics

After a single intravenous dose of bortezomib, plasma concentrations decline in a biphasic manner; a distribution phase of less than 10 minutes is followed by a longer elimination phase of about 5 to 15 hours. Clearance decreases after multiple doses. Protein binding has been reported to be about 83%. Bortezomib has a large volume of distribution suggesting it is widely distributed to peripheral tissues. Peak proteasome inhibition occurs about 1 hour after a dose, with a mean of 61% inhibition and a half-life of about 24 hours. *In-vitro* studies indicate that bortezomib is mainly oxidatively metabolised via the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP1A2; minor metabolism via CYP2D6 and CYP2C9 also occurs. Bortezomib is also a weak inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The major metabolic pathway is deboronation to inactive metabolites.

References.

1. Pekol T, *et al.* Human metabolism of the proteasome inhibitor bortezomib: identification of circulating metabolites. *Drug Metab Dispos* 2005; 33: 771–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Velcade; ***Austral.***: Velcade; ***Austria***: Velcade; ***Belg.***: Velcade; ***Braz.***: Velcade; ***Canad.***: Velcade; ***Chile***: Velcade; ***China***: Velcade (万珂); ***Cz.***: Velcade; ***Denm.***: Velcade; ***Fin.***: Velcade; ***Fr.***: Velcade; ***Ger.***: Velcade; ***Gr.***: Velcade; ***Hong Kong***: Velcade; ***Hung.***: Velcade; ***India***: Bortenat; Mibor; ***Indon.***: Velcade; ***Irl.***: Velcade; ***Israel***: Velcade; ***Ital.***: Velcade; ***Malaysia***: Velcade; ***Mex.***: Velcade; ***Neth.***: Velcade; ***Norw.***: Velcade; ***NZ***: Velcade; ***Philipp.***: Velcade; ***Pol.***: Velcade; ***Port.***: Velcade; ***Rus.***: Milanfore (Миланфор); Velcade (Велкейд); ***S. Afr.***: Velcade; ***Singapore***: Velcade; ***Spain***: Velcade; ***Swed.***: Velcade; ***Switz.***: Velcade; ***Thai.***: Velcade; ***Turk.***: Velcade; ***UK***: Velcade; ***USA***: Velcade; ***Venez.***: Velcade.

Bosutinib *(USAN, rINN)*

Bosutinibum, SKI-606, Бозутиниб.

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile.

$C_{26}H_{29}Cl_2N_5O_3$=530.4

CAS — 380843-75-4.
UNII — 5018V4AEZ0.

Uses and Administration

Bosutinib is an orally active dual SRC family and BCR-ABL tyrosine kinase inhibitor. It is indicated in patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive chronic myeloid leukaemia (p. 694.2) that is resistant to prior therapy or in those who are intolerant to other therapies. An oral dose of 500 mg is taken once daily with food. In the absence of grade 3 adverse effects, this dose may be increased to 600 mg once daily in patients who have an incomplete haematological response by week 8 or an incomplete cytogenetic response by week 12. The dose is reduced in those with hepatic impairment, see Administration in Hepatic Impairment below, and may need to be modified if toxicities occur, see Administration in Subsequent Cycles below. Treatment may be continued until there is disease progression or intolerance to bosutinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Bosutinib is also being investigated in solid tumours and for polycystic kidney disease.

References.

1. Keller G, *et al.* Bosutinib: a dual SRC/ABL kinase inhibitor for the treatment of chronic myeloid leukemia. *Expert Rev Hematol* 2009; 2: 489–97.
2. Keller G, *et al.* Bosutinib. *Recent Results Cancer Res* 2010; 184: 119–27.
3. Boschelli F, *et al.* Bosutinib: a review of preclinical studies in chronic myelogenous leukaemia. *Eur J Cancer* 2010; 46: 1781–9.
4. Cortes JE, *et al.* Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. *J Clin Oncol* 2012; 30: 3486–92.

Administration in hepatic impairment. Exposure to bosutinib is increased in those with hepatic impairment, and a reduced oral dose of 200 mg once daily is recommended in patients with chronic myeloid leukaemia and any degree of hepatic impairment.

Dose adjustments are required if hepatotoxicity occurs during treatment, see Administration in Subsequent Cycles, below.

Administration in subsequent cycles. In chronic myeloid leukaemia, oral bosutinib dosage may need to be modified if toxicities occur.

If myelosuppression occurs, bosutinib should be withheld until the absolute neutrophil count is ≥1000 cells/mm^3 and the platelets are ≥50 000 cells/mm^3. Bosutinib is resumed at the same dose if recovery occurs within 2 weeks; if recovery takes longer than 2 weeks, the daily dose is reduced by 100 mg. If cytopenia recurs the daily dose should be reduced by a further 100 mg upon recovery.

For an increase in liver transaminases >5 times the upper limit of normal (ULN), bosutinib should be withheld until recovery to ≤2.5 times the ULN; the dose should be resumed at 400 mg once daily thereafter. Bosutinib treatment should be stopped if recovery takes longer than 4 weeks or if liver transaminases increase to ≥3 times the ULN with a bilirubin increase >2 times the ULN and alkaline phosphatase <2 times the ULN.

If grade 3 or 4 diarrhoea occurs (≥7 stools/day more than usual), bosutinib should be withheld until recovery to grade 1 or better and the dose restarted at 400 mg once daily.

For other moderate or severe non-haematological toxicities, bosutinib should be withheld until the toxicity has resolved and then resumed at a dose of 400 mg once daily. If appropriate, this may be increased to 500 mg once daily if this higher dose was previously used.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most commonly reported adverse effects with bosutinib are diarrhoea, nausea, vomiting, abdominal pain, thrombocytopenia, anaemia, rash, pyrexia, and fatigue. The gastrointestinal toxicity with bosutinib can be dose-limiting; diarrhoea may be severe. Antidiarrhoeals, antiemetics, and fluid replacement may be required to manage symptoms. Gastritis and gastrointestinal haemorrhage have also been reported.

Myelosuppression (neutropenia, anaemia, and thrombocytopenia) can occur and full blood counts should be undertaken weekly for the first month and then monthly thereafter. Increased liver enzyme values and hepatotoxicity has been seen with bosutinib and liver function tests should be carried out monthly for the first three months of treatment.

Fluid retention occurs with bosutinib and may manifest as pericardial or pleural effusion, pulmonary oedema, or peripheral oedema.

Treatment may need to be modified for gastrotoxicity, myelosuppression, hepatotoxicity, and fluid retention, see Administration in Subsequent Cycles, above.

Hypersensitivity reactions include urticaria and anaphylactic shock, and dermatological effects include pruritus, acne, erythema multiforme, exfoliative rash, and drug eruption. Chest pain, pericarditis, and a prolonged QT interval have also been reported, as have dyspnoea, respiratory failure, and pulmonary hypertension. Increases in blood creatinine levels and acute renal failure have occurred.

Other adverse effects include acute pancreatitis, arthralgia, myalgia, back pain, headache, dizziness, dysgeusia, tinnitus, cough, and hyperkalaemia.

Exposure to bosutinib is increased in patients with hepatic impairment.

Interactions

Bosutinib is metabolised by the cytochrome P450 isoenzyme CYP3A4 and is an inhibitor and substrate for P-glycoprotein. Potent or moderate inhibitors of CYP3A4 or P-glycoprotein should be avoided as an increased plasma concentration of bosutinib is expected. Potent or moderate inducers of CYP3A4 should also be avoided as a reduction in the plasma concentration of bosutinib is expected.

Bosutinib may increase exposure to drugs that are P-glycoprotein substrates.

The bioavailability of bosutinib is pH-dependent and concomitant use with the proton pump inhibitor lansoprazole reduced exposure to bosutinib. If possible, short-acting antacids or H_2-antagonists should be used in place of proton pump inhibitors, and bosutinib doses should be separated from gastric-acid suppressants by at least 2 hours.

References.
1. Abbas R, *et al.* Effect of ketoconazole on the pharmacokinetics of oral bosutinib in healthy subjects. *J Clin Pharmacol* 2011; 51: 1721–7.

Pharmacokinetics

Peak plasma concentrations of bosutinib occur around 4 to 6 hours after a single oral dose. Exposure increases when taken with a high-fat meal. Bosutinib is highly protein bound at around 96%, and is a P-glycoprotein inhibitor and substrate. Metabolism is mainly via the cytochrome P450 isoenzyme CYP3A4 to inactive metabolites. Over 90% of an oral dose is excreted in the faeces and 3% in the urine. The terminal elimination half-life is about 22.5 hours after a single oral dose.

References.
1. Abbas R, *et al.* A phase I ascending single-dose study of the safety, tolerability, and pharmacokinetics of bosutinib (SKI-606) in healthy adult subjects. *Cancer Chemother Pharmacol* 2012; 69: 221–7.
2. Abbas R, *et al.* Evaluation of the pharmacokinetics and safety of bosutinib in patients with chronic hepatic impairment and matched healthy subjects. *Cancer Chemother Pharmacol* 2012. Available at: doi: 10.1007/s00280-012-1987-7

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Bosulif; *USA*: Bosulif.

Brentuximab Vedotin *(rINN)*

Brentuximab Vedotina; Brentuximab Védotine; Brentuximaburn Vedotinum; cAC10-vcMMAE; SGN-35; Брентуксимаб Ведотин.

CAS — 914088-09-8.
UNII — 7XL5I5S668.

Uses and Administration

Brentuximab vedotin is an antibody-drug conjugate consisting of the chimeric CD30-specific monoclonal antibody cAC10 conjugated to monomethyl auristatin E (MMAE), a microtubule disrupting agent. Brentuximab vedotin is used for the treatment of patients with Hodgkin's disease (p. 696.1) after failure of autologous haematopoietic stem cell transplantation or after failure of at least two treatment regimens (in those deemed unsuitable for transplantation). It is also used for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one combination chemotherapy regimen.

The recommended dose is 1.8 mg/kg (up to a maximum body-weight of 100 kg) given as an intravenous infusion over 30 minutes every 3 weeks. Treatment may be continued for a maximum of 16 cycles or until disease progression or unacceptable toxicity occurs. The dose may need to be delayed or reduced (see Administration in Subsequent Cycles, below). Brentuximab vedotin is diluted before infusion to obtain a final concentration ranging from 400 micrograms/mL to 1.8 mg/mL; appropriate infusion fluids include sodium chloride 0.9%, glucose 5%, or Lactated Ringer's solution.

Brentuximab vedotin is under investigation in the treatment of cutaneous T-cell lymphoma.

References.
1. Foyil KV, Bartlett NL. Brentuximab vedotin for the treatment of CD30+ lymphomas. *Immunotherapy* 2011; 3: 475–85.
2. Minich SS. Brentuximab vedotin: a new age in the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma. *Ann Pharmacother* 2012; 46: 377–83.
3. Younes A, *et al.* Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012; 30: 2183–9.
4. Gopal AK, *et al.* Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation. *Blood* 2012; 120: 560–8.
5. van de Donk NW, Dhimolea E. Brentuximab vedotin. *MAbs* 2012; 4: 458–65.

Administration in subsequent cycles. Brentuximab vedotin therapy may need to be delayed or the intravenous dose reduced if toxicity occurs. Licensed product information makes the following recommendations.

In the event of peripheral neuropathy:
- new or worsening grade 2 or 3 toxicity: treatment should be withheld until neuropathy improves to grade 1 or baseline, then brentuximab vedotin restarted at 1.2 mg/kg
- grade 4 toxicity: treatment is stopped

For neutropenia:
- grade 3 or 4 toxicity: treatment should be withheld until neutropenia improves to baseline or grade 2 or lower; growth factor support should be considered for subsequent cycles
- recurrent grade 4 neutropenia despite the use of growth factors: treatment should be stopped or the dose reduced to 1.2 mg/kg

Adverse Effects, Treatment, and Precautions

Bone marrow depression occurs commonly with brentuximab vedotin, especially neutropenia, anaemia, and thrombocytopenia. Neutropenia may be severe and prolonged and force doses to be delayed or reduced, or therapy to be stopped (see Administration in Subsequent Cycles, above). Complete blood counts should be monitored before each dose, and more frequently if neutropenia is severe. Infections occur, and can be serious; opportunistic infections have also been reported. Peripheral neuropathy is common and is mainly sensory, although cases of peripheral motor neuropathy have also been reported. Neuropathy may be cumulative and patients should be monitored for symptoms such as hypoaesthesia or hyperaesthesia, paraesthesia, burning sensations, or neuropathic pain or weakness. Therapy may need to be delayed or stopped, or a dose reduction may be warranted (see Administration in Subsequent Cycles, above).

Other common adverse effects include fatigue, gastrointestinal disturbances, cough, dyspnoea, fever, chills, lymphadenopathy, rash, pruritus, alopecia, headache, dizziness, insomnia, anxiety, myalgia, arthralgia, muscle spasms, peripheral oedema, hyperglycaemia, night sweats, and dry skin. Pain in the back, abdomen, or oropharyngeal area is also common; pain in an extremity can be serious.

Infusion-related reactions have occurred; associated symptoms include chills, nausea, dyspnoea, pruritus, fever, and cough. The infusion should be interrupted and the patient should be pre-medicated for subsequent infusions; premedication may include paracetamol, an antihistamine, and a corticosteroid. If anaphylaxis occurs, the infusion should be immediately and permanently stopped. Tumour lysis syndrome has been reported, especially in those with a high tumour burden, or rapidly proliferating disease. Stevens-Johnson syndrome has occurred; therapy should be stopped. There have been reports of fatal progressive multifocal leukoencephalopathy. Other serious adverse effects that have been reported include pulmonary embolism, pneumonitis, pneumothorax, pyelonephritis, septic shock, and supraventricular arrhythmia.

Interactions

Brentuximab vedotin contains monomethyl auristatin E (MMAE), which is mainly metabolised by cytochrome P450 isoenzyme CYP3A. Use of brentuximab vedotin with ketoconazole increased exposure to MMAE by about 30 to 70% and patients taking strong CYP3A4 inhibitors should be monitored closely for adverse reactions. Use with rifampicin, a potent CYP3A4 inducer, reduced exposure to MMAE by about 30 to 45%.

Pharmacokinetics

Brentuximab vedotin consists of a monoclonal antibody conjugated with monomethyl auristatin E (MMAE); the pharmacokinetic profile of brentuximab vedotin was similar to that of the monoclonal antibody. Peak concentrations of brentuximab vedotin were seen soon after the end of an infusion; time to peak concentrations of MMAE ranged from 1 to 3 days. Steady-state concentrations of brentuximab vedotin and MMAE occurred within 21 days when the drug was given every 3 weeks. No accumulation of brentuximab vedotin was seen with multiple dosing, and MMAE exposure decreased with continued use. Binding of MMAE to plasma proteins *in vitro* ranged from 68 to 82%. *In vivo*, only a small fraction of MMAE released from brentuximab vedotin is metabolised; this metabolism is mainly via oxidation by cytochrome P450 isoenzyme CYP3A4/5. The terminal half-life of brentuximab vedotin is about 4 to 6 days. About 24% of MMAE is recovered in both urine and faeces over a 1-week period; of this recovered MMAE, about 72% is in the faeces, and the majority of the excreted MMAE is unchanged.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Adcetris; *Switz.*: Adcetris; *UK*: Adcetris; *USA*: Adcetris.

Brostallicin *(rINN)*

Brostalicina; Brostallicine; Brostallicinum; PNU-166196 (hydrochloride); Бростальлицин.

4-(2-Bromoacrylamido)-*N*‴-(2-guanidinoethyl)-1,1′,1″,1‴-tetramethyl-*N*,4′:*N*′,4″:*N*″,4‴-quater[pyrrole-2-carboxamide].

$C_{30}H_{35}BrN_{12}O_5$=723.6

CAS — 203258-60-0.
UNII — RPC6R41K4I.

Profile

Brostallicin is an antineoplastic that binds to DNA. It is under investigation for the treatment of soft-tissue sarcomas.

References.
1. ten Tije AJ, *et al.* Phase I and pharmacokinetic study of brostallicin (PNU 166196), a new DNA minor-groove binder, administered intravenously every 3 weeks to adult patients with metastatic cancer. *Clin Cancer Res* 2003; 9: 2957–64.
2. Broggini M, *et al.* Brostallicin: a new concept in minor groove DNA binder development. *Anticancer Drugs* 2004; 15: 1–6.
3. Leahy M, *et al.* Brostallicin, an agent with potential activity in metastatic soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2007; 43: 308–15.
4. Lorusso D, *et al.* Brostallicin (PNU-166196), a new minor groove DNA binder: preclinical and clinical activity. *Expert Opin Invest Drugs* 2009; 18 1939–46.

Broxuridine *(rINN)*

Bromodeoxyuridine; Broxuridina; Broxuridinum; BUDR; NSC-38297; Броксуридин.

5-Bromo-2′-deoxyuridine; 5-Bromo-1-(2-deoxy-β-D-ribofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione.

$C_9H_{11}BrN_2O_5$=307.1

CAS — 59-14-3.
UNII — G34N38R2N1.

Profile

Broxuridine is a thymidine analogue which acts as a radiosensitiser to enhance the effects of radiotherapy. It is also reported to possess antiviral activity. A related compound brivudine (p. 970.1) is used as an antiviral.

Broxuridine is used as a research tool for measuring DNA synthesis. It has been given by intra-arterial infusion, with radiotherapy and other antineoplastic agents, in the treatment of tumours of the brain, head, and neck; it has also been used diagnostically.

References.
1. Freese A, *et al.* The application of 5-bromodeoxyuridine in the management of CNS tumors. *J Neurooncol* 1994; 20: 81–95.
2. Phillips TL, *et al.* Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89-05. *Int J Radiat Oncol Biol Phys* 1995; 33: 339–48.
3. Prados MD, *et al.* Influence of bromodeoxyuridine radiosensitization on malignant glioma patient survival: a retrospective comparison of survival data from the Northern California Oncology Group (NCOG) and Radiation Therapy Oncology Group trials (RTOG) for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys* 1998; 40: 653–9.
4. Prados MD, *et al.* Phase III randomized study of radiotherapy plus procarbazine, lomustine, and vincristine with or without BUdR for treatment of anaplastic astrocytoma: final report of RTOG 9404. *Int J Radiat Oncol Biol Phys* 2004; 58: 1147–52.

Busulfan *(BAN, rINN)*

Bussulfam; Busulfaani; Busulfanas; Busulfano; Busulfanum; Busulphan; Buszulfán; CB-2041; GT-41; Myelosan; NSC-750; WR-19508; Бусульфан.

Tetramethylene di(methanesulphonate); Butane-1,4-diyl di(methanesulphonate).

$C_6H_{14}O_6S_2$=246.3

CAS — 55-98-1.
ATC — L01AB01.

ATC Vet — QL01AB01.
UNII — G1LN9045DK.

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

Ph. Eur. 8: (Busulfan). A white or almost white, crystalline powder. Very slightly soluble in water and in alcohol; freely soluble in acetone and in acetonitrile. Store in airtight containers. Protect from light.

USP 36: (Busulfan). A white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; soluble 1 in 45 of acetone. Store in airtight containers.

Uses and Administration

Busulfan is an antineoplastic with a cell-cycle non-specific alkylating action unlike that of the nitrogen mustards, and having a selective depressant action on bone marrow. In small doses, it depresses granulocytopoiesis and to a lesser extent thrombocytopoiesis but has little effect on lymphocytes. With larger doses, severe bone-marrow depression eventually ensues.

Because of its selective action, busulfan has been used in the palliative treatment of chronic myeloid leukaemia (p. 694.2). It provides symptomatic relief with a reduction in spleen size and a general feeling of well-being. The fall in leucocyte count is usually accompanied by a rise in the haemoglobin concentration. Permanent remission is not induced and resistance to its beneficial effects gradually develops.

Busulfan may be used in patients with polycythaemia vera (p. 695.2) and in some patients with myelofibrosis and primary thrombocythaemia (p. 695.2). It is also used at high doses as part of a conditioning regimen to prepare patients for haemaatopoietic stem cell transplantation, see p. 1937.1.

Busulfan may be given orally or intravenously. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The licensed initial oral dosage of busulfan in **chronic myeloid leukaemia** is 60 micrograms/kg or 1.8 mg/m² daily, with a usual maximum single daily dose of 4 mg. This is continued until the white cell count has fallen to between 15 000 and 25 000 cells/mm³ (typically 12 to 20 weeks). It should be stopped earlier if the platelet count falls below 100 000 cells/mm³. Higher doses may be given if the response after 3 weeks is inadequate but this increases the risk of irreversible damage to the bone marrow and calls for special vigilance. Complete blood counts should be made at least every week and the trends followed closely; if haemorrhagic tendencies occur or there is a steep fall in the white cell count indicating severe bone-marrow depression, busulfan should be withdrawn until marrow function has returned.

Once an initial remission has been attained treatment is stopped and not resumed until the white cell count returns to 50 000 cells/mm³. If this occurs within 3 months, continuous maintenance treatment with a usual dose of 0.5 to 2 mg daily may be given; doses equating to less than 1 whole tablet may be achieved by including busulfan-free days between the treatment days.

In patients with **polycythaemia vera** the usual oral dose is 4 to 6 mg daily, continued for 4 to 6 weeks with careful monitoring of blood counts. Further courses are given when relapse occurs; alternatively, maintenance therapy may be given at half the dose required for induction. Doses of 2 to 4 mg daily have been given for **primary thrombocythaemia** or myelofibrosis.

In conditioning regimens for **haematopoietic stem cell transplantation** busulfan is given in *oral* doses of 1 mg/kg every 6 hours for 4 days, starting 7 days before transplantation; cyclophosphamide is usually given for 2 days, starting 24 hours after the final dose of busulfan. When given by *intravenous* infusion, the recommended dose is 800 micrograms/kg ideal body-weight every 6 hours for 4 days starting 7 days before transplantation. Cyclophosphamide is usually given for 2 days: UK licensed product information states that cyclophosphamide dosing should not be started for at least 24 hours after the last dose of busulfan, while US information permits earlier use although no sooner than 6 hours after the last busulfan dose. Actual body-weight is used for the calculation if it is less than the ideal weight and dose calculations for obese patients should be based on adjusted ideal body weight. Each dose should be diluted in sodium chloride 0.9% or glucose 5% to a final concentration of about 500 micrograms/mL, and given over 2 hours through a central venous catheter using an infusion pump.

For doses in children, see below.

References.
1. Buggia I, *et al.* Busulfan. *Ann Pharmacother* 1994; 28: 1055–62.
2. Socié G, *et al.* Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood* 2001; 98: 3569–74.
3. Ferry C, Socié G. Busulfan-cyclophosphamide versus total body irradiation-cyclophosphamide as preparative regimen before allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia: what have we learned? *Exp Hematol* 2003; 31: 1182–6.
4. Ciurea SO, Andersson BS. Busulfan in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2009; 15: 523–36.

Administration in children. Busulfan may be given in conditioning regimens to prepare children for **haematopoietic stem cell transplantation**. UK licensed product information states that it may be given *orally* to children less than 18 years of age, in accordance with local protocols, up to a maximum dose of 37.5 mg/m² every 6 hours for 4 days, starting 7 days before transplantation; cyclophosphamide is usually given for 2 days, starting 24 hours after the final dose of busulfan. When given *intravenously*, busulfan is licensed for use with cyclophosphamide or melphalan. The recommended dose of busulfan for children up to 17 years of age is weight-based as follows:

- less than 9 kg: busulfan 1 mg/kg
- 9 to 16 kg: busulfan 1.2 mg/kg
- 16 to 23 kg: busulfan 1.1 mg/kg
- 23 to 34 kg: busulfan 950 micrograms/kg
- greater than 34 kg: busulfan 800 micrograms/kg

This dose is given every 6 hours over 4 days to a total of 16 doses, diluted and infused as for adults (see Uses and Administration, above); cyclophosphamide or melphalan should not be started for at least 24 hours after the final dose of busulfan.

For the treatment of **chronic myeloid leukaemia** busulfan may be given orally to paediatric patients in the same dose as that used for adults (see Uses and Administration, above).

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

The major adverse effect of busulfan with standard doses is bone-marrow depression, manifest as leucopenia, thrombocytopenia, and sometimes, anaemia. The nadir of the granulocyte count usually occurs after about 10 to 30 days with recovery occurring over up to 5 months, but busulfan has sometimes caused irreversible or extremely-prolonged bone-marrow depression.

Hyperpigmentation is common, and in a few cases after long-term therapy may be part of a syndrome simulating Addison's disease.

Rarely, progressive interstitial pulmonary fibrosis, known as 'busulfan lung', can occur on prolonged treatment. Gastrointestinal disturbances are rare at usual therapeutic doses but may be dose-limiting where high doses are given before bone marrow transplantation. Other rare adverse effects include dry skin and other skin reactions, liver damage, gynaecomastia, cataract formation, and, at high doses, CNS effects including convulsions.

Busulfan may result in impaired fertility and gonadal function. As with other alkylating agents, it is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. Haemorrhagic cystitis occurred in a patient who had received prolonged therapy with busulfan.[1] High-dose busulfan used in conditioning regimens for haematopoietic stem cell transplantation may increase the risk of late-onset haemorrhagic cystitis.[2,3]

1. Pode D, *et al.* Busulfan-induced hemorrhagic cystitis. *J Urol (Baltimore)* 1983; 130: 347–8.
2. Kondo M, *et al.* Late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 1998; 22: 995–8.
3. Leung AYH, *et al.* Clinicopathological features and risk factors of clinically overt haemorrhagic cystitis complicating bone marrow transplantation. *Bone Marrow Transplant* 2002; 29: 509–13.

Effects on the liver. Jaundice in the terminal phase of chronic myeloid leukaemia in a 31-year-old man was attributed to busulfan which had been taken for 6 years.[1] Busulfan toxicity involving the liver was also reported in a patient who had taken busulfan for 54 months,[2] while hepatitis possibly associated with busulfan therapy has also been described.[3] Dose-dependent veno-occlusive disease (VOD) has been reported in 20 to 40% of patients receiving high-dose busulfan before bone marrow transplantation.[4] Previous radiotherapy, progenitor cell transplantation, three cycles of chemotherapy or more, the use of multiple alkylating agents, or total doses of busulfan in excess of 16 mg/kg can increase the risk of hepatic VOD. A reduced incidence of hepatic VOD has been seen in those patients given high-dose busulfan and cyclophosphamide when the first dose of cyclophosphamide has been delayed for more than 24 hours after the last dose of busulfan.

1. Underwood JCE, *et al.* Jaundice after treatment of leukaemia with busulphan. *BMJ* 1971; 1: 556–7.
2. Poadi MD, *et al.* Portal hypertension in a patient with chronic myeloid leukaemia. *Postgrad Med J* 1977; 53: 267–9.
3. Morris L, Guthrie T. Busulfan-induced hepatitis. *Am J Gastroenterol* 1988; 83: 682–3.
4. Hassan M. The role of busulfan in bone marrow transplantation. *Med Oncol* 1999; 16: 166–76.

Effects on the nervous system. High-dose busulfan, used in conditioning regimens for bone marrow transplantation, has been associated with the development of convulsions,[1-4] both generalised[1,3,4] and myoclonic.[2,4] As a result, the use of prophylactic antiepileptic therapy has been suggested as a component of such regimens.[1,3,4] However, some have not considered the routine use of prophylactic antiepileptics justified.[5]

If an antiepileptic is given, the best drug to choose is uncertain. Many studies have used phenytoin, but the potential for phenytoin to increase the metabolism of busulfan, thereby possibly decreasing its myeloablative efficacy, has been pointed out.[6] In addition, phenytoin plasma concentrations have been found to be subtherapeutic in patients who developed convulsions despite a standard prophylactic dose,[4] and the regimen was subsequently adjusted to take account of plasma concentrations. Clobazam has been suggested as an alternative to phenytoin for prophylaxis of busulfan-induced seizures.[7] A review[8] on the optimal prevention of seizures with high-dose busulfan considered that phenytoin was not the best choice, given its adverse effects and the induction of busulfan metabolism; it was suggested that a benzodiazepine such as clonazepam or lorazepam ought to be considered, and that levetiracetam also showed some promise.

Licensed product information from one manufacturer *Otsuka, USA* states that the recommended dose of their parenteral product is based on studies in which phenytoin was given; since phenytoin increases the clearance of busulfan by 15% or more, exposure should be monitored if other anticonvulsants are used, as an increase in plasma-busulfan might be expected, with increased risk of toxicity.

1. Marcus RE, Goldman JM. Convulsions due to high-dose busulphan. *Lancet* 1984; ii: 1463.
2. Martell RW, *et al.* High-dose busulfan and myoclonic epilepsy. *Ann Intern Med* 1987; 106: 173.
3. Sureda A, *et al.* High-dose busulfan and seizures. *Ann Intern Med* 1989; 111: 343–4.
4. Grigg AP, *et al.* Busulphan and phenytoin. *Ann Intern Med* 1989; 111: 1049–50. Correction. *ibid.*; 112: 313.
5. Hugh-Jones K, Shaw PJ. No convulsions in children on high-dose busulphan. *Lancet* 1985; i: 220.
6. Fitzsimmons WE, *et al.* Anticonvulsants and busulfan. *Ann Intern Med* 1990; 112: 552–3.
7. Schwarer AP, *et al.* Clobazam for seizure prophylaxis during busulfan chemotherapy. *Lancet* 1995; 346: 1238.
8. Eberly AL, *et al.* Optimal prevention of seizures induced by high-dose busulfan. *Pharmacotherapy* 2008; 28: 1502–10.

Effects on the skin and hair. For the effect of radiotherapy in precipitating skin lesions in busulfan-treated patients, see under Precautions, below.

Permanent alopecia has been reported after use of busulfan.[1]

1. Tosti A, *et al.* Permanent alopecia after busulfan chemotherapy. *Br J Dermatol* 2005; 152: 1056–8.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2. Careful attention should be given to monitoring blood counts during therapy. This should be done at least weekly at the start of standard dose therapy. With high dose therapy blood counts should be monitored daily, as should liver function. Prophylactic anticonvulsants should be used during high dose therapy (see Effects on the Nervous System, above).

Busulfan should be stopped if lung toxicity develops. The use of oxygen may exacerbate possible lung toxicity; if anaesthesia is required the concentration of oxygen should be minimised.

Handling. Busulfan is irritant; avoid contact with skin and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies busulfan 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 28/09/11)

Radiotherapy. Severe cutaneous reactions occurred in patients given radiotherapy at least 30 days after combined chemotherapy with high-dose busulfan.[1]

It is possible that radiotherapy could worsen subclinical lung injury caused by busulfan.

1. Vassal G, *et al.* Radiosensitisation after busulphan. *Lancet* 1987; i: 371.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Phenytoin increases the metabolism of busulfan (see Effects on the Nervous System, above).

Antifungals. Giving *itraconazole* with busulfan resulted in a decrease in the clearance of busulfan; *fluconazole* had no such effect.[1] Busulfan doses may need to be decreased if itraconazole is also given.

1. Buggia I, *et al.* Itraconazole can increase systemic exposure to busulfan in patients given bone marrow transplantation. *Anticancer Res* 1996; 16: 2083–8.

Antineoplastics. When *tioguanine* was given with busulfan for chronic myeloid leukaemia, several cases of hepatic nodular regenerative hyperplasia, with abnormal liver function tests, portal hypertension, and oesophageal varices were noted. There were no cases in patients given busulfan alone, and the mechanism of this possible interaction is unclear.[1,2]

1. Key NS, *et al.* Oesophageal varices associated with busulfan-thioguanine combination therapy for chronic myeloid leukaemia. *Lancet* 1987; ii: 1050–2.
2. Shepherd PCA, *et al.* Thioguanine used in maintenance therapy of chronic myeloid leukaemia causes non-cirrhotic portal hypertension. *Br J Haematol* 1991; 79: 185–92.

Antiprotozoals. In patients who received either high-dose oral or intravenous busulfan as part of a myeloablative regimen before stem cell transplantation, the use of *metronidazole* significantly increased plasma concentrations of busulfan and the degree of associated toxicity, including elevation of liver function tests, veno-occlusive disease, and/or mucositis.[1,2]

1. Nilsson C, *et al.* The effect of metronidazole on busulfan pharmacokinetics in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; 31: 429–35.
2. Gulbis AM, *et al.* Busulfan and metronidazole: an often forgotten but significant drug interaction. *Ann Pharmacother* 2011; 45: e39.

Pharmacokinetics

Busulfan is well absorbed after oral dosage, although intra- and interpatient bioavailability vary widely. Busulfan is lipophilic and crosses the blood-brain barrier; concentrations in the CSF have been reported as being comparable to those in plasma. About 30% of circulating drug is irreversibly bound to plasma proteins, mainly to albumin; the level of reversible binding has been variably reported to be insignificant at around 7%, or to be about 55%. The plasma elimination half-life is about 2 to 3 hours. Busulfan is extensively metabolised in the liver, mainly by conjugation with glutathione, either spontaneously or mediated by the enzyme glutathione-S-transferase. About 12 inactive metabolites have been identified, which are excreted in the urine. About 1% of busulfan is excreted unchanged. Elimination in the faeces is considered to be negligible.

References.

1. Nath CE, *et al.* Variability in the pharmacokinetics of intravenous busulphan given as a single daily dose to paediatric blood or marrow transplant recipients. *Br J Clin Pharmacol* 2008; 66: 50–9.
2. Salinger DH, *et al.* Development of a population pharmacokinetics-based sampling schedule to target daily intravenous busulfan for outpatient clinic administration. *J Clin Pharmacol* 2010; 50: 1292–1300.
3. Bartelink IH, *et al.* Body weight-dependent pharmacokinetics of busulfan in paediatric haematopoietic stem cell transplantation patients: towards individualized dosing. *Clin Pharmacokinet* 2012; 51: 331–45.

Genetic factors. Busulfan is metabolised in the liver via conjugation with glutathione; this can be mediated via the enzyme glutathione-S-transferase (GST). Genetic variants can result in altered enzymatic activity, and affect busulfan metabolism. A pharmacokinetic study in children given intravenous busulfan found that carriers of GSTA1*B allele had a higher exposure to busulfan than non-carriers; busulfan clearance in carriers was reduced by about 30%. While genetic status may provide some explanation for pharmacokinetic variability, busulfan exposure is also dependent on age and body-weight; GSTA1*B carriers were also significantly younger and weighed less, confounding the interpretation. Nonetheless, genotype may be useful in dosing decisions.[1]

1. Johnson L, *et al.* Glutathione S-transferase A1 genetic variants reduce busulfan clearance in children undergoing hematopoietic cell transplantation. *J Clin Pharmacol* 2008; 48: 1052–62.

Metabolism. In a study of the pharmacokinetics of high-dose busulfan in 5 patients receiving 1 mg/kg orally every six hours for 4 days, the mean elimination half-life decreased from about 3.4 hours after the first dose to about 2.3 hours after the final dose, suggesting that busulfan may induce its own metabolism.[1]

Genetic factors may also affect metabolism of busulfan, see above.

1. Hassan M, *et al.* Pharmacokinetic and metabolic studies of high-dose busulphan in adults. *Eur J Clin Pharmacol* 1989; 36: 525–30.

Therapeutic drug monitoring. The value of therapeutic drug monitoring for busulfan in conditioning regimens for haematopoietic stem cell transplantation has been reviewed,[1,2] and suggested to maximise engraftment and minimise toxicity and relapse. In regimens using busulfan with cyclophosphamide, steady-state plasma concentrations of busulfan above 600 micrograms/litre appeared to favour engraftment.[1] A pharmacokinetic analysis found that in patients with graft rejections, busulfan trough concentrations were below 150 nanograms/mL; steady-state concentrations also tended to be lower in this group but not significantly so.[3]

The bioavailability of oral busulfan is variable, particularly in children; intravenous conditioning regimens, adjusted on the basis of first-dose pharmacokinetics and therapeutic drug monitoring, have been used to overcome this problem.[4,5] A study found a significant correlation between busulfan concentration in plasma and saliva after oral dosing in children; busulfan saliva analysis may therefore be a useful, non-invasive alternative to plasma analysis.[6]

1. McCune JS, *et al.* Plasma concentration monitoring of busulfan: does it improve clinical outcome? *Clin Pharmacokinet* 2000; 39: 155–65.
2. Russell JA, Kangarloo SB. Therapeutic drug monitoring of busulfan in transplantation. *Curr Pharm Des* 2008; 14: 1936–49.
3. Chandy M, *et al.* Randomized trial of two different conditioning regimens for bone marrow transplantation in thalassemia—the role of busulfan pharmacokinetics in determining outcome. *Bone Marrow Transplant* 2005; 36: 839–45.
4. Tran H, *et al.* Pharmacokinetics and individualized dose adjustment of intravenous busulfan in children with advanced hematologic malignancies undergoing allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2004; 10: 805–12.
5. Kletzel M, *et al.* Pharmacokinetics of a test dose of intravenous busulfan guide dose modifications to achieve an optimal area under the curve of a single daily dose of intravenous busulfan in children undergoing a reduced-intensity conditioning regimen with hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2006; 12: 472–9.
6. Rauh M, *et al.* Quantification of busulfan in saliva and plasma in haematopoietic stem cell transplantation in children: validation of liquid chromatography tandem mass spectrometry method. *Clin Pharmacokinet* 2006; 45: 305–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Busilvex; Myleran; *Austral.*: Busulfex; Myleran; *Austria*: Busilvex; Myleran; *Belg.*: Busilvex; Myleran; *Braz.*: Myleran; *Canad.*: Busulfex; Myleran; *Chile*: Myleran; *China*: Busulfex (白舒非); Myleran (马利兰); *Cz.*: Busilvex; Myleran; *Denm.*: Busilvex; *Fr.*: Busilvex; Myleran; *Ger.*: Busilvex; Myleran; *Gr.*: Busilvex; Myleran; *Hong Kong*: Busulfex; Myleran; *India*: Bucelon; Busuphan; Mylefan; Myleran; Myran; Mysulfan; *Irl.*: Busilvex; Myleran; *Israel*: Busulfex; Myleran; *Ital.*: Busilvex; Myleran; *Jpn*: Busulfex; *Malaysia*: Busulfex; Myleran; *Mex.*: Myleran; *Neth.*: Busilvex; Myleran; *Norw.*: Busilvex; *NZ*: Myleran; *Pol.*: Busilvex; Myleran; *Port.*: Busilvex; Myleran; *Rus.*: Myleran (Милеран); *S. Afr.*: Busilvex†; Myleran; *Singapore*: Busulfex; Myleran; *Spain*: Busilvex; *Swed.*: Busilvex; Myleran; *Switz.*: Busilvex; *Thai.*: Busulfex; Myleran; *Turk.*: Busilvex; Busulfex; Myleran; *UK*: Busilvex; Myleran; *USA*: Busulfex; Myleran.

Multi-ingredient Preparations. *Singapore*: Myran.

Pharmacopoeial Preparations
BP 2014: Busulfan Tablets;
USP 36: Busulfan Tablets.

Cabazitaxel *(USAN, rINN)*

Cabazitaxelum; RPR-116258A; XRP-6258; Кабазитаксел.
1-Hydroxy-7β,10β-dimethoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-((2*R*,3*S*)-3-[[(*tert*-butoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate).
$C_{45}H_{57}NO_{14}$=835.9
CAS — 183133-96-2.
UNII — 51F690397J.

Uses and Administration

Cabazitaxel is a semisynthetic taxane similar to paclitaxel (see p. 839.3) that is manufactured from a taxane precursor derived from the needles of the yew tree. It is used with prednisone or prednisolone in the treatment of hormone-refractory metastatic prostate cancer (p. 712.3), in patients previously treated with a docetaxel-containing regimen.

Cabazitaxel is given by intravenous infusion over 1 hour diluted in at least 250 mL sodium chloride 0.9% or glucose 5% to a final concentration of between 100 to 260 micrograms/mL; infusion is via a 0.22 micrometre in-line filter and PVC containers and polyurethane infusion sets should not be used. Cabazitaxel 25 mg/m² is given every 3 weeks, with oral prednisone or prednisolone 10 mg given daily.

At least 30 minutes before each dose of cabazitaxel, an intravenous dose of an antihistamine (diphenhydramine 25 mg or equivalent), a corticosteroid (dexamethasone 8 mg or equivalent), and a histamine H_2-antagonist (ranitidine 50 mg or equivalent) should be given. Prophylaxis with an antiemetic is also recommended and can be given orally or intravenously as needed. Patients at high risk of neutropenia may need granulocyte colony-stimulating factor, see Adverse Effects, Treatment, and Precautions, below.

Toxicity may require the cabazitaxel dose to be modified, see Administration in Subsequent Cycles, below.

References.

1. de Bono JS, *et al.* TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; 376: 1147–54. Correction. *ibid.* 2011; 377: 720.
2. Agarwal N, *et al.* Cabazitaxel for the treatment of castration-resistant prostate cancer. *Future Oncol* 2011; 7: 15–24.
3. Michielsen DP, *et al.* Cabazitaxel for the treatment of prostate cancer. *Expert Opin Pharmacother* 2011; 12: 977–82.
4. Paller CJ, Antonarakis ES. Cabazitaxel: a novel second-line treatment for metastatic castration-resistant prostate cancer. *Drug Des Devel Ther* 2011; 5: 117–24.
5. Oudard S. TROPIC: phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. *Future Oncol* 2011; 7: 497–506.
6. Villanueva C, *et al.* Cabazitaxel: a novel microtubule inhibitor. *Drugs* 2011; 71: 1251–8. Correction. *ibid.*; 1720.

Administration in subsequent cycles. Intravenous dose of cabazitaxel should be modified for the following toxicities:

- febrile neutropenia, or neutropenia of grade 3 or above for more than 1 week despite treatment including granulocyte colony-stimulating factor: delay cabazitaxel until neutrophil count is above 1500 cells/mm³ and fever has improved or resolved, then reduce dose to 20 mg/m².
Secondary prophylaxis with a granulocyte colony-stimulating factor is recommended.
- persistent diarrhoea (despite treatment), or diarrhoea of grade 3 or above: delay cabazitaxel until improvement or resolution of symptoms, then reduce dose to 20 mg/m².
- peripheral neuropathy of grade 2 or above: delay cabazitaxel until improvement or resolution of symptoms, then reduce dose to 20 mg/m².

If a patient continues to have any of the above adverse effects while on the reduced dose, cabazitaxel treatment should be stopped.

Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Neutropenia is common during cabazitaxel treatment and fatalities have been reported. Granulocyte colony-stimulating factor may be given to reduce the risk, and prophylaxis and/or treatment should be considered in high-risk patients such as those aged 65 years and over, those with poor performance status, those with extensive prior radiotherapy, or those with previous episodes of febrile neutropenia. Cabazitaxel should not be started or continued while neutrophil counts are 1500 cells/mm³ or below if counts increase above this level then use may be continued using a modified dose (see Uses and Administration, above). Blood counts should be monitored every week during the first treatment cycle of cabazitaxel, and before each cycle thereafter.

To prevent hypersensitivity reactions, all patients should be given premedication with an antihistamine, corticosteroid, and histamine H_2-antagonist (see Uses and Administration, above). If a severe hypersensitivity reaction occurs cabazitaxel should be stopped immediately and not restarted; symptoms include hypotension, bronchospasm, and rash, that may occur within a few minutes of the infusion. Cabazitaxel should not be used in patients hypersensitive to polysorbate 80, which is present in the formulation.

Peripheral neuropathy and gastrointestinal disturbances are common; diarrhoea may be severe and fatalities have been reported. Treatment should be delayed or the dose reduced for peripheral neuropathy, or severe or persistent diarrhoea (see Uses and Administration, above). Other common adverse effects include anaemia, leucopenia, thrombocytopenia, fatigue, haematuria, dyspnoea, dysgeusia, cough, arthralgia, myalgia, alopecia, anorexia, dehydration, hyperglycaemia, hypokalaemia, anxiety, confusion, sciatica, conjunctivitis, increased lachrymation, tinnitus, vertigo, tachycardia, hypotension or hypertension, deep-vein thrombosis, flushing, dry skin, and urinary disorders. Arrhythmias, peripheral oedema, increases in liver enzymes, urinary-tract infection, dizziness, headache, pyrexia, muscle spasms, and pain including chest pain have also been reported. Renal failure, occasionally fatal, has occurred. Other rare adverse effects that have led to death include cardiac arrest or cardiac failure, ventricular fibrillation, and cerebral haemorrhage.

Some adverse effects such as neutropenia, fatigue, pyrexia, dizziness, dehydration, and urinary-tract infections occurred more frequently in elderly patients (65 years and over), who may require additional monitoring.

Cabazitaxel is metabolised in the liver and so should not be used in patients with hepatic impairment (defined as total bilirubin > the upper limit of normal, or aspartate aminotransferase and/or alanine aminotransferase ≥ 1.5 times the upper limit of normal).

Interactions

For a general discussion of antineoplastic drug interactions, see p. 733.3.

Cabazitaxel is mainly metabolised via the cytochrome P450 isoenzyme CYP3A4. Potent inhibitors or inducers of this enzyme may affect exposure to cabazitaxel, and their use together should be avoided. Caution is advised when cabazitaxel is used with moderate inhibitors.

In vitro studies suggest that the potential for cabazitaxel to inhibit or induce CYP isoenzymes is low.

Pharmacokinetics

Cabazitaxel is equally distributed between blood and plasma *in vitro*; binding to plasma proteins is about 90%, mainly to albumin and lipoproteins. Cabazitaxel is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4 and CYP3A5, and to a lesser extent by CYP2C8. Renal excretion of cabazitaxel and its metabolites accounts for a small portion of the dose (about 4%); most of the dose (76%) is excreted via the faeces as metabolites. After a one-hour intravenous infusion, cabazitaxel follows a three-compartment pharmacokinetic model with α, β, and γ half-lives of 4 minutes, 2 hours, and 95 hours, respectively.

Cabazitaxel crosses the blood-brain barrier and the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Jevtana; *Belg.*: Jevtana; *Braz.*: Jevtana; *Denm.*: Jevtana; *Fr.*: Jevtana; *Ger.*: Jevtana; *Irl.*: Jevtana; *Israel*: Jevtana; *Neth.*: Jevtana; *Norw.*: Jevtana; *Spain*: Jevtana; *Swed.*: Jevtana; *Switz.*: Jevtana; *UK*: Jevtana; *USA*: Jevtana.

Cabozantinib *(USAN, pINN)*

Cabozantinibum; XL-184 (cabozantinib or cabozantinib s-malate); Кабозантиниб.

N-[4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

$C_{28}H_{24}FN_3O_5$=501.5

CAS — 849217-68-1.

UNII — 1C39JW444G.

Cabozantinib s-Malate *(USAN, pINNM)*

Cabozantinib, Malate de; Cabozantinibi Malas; Malato de cabozantinib; XL-184 (cabozantinib or cabozantinib s-malate); Кабозантиниба Малат.

$C_{28}H_{24}FN_3O_5.C_4H_6O_5$=635.6

CAS — 1140909-48-3.

UNII — DR7ST46X58.

Uses and Administration

Cabozantinib is a tyrosine kinase inhibitor that targets multiple receptor kinases including MET (mesenchymal-epithelial transition factor, hepatocyte growth factor receptor/HGFR), RET (rearranged during transfection), and VEGF (vascular endothelial growth factor). It is used in the treatment of progressive, metastatic medullary thyroid cancer (p. 716.1). Doses are given as the s-malate but expressed as the base; 177.4 mg of cabozantinib s-malate is equivalent to about 140 mg cabozantinib.

The usual oral dose is the equivalent of cabozantinib 140 mg once daily; capsules should be taken on an empty stomach and swallowed whole. A missed dose should not be taken within 12 hours of the next dose. Dose adjustments may be required for toxicities, see Administration in Subsequent Cycles, below. Treatment is continued until disease progression or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For patients who must also take a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, the daily dose of cabozantinib should be reduced by 40 mg. The original dose of cabozantinib may be restarted 2 or 3 days after the inhibitor has been stopped. For patients who must take a potent CYP3A4 inducer, the daily dose of cabozantinib should be increased by 40 mg to a maximum dose of 180 mg daily. The original dose of cabozantinib may be restarted 2 or 3 days after the inducer has been stopped.

Cabozantinib is also under investigation for the treatment of other solid neoplasms including prostate cancer and renal cell carcinoma.

References.
1. Durante C, *et al.* XL184 (cabozantinib) for medullary thyroid carcinoma. *Expert Opin Invest Drugs* 2011; 20: 407–413.
2. Kurzrock R, *et al.* Activity of XL184 (cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol* 2011; 29: 2660–6.
3. Nagilla M, *et al.* Cabozantinib for the treatment of advanced medullary thyroid cancer. *Adv Therapy* 2012; 29: 925–34.
4. Hart CD, De Boer RH. Profile of cabozantinib and its potential in the treatment of advanced medullary thyroid cancer. *Onco Targets Ther* 2013; 6: 1–7.

Administration in subsequent cycles. Cabozantinib treatment may need to be modified if toxicities occur. It should be withheld for grade 4 haematological adverse effects, for grade 3 or higher non-haematological reactions, or for intolerable grade 2 reactions. When reactions have resolved or improved to grade 1, the oral daily dose of cabozantinib should be reduced as follows:

- in those previously taking 140 mg: resume treatment at 100 mg
- in those previously taking 100 mg: resume treatment at 60 mg
- in those previously taking 60 mg: resume treatment at 60 mg if tolerated, otherwise stop treatment

Adverse Effects and Precautions

The most commonly reported adverse effects with cabozantinib are diarrhoea or constipation, stomatitis, nausea and vomiting, abdominal pain, dysgeusia, oral pain, anorexia and decreased body weight, palmar-plantar erythrodysesthesia syndrome, fatigue, hair colour changes, and hypertension. Other less common adverse effects include other gastrointestinal disorders such as dyspepsia or dysphagia, arthralgia, muscle spasms, musculoskeletal chest pain, dizziness, peripheral neuropathy, anxiety, dysphonia, rash, dry skin, alopecia, and hypotension. Reversible posterior leucoencephalopathy syndrome has been reported, and any patients reporting seizures, headache, visual disturbances, confusion, or altered mental state should be evaluated for this. Increased concentrations of thyroid-stimulating hormone, increased liver enzyme values, hyperbilirubinaemia, neutropenia, thrombocytopenia, lymphopenia, hypocalcaemia, hypophosphataemia, hypomagnesaemia, hypokalaemia, and hyponatraemia have also been noted. Proteinuria has sometimes occurred; monitoring is recommended.

Gastrointestinal perforations and fistulas have occurred, as have tracheal or oesophageal fistulas. Serious haemorrhage has been reported and cabozantinib should not be used in patients with recent haemorrhage or haemoptysis. An increased incidence of thrombotic events, including venous and arterial thromboembolism, has also been associated with cabozantinib.

Osteonecrosis of the jaw has occurred with cabozantinib and an oral examination should be carried out before starting treatment and periodically thereafter. Wound complications have also been reported and treatment should be stopped at least 28 days before scheduled surgery, including invasive dental procedures; it may be restarted when healing is deemed adequate. Where dehiscence or wound healing complications occur during treatment, cabozantinib should be withheld.

Cabozantinib should be permanently stopped for visceral perforation or fistula formation, severe haemorrhage, serious arterial thromboembolism, nephrotic syndrome, malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite medical management, osteonecrosis of the jaw, or reversible posterior leucoencephalopathy syndrome.

Interactions

Cabozantinib is a substrate of the cytochrome P450 isoenzyme CYP3A4. Exposure to cabozantinib was increased by 38% when it was given with the CYP3A4 inhibitor ketoconazole, and potent CYP3A4 inhibitors should be avoided during treatment. Conversely, exposure to cabozantinib was decreased by 77% when it was given with the CYP3A4 inducer rifampicin and prolonged use of potent CYP3A4 inducers should avoided. The dose cabozantinib may need to be adjusted if CYP3A4 inhibitors or inducers must be used, see Uses and Administration, above.

Pharmacokinetics

Peak plasma concentrations of cabozantinib occur between 2 to 5 hours after an oral dose, and steady-state concentrations are seen by day 15. Exposure is increased when it is taken with a high-fat meal. Cabozantinib is highly-bound to plasma proteins (over 99%). It is metabolised by the cytochrome P450 isoenzyme CYP3A4; CYP2C9 is a minor route. It is excreted via the faeces and urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Cometriq.

Cancer Vaccines

Vacunas contra el cáncer.

Profile

Vaccines are under investigation for many neoplastic diseases including breast, colorectal, head and neck, lung, ovarian, pancreatic, prostate, and renal cancers, lymphoma, and melanoma. Vaccines can be either preventative or therapeutic. Vaccines for the treatment of cancer are designed to stimulate an antibody response and can be allogeneic or autologous and based on dendritic cells, peptides or proteins, whole tumour cells, RNA or DNA, bacterial or viral vectors, or heat shock proteins.

BCG vaccine can be used as immunotherapy to treat bladder cancer (see p. 2378.2), and a human papillomavirus (HPV) vaccine for the prevention of cervical cancer is available in some countries (see p. 2392.2). A therapeutic vaccine targeting epidermal growth factor is used in some countries for non-small cell lung cancer. Sipuleucel-T (p. 857.1) and vitespen (p. 887.1) are examples of personalised cancer vaccines.

Reviews.
1. Eager R, *et al.* Lung cancer vaccines. *Curr Gene Ther* 2007; 7: 469–84.
2. Lowe DB, *et al.* Towards progress on DNA vaccines for cancer. *Cell Mol Life Sci* 2007; 64: 2391–2403.
3. Doehn C, *et al.* Prostate cancer vaccines: current status and future potential. *BioDrugs* 2008; 22: 71–84.
4. de Gruijl TD, *et al.* Whole-cell cancer vaccination: from autologous to allogeneic tumor- and dendritic cell-based vaccines. *Cancer Immunol Immunother* 2008; 57: 1569–77.
5. Ebben JD, *et al.* Tumour vaccine approaches for CNS malignancies: progress to date. *Drugs* 2009; 69: 241–9.
6. Pilla L, *et al.* Multipeptide vaccination in cancer patients. *Expert Opin Biol Ther* 2009; 9: 1043–55.
7. Shumway NM, *et al.* Therapeutic breast cancer vaccines: a new strategy for early-stage disease. *BioDrugs* 2009; 23: 277–87.
8. Venuti A. Progress and challenges in the vaccine-based treatment of head and neck cancers. *J Exp Clin Cancer Res* 2009; 28: 69.
9. Eggermont AM. Therapeutic vaccines in solid tumours: can they be harmful? *Eur J Cancer* 2009; 45: 2087–90.
10. Chen X, *et al.* Novel strategies for improved cancer vaccines. *Expert Rev Vaccines* 2009; 8: 567–76.
11. Mocellin S, *et al.* Peptide-based anticancer vaccines: recent advances and future perspectives. *Curr Med Chem* 2009; 16: 4779–96.
12. Ekstoglu EA, *et al.* Dendritic cells as therapeutic agents against cancer. *Front Biosci* 2010; 15: 321–47.
13. Copier J, Dalgleish A. Whole-cell vaccines: a failure or a success waiting to happen? *Curr Opin Mol Ther* 2010; 12: 14–20.
14. Rodríguez PC, *et al.* Clinical development and perspectives of CIMAvax EGF, Cuban vaccine for non-small-cell lung cancer therapy. *MEDICC Rev* 2010; 12: 17–23.

Capecitabine *(BAN, USAN, rINN)*

Capecitabina; Capécitabine; Capecitabinum; Kapecitabin; Kapesitabiini; Kapesitabin; Ro-09-1978/000; Капецитабин.

Pentyl 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinecarbamate.

$C_{15}H_{22}FN_3O_6$=359.4

CAS — 154361-50-9; 158798-73-3.

ATC — L01BC06.

ATC Vet — QL01BC06.

UNII — 6804DJ8Z9U.

Pharmacopoeias. In *US.*

USP 36: (Capecitabine). A white to off-white crystalline powder. Sparingly soluble in water; soluble in alcohol and in acetonitrile; freely soluble in methyl alcohol. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Capecitabine is a prodrug that is converted to fluorouracil (p. 795.3) in body tissues. It is given orally for the treatment of metastatic colorectal cancer (p. 706.3) and is also used for the adjuvant treatment of patients after surgery for Dukes C colon cancer. Capecitabine is given with docetaxel for the treatment of locally advanced or metastatic breast cancer (p. 702.1) after failure of anthracycline-containing chemotherapy. It may be given as monotherapy after failure of taxanes and anthracycline-containing regimens for patients with breast cancer and for whom further anthracycline-containing therapy is not indicated. Capecitabine with lapatinib (p. 815.1) is used for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress human epidermal receptor type 2 (HER2). Capecitabine is also used with a platinum-based regimen for the first-line treatment of gastric cancer (p. 706.1).

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

For *monotherapy* in **colon, colorectal,** or in **breast** cancer, the recommended initial oral dose is 1.25 g/m^2 given twice daily (for the suggestion that lower initial doses may be favoured in the USA see Administration, p. 758.1). Doses are given for 14 days, followed by a 7-day rest period.

Adjuvant treatment for colon cancer is recommended for a total of 6 months.

For *combination* therapy in **breast** cancer, when given with docetaxel, capecitabine is given in the same dose as listed above; docetaxel is given at 75 mg/m² as a 1-hour intravenous infusion every 3 weeks. However, when used with lapatinib tosilate, a different regimen is used, see Uses and Administration, under Lapatinib Tosilate, p. 815.1.

In *combination* therapy in **colorectal** or **gastric** cancer, the recommended initial oral dose of capecitabine is 0.8 to 1 g/m² twice daily for 14 days, followed by a 7-day rest period. Alternatively, capecitabine 625 mg/m² twice daily is given continuously.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Doses should be modified in subsequent cycles according to toxicity. Capecitabine doses should be reduced in patients with renal impairment (see below).

Capecitabine is also under investigation in the treatment of other malignancies.

References.
1. Sun W. Evolution of capecitabine dosing in colorectal cancer. *Clin Colorectal Cancer* 2010; 9: 31–9.
2. Naughton M. Evolution of capecitabine dosing in breast cancer. *Clin Breast Cancer* 2010; 10: 130–5.
3. Norman G, *et al.* Capecitabine for the treatment of advanced gastric cancer. *Health Technol Assess* 2010; 14 (suppl. 2): 11–17.
4. Ma Y, *et al.* Capecitabine for the treatment for advanced gastric cancer: efficacy, safety and ethnicity. *J Clin Pharm Ther* 2012; 37: 266–75.
5. O'Shaughnessy JA, *et al.* Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. *Oncologist* 2012; 17: 476–84.
6. Fernández-Martos C, *et al.* The role of capecitabine in locally advanced rectal cancer treatment: an update. *Drugs* 2012; 72: 1057–73.
7. NICE. Capecitabine for the treatment of advanced gastric cancer (issued July 2010, reviewed May 2013). Available at: http://www.nice.org.uk/nicemedia/live/13049/49875/49875.pdf (accessed 08/10/13)
8. Li Q, *et al.* Clinical efficacy of including capecitabine in neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2013; 8: e53403.

Administration. Severe toxicity has been reported when capecitabine was given after a fluorouracil and folinic acid regimen to patients with colorectal cancer; a comparable effect was not seen when the treatments were given in the reverse order.[1] Although the mechanism of this sequence-specific toxicity was not determined, the authors suggested that an interaction with intracellularly retained folate was a possible cause.

Interestingly, it has been suggested that aggressive dietary folate supplementation policies in the USA may also contribute to the increased rate of major toxicity seen with capecitabine in phase III studies there, compared with Europe and Asia. In contrast to European practice, oncologists in the USA therefore rarely prescribed the recommended initial oral dose of 1.25 g/m² twice daily, tending to prefer a dose of 1 g/m² twice daily.[2]

1. Hennig IM, *et al.* Severe sequence-specific toxicity when capecitabine is given after fluorouracil and leucovorin. *J Clin Oncol* 2008; 26: 3411–17.
2. Midgley R, Kerr DJ. Capecitabine: have we got the dose right? *Nat Clin Pract Oncol* 2009; 6: 17–24.

Administration in the elderly. A review noted that the pharmacokinetics of capecitabine were not affected by age in those patients with normal renal function. However, toxicity may be increased in some elderly patients, and reduced doses may be used.[1]

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in renal impairment. Renal impairment increases systemic exposure to 5′-deoxy-5-fluorouridine, a metabolite of capecitabine. An increase in the severity of adverse effects appears to correlate with decreased renal function and increased exposure to this metabolite.[1]

Licensed product information suggests the following dosage adjustments based on creatinine clearance (CC):

- mild renal impairment, CC 51 to 80 mL/minute: no dosage adjustment necessary
- moderate renal impairment, CC 30 to 50 mL/minute: when the starting dose is 1.25 g/m² twice daily, a dose reduction of 25%, to about 950 mg/m² twice daily is recommended; however, when the starting dose is 1 g/m² twice daily, no dose reduction is required
- severe renal impairment, CC below 30 mL/minute: capecitabine is contra-indicated

1. Poole C, *et al.* Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. *Cancer Chemother Pharmacol* 2002; 49: 225–34.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p. 797.1. Diarrhoea (which may be severe), nausea and vomiting, abdominal pain, stomatitis, and palmar-plantar erythrodysesthesia syndrome (erythema and desquamation of hands and feet) occur commonly with capecitabine, and may be dose-limiting. Other common adverse effects include fatigue, asthenia, and anorexia. Rashes, alopecia, erythema, dryness of the skin, pruritus, skin pigmentation disorders, and nail disorders can occur. Other adverse effects are fever, pain, arthralgia, constipation, dyspepsia, paraesthesia, headache, dizziness, insomnia, depression, eye irritation, hypo- or hypercalcaemia, and dehydration. Encephalopathy, cardiotoxicity, thromboembolism, and bone-marrow depression have all been reported. Hyperbilirubinaemia has occurred. Severe toxicity has been seen in patients with dihydropyrimidine dehydrogenase deficiency.

Doses of capecitabine should be reduced in patients with moderate renal impairment and its use is contra-indicated in those with severe renal or hepatic impairment.

Effects on blood lipids. Severe hypertriglyceridaemia has been reported with oral capecitabine;[1] patients had high baseline triglyceride concentrations at the start of capecitabine. Despite the introduction of lipid-lowering therapy, triglyceride concentrations remained above baseline, and only decreased several weeks after stopping capecitabine. A prospective study suggested an incidence of hypertriglyceridaemia of 3.7% in patients treated with capecitabine, either as monotherapy or with oxaliplatin, for colorectal cancer.[2]

1. Kurt M, *et al.* Capecitabine-induced severe hypertriglyceridemia: report of two cases. *Ann Pharmacother* 2006; 40: 328–31.
2. Michie CO, *et al.* The frequency and severity of capecitabine-induced hypertriglyceridaemia in routine clinical practice: a prospective study. *Br J Cancer* 2010; 103: 617–21.

Effects on the eyes. A report of severe ocular irritation with corneal deposits and impaired visual acuity in 2 patients given capecitabine.[1] Symptoms resolved within several weeks of stopping the drug.

1. Waikhom B, *et al.* Severe ocular irritation and corneal deposits associated with capecitabine use. *N Engl J Med* 2000; 343: 740–1. Correction. *ibid.*: 1428.

Effects on the heart. Acute ischaemic chest pain has been reported, usually within a few days of starting capecitabine.[1-3] Symptoms from case reports[1] and incidence in Phase III studies[4] were similar to those in patients given fluorouracil. While symptoms have generally been reported to be reversible, fatal myocardial infarction has occurred.[2] One patient had also had cardiotoxicity with fluorouracil treatment,[1] but others had no apparent risk factors.[2] Capecitabine-induced cardiotoxicity without chest pain has also been reported;[5] myocardial ischaemia and a significant decrease in ejection fraction were apparent on exertion.

1. Frickhofen N, *et al.* Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. *Ann Oncol* 2002; 13: 797–801.
2. Kuppens IELM, *et al.* Capecitabine induces severe angina-like chest pain. *Ann Intern Med* 2004; 140: 494–5.
3. Bertolini A, *et al.* Acute cardiotoxicity during capecitabine treatment: a case report. *Tumori* 2001; 87: 200–6.
4. van Cutsem E, *et al.* Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol* 2002; 13: 484–5.
5. Goldsmith YB, *et al.* Capecitabine-induced coronary vasospasm. *J Clin Oncol* 2008; 26: 3802–4.

Effects on the nervous system. Peripheral neuropathy,[1] encephalopathy,[2,3] and cerebellar ataxia[4] have been reported with capecitabine use.

1. Saif MW, *et al.* Peripheral neuropathy associated with capecitabine. *Anticancer Drugs* 2004; 15: 767–71.
2. Niemann B, *et al.* Toxic encephalopathy induced by capecitabine. *Oncology* 2004; 66: 331–5.
3. Videnovic A, *et al.* Capecitabine-induced multifocal leukoencephalopathy: a report of five cases. *Neurology* 2005; 65: 1792–4.
4. Lam MSH, *et al.* Capecitabine-associated cerebellar ataxia. *Am J Health-Syst Pharm* 2008; 65: 2032–5.

Effects on the skin and nails. While hand-foot syndrome appears to be common in patients treated with capecitabine (see Palmar-plantar Erythrodysesthesia Syndrome, below), other skin eruptions have been rarely reported.[1] Onychomadesis (total separation of the nail-bed) and onycholysis have occurred.[2,3] Pyogenic granuloma has been seen with the use of capecitabine,[1] as has re-pigmentation of chemotherapy-induced vitiligo.[4] Stevens-Johnson syndrome has also been reported.[5]

1. Piguet V, Borradori L. Pyogenic granuloma-like lesions during capecitabine therapy. *Br J Dermatol* 2002; 147: 1270–2.
2. Chen G-Y, *et al.* Onychomadesis and onycholysis associated with capecitabine. *Br J Dermatol* 2001; 145: 521–2.
3. Chen G-Y, *et al.* Exudative hyponychial dermatitis associated with capecitabine and docetaxel combination chemotherapy for metastatic breast carcinoma: report of three cases. *Br J Dermatol* 2003; 148: 1071–3.
4. Schmid-Wendtner M-H, *et al.* Leopard-like vitiligo with capecitabine. *Lancet* 2001; 358: 1575.
5. Sendur MA, Kilickap S. Stevens-Johnson syndrome after treatment with capecitabine. *Clin Oncol (R Coll Radiol)* 2008; 20: 202–3.

Hypersensitivity. A patient was successfully given fluorouracil by continuous infusion despite previous hypersensitivity to capecitabine. The authors supposed that the hypersensitivity was likely to have been caused by capecitabine or intermediate metabolites, and suggested a lack of cross-sensitivity between capecitabine and fluorouracil.[1]

1. Liu CY. Fluorouracil for allergic reactions to capecitabine. *Ann Pharmacother* 2002; 36: 1897–9.

Palmar-plantar erythrodysesthesia syndrome. Hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome, p. 730.1) has been reported to be common with use of capecitabine given either as monotherapy[1] or as part of combination chemotherapy regimens.[2,3] The syndrome developed within the first 2 cycles of monotherapy,[1] but within the first 3 cycles in combination therapy,[3] which was attributed to dose modifications of capecitabine in the latter case. Use with docetaxel, and previous chemotherapy-induced stomatitis were found to be significant risk factors for its occurrence.[3] The only effective management is treatment interruption and dose modification.[4] Supportive measures to reduce pain and discomfort and prevent secondary infection are important.[5] General recommended strategies include submersion of hands and feet in cold water, wound care, and avoidance of extreme temperature changes, tight-fitting clothing, or skin friction. Emollient creams may be of benefit for both prophylaxis and treatment. Other strategies that have been proposed include the use of amifostine, topical or systemic corticosteroids, and nicotine patches; however, use of these drugs for capecitabine-induced hand-foot syndrome remains unproven. While pyridoxine cannot be recommended for prophylaxis, some consider it a reasonable choice for treatment, since benefit has been reported with its use with topical emollients.[4] Concurrent treatment with celecoxib has been reported to reduce the incidence of hand-foot syndrome induced by capecitabine.[6,7] For reference to the use of vitamin E to alleviate palmar-plantar erythrodysesthesia syndrome caused by capecitabine and docetaxel, see Chemotherapy-induced Toxicity, under Uses of Vitamin E, p. 2120.1.

As a result of capecitabine-induced hand-foot syndrome, fingerprint misidentification has been reported.[8,9]

1. Abushullaih S, *et al.* Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. *Cancer Invest* 2002; 20: 3–10.
2. Park YH, *et al.* High incidence of severe hand-foot syndrome during capecitabine-docetaxel combination chemotherapy. *Ann Oncol* 2003; 14: 1691–2.
3. Heo YS, *et al.* Hand-foot syndrome in patients treated with capecitabine-containing combination chemotherapy. *J Clin Pharmacol* 2004; 44: 1166–72.
4. Gressett SM, *et al.* Management of hand-foot syndrome induced by capecitabine. *J Oncol Pharm Pract* 2006; 12: 131–41.
5. Scheithauer W, Blum J. Coming to grips with hand-foot syndrome: insights from clinical trials evaluating capecitabine. *Oncology (Huntingt)* 2004; 18: 1161–8, 1173.
6. Lin E, *et al.* Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. *Oncology (Huntingt)* 2002; 16 (12 suppl 14): 31–7.
7. Lin EH, *et al.* Retrospective study of capecitabine and celecoxib in metastatic colorectal cancer: potential benefits and COX-2 as the common mediator in pain, toxicities and survival? *Am J Clin Oncol* 2006; 29: 232–9.
8. García-Saénz JA, *et al.* Elementary, my dear Watson. *J Clin Oncol* 2007; 25: 1815–6.
9. Wong M, *et al.* Travel warning with capecitabine. *Ann Oncol* 2009; 20: 1281.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies capecitabine 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 29/09/11)

Toxicity. Sequence-specific toxicity has been reported when capecitabine was given after fluorouracil and folinic acid, see Administration, above.

Tumour lysis syndrome. A fatal case of tumour lysis syndrome (p. 730.2) has been reported after the use of capecitabine.[1]

1. Kurt M, *et al.* Tumor lysis syndrome following a single dose of capecitabine. *Ann Pharmacother* 2004; 38: 902.

Interactions

As for Fluorouracil, p. 797.3. Altered coagulation parameters and bleeding have occurred in patients on warfarin or phenprocoumon given capecitabine. Increased phenytoin plasma concentrations and symptoms of toxicity during use with capecitabine have been reported. Antacids containing aluminium or magnesium hydroxides cause a small increase in capecitabine plasma concentration. The maximum tolerated dose of capecitabine is reduced when it is given with either folinic acid or interferon alfa. Use with sorafenib increased exposure to capecitabine.

Antivirals. For reference to a fatal interaction between capecitabine and *brivudine*, see Antivirals, under Interactions of Fluorouracil, p. 797.3.

Folate. For the suggestion that an interaction between capecitabine and intracellularly retained folate led to increased toxicity in patients with colorectal cancer, see Administration, above.

Pharmacokinetics

Capecitabine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur at about 1.5 hours. Food reduces the rate and extent of absorption. Plasma protein binding of capecitabine is less than 60%. Capecitabine is hydrolysed in the liver to 5'-deoxy-5-fluorocytidine (5'-DFCR), which is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR; doxifluridine—p. 782.3) and subsequently to the active 5-fluorouracil in body tissues, via the enzyme thymidine phosphorylase. 5-Fluorouracil is further metabolised, as discussed on p. 798.1. About 3% of a dose of capecitabine is excreted in the urine unchanged.

References.
1. Reigner B, *et al.* Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin Cancer Res* 1998; 4: 941–8.
2. Reigner B. *et al.* Clinical pharmacokinetics of capecitabine. *Clin Pharmacokinet* 2001; 40: 85–104.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Apecitab; Capebina; Capecit; Capectan; Capefas; Categor; Catepen; Derebel; Xeloda; ***Austral.***: Xeloda; ***Austria***: Xeloda; ***Belg.***: Xeloda; ***Braz.***: Xeloda; ***Canad.***: Xeloda; ***Chile***: Xeloda; ***China***: Xeloda (希罗达); ***Cz.***: Xeloda; ***Denm.***: Xeloda; ***Fin.***: Xeloda; ***Fr.***: Xeloda; ***Ger.***: Xeloda; ***Gr.***: Xeloda; ***Hong Kong***: Xeloda; ***Hung.***: Xeloda; ***India***: Capecite; Capibine; Captabin; Capxcel; Caxeta; Naprocap; ***Indon.***: Xeloda; ***Irl.***: Xeloda; ***Israel***: Xeloda; ***Ital.***: Xeloda; ***Jpn***: Xeloda; ***Malaysia***: Xeloda; ***Mex.***: Xeloda; ***Neth.***: Capecitastad; Coloxet; Vopecidex; Xeloda; ***Norw.***: Xeloda; ***NZ***: Xeloda; ***Philipp.***: Xeloda; ***Pol.***: Xeloda; ***Port.***: Xeloda; ***Rus.***: Xeloda (Кселода); ***S.Afr.***: Xeloda; ***Singapore***: Xeloda; ***Spain***: Xeloda; ***Swed.***: Xeloda; ***Switz.***: Xeloda; ***Thai.***: Xeloda; ***Turk.***: Xeloda; ***UK***: Xeloda; ***Ukr.***: Xeloda (Кселода); ***USA***: Xeloda; ***Venez.***: Xeloda.

Pharmacopoeial Preparations
USP 36: Capecitabine Tablets.

Carboplatin *(BAN, USAN, rINN)*

Carboplatine; Carboplatino; Carboplatinum; CBDCA; JM-8; Karboplatiini; Karboplatin; Karboplatina; Karboplatyna; NSC-241240; Карбоплатин.

cis-Diammine(cyclobutane-1,1-dicarboxylato)platinum.

$C_6H_{12}N_2O_4Pt$=371.3

CAS — 41575-94-4.

ATC — L01XA02.

ATC Vet — QL01XA02.

UNII — BG3F62OND5.

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

Ph. Eur. 8: (Carboplatin). A colourless, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol and in acetone. Protect from light.

USP 36: (Carboplatin). A 1% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

Incompatibility. Carboplatin reacts with aluminium causing loss of potency and forming a precipitate. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving carboplatin.

Stability. About 5% of the initial carboplatin concentration was lost over 24 hours when solutions were diluted in sodium chloride 0.9% and stored at 25 degrees; lesser amounts of degradation were seen at lower sodium chloride concentrations, but carboplatin was apparently stable over this period if diluted with glucose 5%.[1] The authors suggested that chloride-containing infusion solutions are not suitable for carboplatin, not only because of the loss of active drug but because of the possibility that conversion to cisplatin may be occurring, with a risk of increased toxicity.[1] This has been contested by the manufacturers (*Bristol-Myers, USA*), who found that only 0.5% or 0.7%, depending on formulation, of a carboplatin solution in sodium chloride 0.9%, had been converted to cisplatin after 24 hours.[2] However, the total degradation of carboplatin was not measured. In another study, the authors calculated the time to 5% degradation of carboplatin at 25 degrees as 29.2 hours in sodium chloride 0.9% compared with 52.7 hours in water.[3] They concluded that carboplatin should not be diluted in sodium chloride 0.9% when intended for continuous infusion over a prolonged period.[3] Carboplatin in glucose 5% was reported to be stable for 7 days at 25 degrees in PVC bags when protected from light.[4]

1. Cheung Y-W, *et al.* Stability of cisplatin, iproplatin, carboplatin, and tetraplatin in commonly used intravenous solutions. *Am J Hosp Pharm* 1987; 44: 124–30.
2. Perrone RK, *et al.* Extent of cisplatin formation in carboplatin admixtures. *Am J Hosp Pharm* 1989; 46: 258–9.
3. Allsopp MA, *et al.* The degradation of carboplatin in aqueous solutions containing chloride or other selected nucleophiles. *Int J Pharmaceutics* 1991; 69: 197–210.
4. Diaz Amador F, *et al.* Stability of carboplatin in polyvinyl chloride bags. *Am J Health-Syst Pharm* 1998; 55: 602, 604.

Uses and Administration

Carboplatin is an analogue of cisplatin with similar actions and uses (see p. 766.2). It is used in the treatment of advanced ovarian cancers and of small-cell lung cancer, both alone and combined with other antineoplastics. It has also been tried as an alternative to cisplatin in other solid tumours (see below).

Carboplatin is given by intravenous infusion over 15 minutes to 1 hour. In the UK an initial dose of 400 mg/m^2 is licensed for use as a single agent in previously untreated patients with normal renal function, reduced by 20 to 25% (to 300 to 320 mg/m^2) in patients who have previously been treated with myelosuppressive therapy or who have poor performance status. In the USA an initial dose of 360 mg/m^2 is licensed as a single agent in previously treated patients with recurrent disease, and an initial dose of 300 mg/m^2 when used with cyclophosphamide in previously untreated patients.

Dosage adjustments are necessary in patients with renal impairment (see below) and when carboplatin is given as part of a combination regimen. The dose in mg may be calculated using the Calvert formula as described under Administration, below. Subsequent doses should be adjusted according to the nadir of the white cell and platelet counts (see also Bone-marrow Depression, p. 730.3), and should not be given more frequently than every 4 weeks.

Administration. Pharmacokinetic studies by Calvert and colleagues[1] have indicated that the dose of carboplatin to produce a desired area under the concentration-time curve (AUC) could be calculated, based on the patient's glomerular filtration rate (GFR), as:

$$\text{Dose in mg} = \text{target AUC} \times (\text{GFR} + 25)$$

It should be noted that the resultant dose is given in mg and not in mg/m^2. This formula was found to be useful in patients with higher than normal as well as reduced GFR. Suggested target AUCs were 5 mg/mL per minute in previously treated patients and 7 mg/mL per minute in those who had not previously received chemotherapy. In combination therapy the appropriate AUC value depended on the other drugs used: an AUC of 4.5 mg/mL per minute gave acceptable results when carboplatin was used with bleomycin and etoposide for testicular teratoma.

However, determination of GFR may be a problem: clearance of technetium-99m-labelled diethylenetriamine penta-acetic acid (DTPA) or chromium-51-labelled edetic acid is more accurate than 24-hour creatinine clearance, with the first of these more convenient than the second.[2] (It has been suggested that creatinine clearance should not be used to estimate GFR for the Calvert equation.[3]) Nonetheless, radioisotopic determination of GFR is still an elaborate procedure, and may be less accurate in children than adults.[4,5] Chatelut and colleagues have proposed formulas[4,6,7] for determining clearance of carboplatin in both adults and children.

It has been suggested that the Calvert and Chatelut formulas are not sufficiently accurate for use in **children**, or in adults with very severe renal impairment. Bayesian methods are the technique of choice where serum carboplatin concentrations can be monitored.[3] However, a study in children showed that dosage based on determination of the GFR results in more consistent carboplatin exposure than dosage based on body-surface.[8] A comparison of calculation methods for carboplatin dosing in children found marked differences with the use of different GFR formulas.[5] GFR calculations according to Léger with the dose formula of Newell, or dose calculation by the method of Chatelut were considered to have low bias and only small age-dependent differences, whereas calculation methods with several steps or conversion procedures were prone to considerable error; the authors stated that the usefulness of dose calculations based solely on the serum creatinine should be critically questioned, and recommended the use of limited sampling strategies, therapeutic drug monitoring, and the precise determination of GFR.[5] There has also been a report of the successful use of the Calvert formula in 2 Japanese patients undergoing haemodialysis.[9]

1. Calvert AH, *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; 7: 1748–56.
2. Millward MJ, *et al.* Carboplatin dosing based on measurement of renal function—experience at the Peter MacCallum Cancer Institute. *Aust N Z J Med* 1996; 26: 372–9.
3. Duffull SB, Robinson BA. Clinical pharmacokinetics and dose optimisation of carboplatin. *Clin Pharmacokinet* 1997; 33: 161–83.
4. Chatelut E, *et al.* Population pharmacokinetics of carboplatin in children. *Clin Pharmacol Ther* 1996; 59: 436–43.
5. Würthwein G, *et al.* Carboplatin dosing in children: calculation by different formulae. *Onkologie* 2011; 34: 16–22.
6. Chatelut E, *et al.* Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995; 87: 573–80.
7. Hulin A, *et al.* Suivi thérapeutique pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique du carboplatine. *Therapie* 2010; 65: 157–62.
8. Thomas H, *et al.* Prospective validation of renal-function-based carboplatin dosing in children with cancer: a United Kingdom Children's Cancer Study Group Trial. *J Clin Oncol* 2000; 18: 3614–21.
9. Oguri T, *et al.* Pharmacokinetic analysis of carboplatin in patients with cancer who are undergoing hemodialysis. *Cancer Chemother Pharmacol* 2010; 66: 813–17.

Administration in the elderly. A review[1] found no data to support dose reduction of carboplatin based on age alone and noted that the use of the Calvert and Chatelut formulas (see Administration, above) allows for safe and accurate dosing by taking into account renal function changes associated with age.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in renal impairment. The initial dose of carboplatin is usually determined using a formula (see Administration, above). If this approach is not adopted, US licensed product information suggests the following initial intravenous dose of carboplatin, based on creatinine clearance (CC):

- CC 41 to 59 mL/minute: 250 mg/m^2
- CC 16 to 40 mL/minute: 200 mg/m^2

The incidence of severe leucopenia, neutropenia, or thrombocytopenia has been about 25% in renally-impaired patients who received single-agent carboplatin therapy at the above doses. The data for patients with more severe renal impairment are too limited to allow dosage recommendations.

Malignant neoplasms. A preliminary review[1] of carboplatin, concluded that it was active in ovarian cancer (p. 711.2), with similar responses to those seen with cisplatin; its activity in small-cell lung cancer (p. 710.2), seminoma, and squamous cell carcinomas of the head and neck seemed likely to be comparable, whereas results in gastrointestinal and breast cancers, lymphomas and leukaemias, melanoma, mesothelioma, renal carcinoma, and sarcoma were, generally unimpressive. A subsequent review[2] suggested that in testicular cancer, where there was a prospect of cure, cisplatin, which appeared to give better results in some studies should be preferred. However, in ovarian cancer, where treatment was largely palliative, carboplatin had the advantage of being better tolerated. A further review[3] of randomised studies concurred that carboplatin was equivalent to cisplatin in suboptimally debulked ovarian cancer and extensive-stage small-cell lung cancer, and was inferior to cisplatin in testicular cancer. It was also concluded that carboplatin was inferior to cisplatin in head and neck and oesophageal cancers. There was insufficient comparative evidence for other cancers for which cisplatin has a role.

1. Wagstaff AJ, *et al.* Carboplatin: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of cancer. *Drugs* 1989; 37: 162–90.
2. Anonymous. Cisplatin or carboplatin for ovarian and testicular cancer? *Drug Ther Bull* 1994; 32: 62–3.
3. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999; 17: 409–22.

Adverse Effects, Treatment, and Precautions

The adverse effects of carboplatin are similar to those of cisplatin (p. 767.1); nephrotoxicity and gastrointestinal toxicity are less severe than with cisplatin and reversible myelosuppression is the dose-limiting toxicity; platelet counts reach a nadir between 14 and 21 days after a dose, with recovery within 35 days, but recovery from leucopenia may be slower. Myelosuppression may be more severe and prolonged in patients with impaired renal function. Carboplatin should therefore be given at reduced doses to these patients and should be avoided if creatinine clearance is 20 mL/minute or less. Weekly blood counts and regular renal and hepatic function tests are recommended in all patients during therapy. Neurological function including assessment of hearing should also be monitored.

Incidence of adverse effects. The manufacturers analysed the adverse effects of carboplatin in studies involving 710 patients.[1] Myelosuppression was the dose-limiting toxicity: leucopenia occurred in 55% of the evaluable patients. Leucopenia and thrombocytopenia result in symptomatic events such as infection or bleeding in a minority of patients. Anaemia was frequent (59%) and required transfusional support in about one-fifth of the patients. Nephrotoxicity and serum electrolyte loss were much less of a problem; no high-volume fluid hydration or electrolyte supplementation was given during treatment. Vomiting occurred in about half the patients, and a further 25% had nausea without vomiting. Peripheral neurotoxi-

city was reported in 6% of evaluable patients and clinical ototoxicity occurred in only 8 cases or about 1% (but see also Effects on the Ears, below). Increases in liver enzyme values have also been reported, as well as, more rarely, alopecia, rash, a flu-like syndrome, and local effects at the injection site.

1. Canetta R, *et al.* Carboplatin: the clinical spectrum to date. *Cancer Treat Rev* 1985; **12** (suppl A): 125–36.

Effects on the ears. Carboplatin is less ototoxic than cisplatin, but ototoxicity is still common with carboplatin when used in high doses, for example, as part of conditioning regimens for bone marrow transplantation.[1,2] Long-term audiometric follow-up has been advised in young children given carboplatin-based chemotherapy, as ototoxicity may only be evident some years after treatment.[3] There was some evidence that sodium thiosulfate reduced carboplatin-induced hearing loss, when carboplatin was used for CNS malignancy.[4,5]

1. Frellich RJ, *et al.* Hearing loss in children with brain tumors treated with cisplatin and carboplatin-based high-dose chemotherapy with autologous bone marrow rescue. *Med Pediatr Oncol* 1996; **26**: 95–100.
2. Parsons SK, *et al.* Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. *Bone Marrow Transplant* 1998; **22**: 669–74.
3. Jehanne M, *et al.* Analysis of ototoxicity in young children receiving carboplatin in the context of conservative management of unilateral or bilateral retinoblastoma. *Pediatr Blood Cancer* 2009; **52**: 637–43.
4. Neuwelt EA, *et al.* First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. *J Pharmacol Exp Ther* 1998; **286**: 77–84.
5. Doolittle ND, *et al.* Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. *Clin Cancer Res* 2001; **7**: 493–500.

Effects on the eyes. Cortical blindness developed in 2 patients with impaired renal function receiving high-dose carboplatin;[1] although 10 cases of visual disturbances in patients receiving carboplatin had been reported to the manufacturers, none of these had sudden blindness and it was thought that the effect represented CNS toxicity in the presence of poor renal excretion. It was concluded that it was unwise to give high-dose carboplatin to patients whose glomerular filtration rate is less than 50 mL/minute.

Severe ocular and orbital toxicity has been reported after intracarotid injection of carboplatin for the treatment of recurrent glioblastomas.[2]

1. O'Brien MER, *et al.* Blindness associated with high-dose carboplatin. *Lancet* 1992; **339**: 558.
2. Watanabe W, *et al.* Severe ocular and orbital toxicity after intracarotid injection of carboplatin for recurrent glioblastomas. *Graefes Arch Clin Exp Ophthalmol* 2002; **240**: 1033–5.

Effects on the heart. Atrial flutter has been reported following the first dose of a second course of carboplatin.[1] The patient spontaneously reverted to sinus rhythm after 24 hours.

1. Zakaria S, *et al.* Atrial flutter associated with carboplatin administration. *Ann Pharmacother* 2011; **45**: e59.

Effects on the kidneys. Although carboplatin is reported to be much less nephrotoxic than cisplatin it is not devoid of adverse effects on the kidney.[1-8] Salt wasting nephropathy (similar to that seen with cisplatin),[1] and decreased creatinine clearance[2] and glomerular filtration rate[3] have occurred, as has acute renal failure, including in 2 patients given intraperitoneal carboplatin[4] (although these patients had been heavily pretreated with cisplatin). It has been suggested that renal toxicity may be more likely at cumulative carboplatin doses of about 750 mg/m² or more,[3] and there is some evidence to suggest that intensive hydration may ameliorate nephrotoxic effects.[2]

1. Welborn J, *et al.* Renal salt wasting and carboplatinum. *Ann Intern Med* 1988; **108**: 640.
2. Reed E, Jacob J. Carboplatin and renal dysfunction. *Ann Intern Med* 1989; **110**: 409.
3. Smit EF, *et al.* Carboplatin and renal function. *Ann Intern Med* 1989; **110**: 1034.
4. McDonald BR, *et al.* Acute renal failure associated with the use of intraperitoneal carboplatin: a report of two cases and review of the literature. *Am J Med* 1991; **90**: 386–91.
5. Prenkel J, *et al.* Acute renal failure in high dose carboplatin chemotherapy. *Med Pediatr Oncol* 1995; **25**: 473–4.
6. Agraharkar M, *et al.* Carboplatin-related hematuria and acute renal failure. *Am J Kidney Dis* 1998; **32**: E5.
7. Butani L, *et al.* End-stage renal disease after high-dose carboplatinum in preparation of autologous stem cell transplantation. *Pediatr Transplant* 2003; **7**: 408–12.
8. Tarrass F, *et al.* End-stage renal disease following carboplatin chemotherapy for a nasopharyngeal carcinoma. *Ren Fail* 2007; **29**: 1049–51.

Hypersensitivity. In one series, 12% of 205 patients treated with carboplatin developed a hypersensitivity reaction after a median of 8 courses of platinum therapy.[1] Symptoms were at least moderately severe in half of the patients. Reactions to cisplatin might be anticipated in patients who have been previously sensitised to carboplatin although they do not necessarily occur (see p. 768.1). In another study,[2] patients receiving more than 7 courses of carboplatin therapy were given a skin test before each course in an attempt to identify patients at risk for hypersensitivity reactions. The test consisted of 0.02 mL of an undiluted aliquot of their planned infusion, injected intradermally 1 hour before the dose. A negative skin test accurately predicted the absence of a hypersensitivity reaction. In a further extended report[3] by the same group, the skin test had been given about 30 minutes before carboplatin doses in 126 women who had already received at least 6 courses of a platinum-based regimen for a gynaecological cancer. Of 668 negative skin tests, a hypersensitivity reaction developed on 10 occasions (in 7 patients), giving a false-negative rate of 1.5%. None of the reactions were severe. Of the 39 patients who had a positive skin test, 7 elected to receive the dose of carboplatin; 6 of these developed a hypersensitivity reaction but none were severe.

The use of a desensitisation regimen has been successful in a small number of patients,[4,5] although others have not found it useful.[6]

1. Markman M, *et al.* Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999; **17**: 1141–5.
2. Zanotti KM, *et al.* Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol* 2001; **19**: 3126–9.
3. Markman M, *et al.* Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003; **21**: 4611–14.
4. Markman M, *et al.* Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol* 2004; **130**: 25–8.
5. Genc DB, *et al.* Clinical features and management of carboplatin-related hypersensitivity reactions in pediatric low-grade glioma. *Support Care Cancer* 2012; **20**: 385–93.
6. Lafay-Cousin L, *et al.* Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. *Cancer* 2008; **112**: 892–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies carboplatin 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 26/08/11)

Pregnancy. For a report of the successful use of carboplatin-based chemotherapy during pregnancy, with no adverse effects on the infant, see Pregnancy, under Cisplatin, p. 768.2.

Interactions

As for Cisplatin, p. 768.2. When used with docetaxel, clearance of carboplatin has been reported to be about 50% higher than values reported for carboplatin monotherapy.

Pharmacokinetics

Intravenous carboplatin exhibits a biphasic elimination and is excreted mainly in the urine, about 70% of a dose being excreted within 24 hours, the majority in the first 6 hours. About a third of a dose is excreted unchanged. The terminal *half-life* (as free platinum) is reported to be about 6 hours. (For the effect of docetaxel on carboplatin clearance, see Interactions, above.) Platinum from carboplatin slowly becomes protein bound, and is subsequently excreted with a *half-life* of 5 days or more.

References.

1. van der Vijgh WJF. Clinical pharmacokinetics of carboplatin. *Clin Pharmacokinet* 1991; **21**: 242–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Carbokebir; Carboplat; Carboxtie; Omilipis; TCO-Carbo; *Belg.*: Carbosin; *Braz.*: B-Platin; Biocarbo; Citoplatina; Fauldcarbo; Kemocarb; Oncoplatin; Paraplatin; Platamine; Tecnocarb; Tevacarbo; Vancel; *Chile*: Oncocarb†; Paraplatin†; *China*: Bobei (波贝); Paraplatin (伯尔定); *Cz.*: Carbomedac; Carbosol; Cycloplatin; *Denm.*: Carbomedac; *Fin.*: Carbosin; Paraplatin†; *Fr.*: Paraplatine†; *Ger.*: Axicarb; Carbo-cell; Carbomedac; Haemato-carb; Neocarbo†; Ribocarbo; *Gr.*: Carboplamin; Carboplan; Carbosin; Emorzim; Megaplatin; Paraplatin; Vadeplatin; *Hong Kong*: Paraplatin; *Hung.*: Cycloplatin; Paraplatin†; *India*: Biocarb; Blastocarb; Blastoplatin; Carbokem; Carbopa; Carboplan; Carboteen; Carbotinal; Cytocarb; Ducarb; Karplat; Kemocarb; Naproplat; Neocarb; Neoplatin; Oncocarbin; Paraplatin; *Indon.*: Actoplatin; Carbosin; Paraplatin†; *Irl.*: Paraplatin†; *Ital.*: Paraplatin; *Malaysia*: Carbosin†; *Mex.*: Acoplasic; Bagotanilo†; Blastocarb; Boplatex; Carboplat; Carbotec; Ilacap†; Kemocarb; Paraplatin; *Neth.*: Carbosin; *NZ*: Carbaccord; Paraplatin†; *Philipp.*: Biovinate; Bonaplatin†; Carbosin; Carbotinol; Crobextin†; Kemocarb; Naproplat; Paraplatin†; *Pol.*: Cycloplatin†; Paraplatin†; *Port.*: Nealorin†; Novoplatinum; *Rus.*: Blastocarb (Бластокарб); Carbotera (Карботера); Cycloplatin (Циклоплатин); Paract (Паракт); Paraplatin (Параплатин); *S.Afr.*: Carbosin; Paraplatin†; *Singapore*: Carbotinol; Paraplatin; *Spain*: Paraplatin; *Swed.*: Paraplatin†; *Switz.*: Paraplatin; *Thai.*: Blastocarb; Carbosin; Kemocarb; Neoplatin; Paraplatin; *Turk.*: Carbodex; Carbosin; Carmen; Paraplatin†; Platinwas; *UK*: Paraplatin; *USA*: Paraplatin; *Venez.*: Bioplatinex; Oplat.

Pharmacopoeial Preparations
BP 2014: Carboplatin Injection;
USP 36: Carboplatin for Injection.

Carfilzomib *(USAN, rINN)*

Carfilzomibum; PR-171; Карфилзомиб.

(2*S*)-*N*-[(1*S*)-1-Benzyl-2-[[(1*S*)-3-methyl-1-[[(2*R*)-2-methyloxiran-2-yl]carbonyl]butyl]amino]-2-oxoethyl]-4-methyl-2-[[(2*S*)-2-[(morpholin-4-ylacetyl)amino]-4-phenylbutanoyl]amino]pentanamide.

$C_{40}H_{57}N_5O_7$=719.9

CAS — 868540-17-4.

UNII — 72X6E3J5AR.

Uses and Administration

Carfilzomib is an irreversible inhibitor of the 20S proteasome, a core unit within the 26S proteasome (see also Bortezomib, p. 752.1), that disrupts tumour cell turnover and induces apoptosis. It is used for the treatment of multiple myeloma (p. 699.2) in patients who have received at least 2 prior therapies including bortezomib and an immune modulator, and whose disease has progressed on or within 60 days of completing the last therapy. Carfilzomib is given intravenously over 2 to 10 minutes on 2 consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest to give a 28-day treatment cycle. In cycle 1, a dose of carfilzomib 20 mg/m² is given. If tolerated, the dose is increased in subsequent cycles to 27 mg/m². Treatment may be continued until disease progression or unacceptable toxicity occurs.

The dose of carfilzomib should be calculated using the patient's actual body-surface at baseline up to a maximum of 2.2 m². Dose adjustments only need to be made when the patient's weight shows greater than 20% change from the previous measurement.

To reduce the incidence and severity of infusion reactions premedication with dexamethasone 4 mg orally or intravenously should be given before each dose of carfilzomib in cycle 1, and before each dose during the first cycle of dose escalation. Premedication with dexamethasone should also be used if infusion reactions develop or reappear in subsequent cycles.

Doses should be modified if toxicity occurs, see Administration in Subsequent Cycles, below.

References.

1. Khan ML, Stewart AK. Carfilzomib: a novel second-generation proteasome inhibitor. *Future Oncol* 2011; **7**: 607–12.
2. Khan RZ, Badros A. Role of carfilzomib in the treatment of multiple myeloma. *Expert Rev Hematol* 2012; **5**: 361–72.

Administration in subsequent cycles. Intravenous doses of carfilzomib should be modified if marked toxicity occurs. Doses can be decreased from 27 mg/m² to 20 mg/m² (one dose level), or from 20 mg/m² to 15 mg/m² (one dose level). For specific toxicities, the following adjustments are recommended:

For *haematological toxicity* (grade 3 or 4 neutropenia and grade 4 thrombocytopenia), carfilzomib should be withheld. If there is full recovery before the next scheduled dose carfilzomib may be continued at the same dose. If there is recovery to grade 2 neutropenia or grade 3 thrombocytopenia, carfilzomib should be reduced by one dose level. If tolerated, the reduced dose may be increased to the previous level.

For *cardiotoxicity* (grade 3 or 4, new-onset or worsening of heart failure, decreased left ventricular function, or myocardial ischaemia), *pulmonary complications* (grade 3 or 4), *pulmonary hypertension*, *hepatotoxicity* (grade 3 or 4, increases in liver transaminases, bilirubin, or other liver abnormality), or peripheral neuropathy (grade 3 or 4), carfilzomib should be withheld until toxicity has resolved or organ function has returned to baseline. A reduction of carfilzomib by one dose level should be considered when restarting treatment. If tolerated, the reduced dose may be increased to the previous level.

For *renal toxicity* (serum creatinine ≥twice baseline), carfilzomib should be withheld until renal function has returned to grade 1 or baseline. If toxicity is due to carfilzomib, treatment should be reduced by one dose level when restarting. However, if toxicity is not due to carfilzomib, treatment may be restarted at the previous dose. If tolerated, the reduced dose may be increased to the previous level.

Adverse Effects and Precautions

For a general outline see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects of carfilzomib include fatigue, fever, gastrointestinal disturbances, and dyspnoea; treatment should be withheld if dyspnoea occurs. Anaemia

and thrombocytopenia are also very common. The platelet count should be monitored frequently during treatment; the nadir of the count usually occurs around day 8. Other haematological toxicities such as neutropenia, lymphopenia, and leucopenia also occur commonly. Neutropenia and thrombocytopenia may be dose limiting.

Other common adverse reactions include peripheral neuropathy, headache, cough, peripheral oedema, pain, insomnia, muscle spasms, asthenia, electrolyte disturbances, respiratory-tract infections, dizziness, hypoaesthesia, anorexia, hyperglycaemia, and increases in blood creatinine. Acute renal failure has been reported.

Cardiovascular adverse effects include hypertension, myocardial ischaemia, and myocardial infarction. Pulmonary hypertension and new onset or worsening of pre-existing heart failure have been reported. Carfilzomib should be withheld or stopped if serious cardiac events occur.

Infusion reactions can occur immediately following, or up to 24 hours after, carfilzomib administration. Reactions include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, dyspnoea, hypotension, syncope, chest tightness, or angina. Dexamethasone should be given before carfilzomib infusions, see Uses and Administration, p. 760.3.

Tumour lysis syndrome has been reported with carfilzomib; patients with multiple myeloma and a high tumour burden may be at increased risk. If tumour lysis syndrome occurs, treatment should be interrupted until symptoms have resolved.

Hepatotoxicity may occur with increases in liver enzyme values and bilirubin. Hepatic failure has been reported. Liver enzymes should be monitored frequently and treatment withheld for severe increases in transaminases, bilirubin, or other liver abnormalities.

Reactivation of herpes zoster has occurred and antiviral prophylaxis should be considered for patients with a history of herpes zoster infection.

Pharmacokinetics

Carfilzomib was about 97% bound to plasma proteins when tested *in vitro*. It is rapidly and extensively metabolised. The main metabolic pathways are peptidase cleavage and epoxide hydrolysis to inactive metabolites. Cytochrome P450 isoenzymes play only a minor role in the overall metabolism. Carfilzomib is rapidly cleared with a half-life of 1 hour or less on day 1 of cycle 1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Kyprolis.

Carmofur *(rINN)*

Carmofurum; HCFU; Karmofuur; Кармофур.

5-Fluoro-*N*-hexyl-3,4-dihydro-2,4-dioxo-1-(2*H*)-pyrimidinecarboxamide; 1-Hexylcarbamoyl-5-fluorouracil.

$C_{11}H_{16}FN_3O_3$=257.3

CAS — 61422-45-5.

ATC — L01BC04.

ATC Vet — QL01BC04.

UNII — HA82M3RAB2.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Carmofur is an orally active derivative of fluorouracil (p. 795.2) and has similar actions. It is used in the adjuvant treatment of colorectal and breast cancer, and has also been used in ovarian cancer. Carmofur has been associated with the development of neurological disorders including leukoencephalopathy. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

References.

1. Yamada T, *et al.* Leukoencephalopathy following treatment with carmofur: a case report and review of the Japanese literature. *Asia Oceania J Obstet Gynaecol* 1989; 15: 161–8.
2. Sakamoto J, *et al.* An individual patient data meta-analysis of long supported adjuvant chemotherapy with oral carmofur in patients with curatively resected colorectal cancer. *Oncol Rep* 2001; 8: 697–703.
3. Nakamura T, *et al.* Optimal duration of oral adjuvant chemotherapy with Carmofur in the colorectal cancer patients: the Kansai Carmofur Study Group trial III. *Int J Oncol* 2001; 19: 291–8.
4. Tominaga T, *et al.* Postoperative chemoendocrine therapy for women with node-positive stage II breast cancer with combined cyclophosphamide, tamoxifen, and 1-hexylcarbamoyl-5-fluorouracil. *Eur J Surg* 2001; 167: 598–604.
5. Iwagaki H, *et al.* Post-operative adjuvant chemotherapy for colorectal cancer with 5-fluorouracil (5-FU) infusion combined with 1-hexylcarbamoyl-5-fluorouracil (HCFU) oral administration after curative resection. *Anticancer Res* 2001; 21: 4163–8.
6. Morimoto K, Koh M. Postoperative adjuvant use of carmofur for early breast cancer. *Osaka City Med J* 2003; 49: 77–83.
7. Tominaga T, *et al.* 1-Hexylcarbamoyl-5-fluorouracil + cyclophosphamide + tamoxifen versus CMF + tamoxifen in women with lymph node-positive breast cancer after primary surgery: a randomized controlled trial. *Oncol Rep* 2004; 12: 797–803.
8. Sakamoto J, *et al.* An individual patient data meta-analysis of adjuvant therapy with carmofur in patients with curatively resected colon cancer. *Jpn J Clin Oncol* 2005; 35: 536–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Mifurol (喷福禄); *Fin.*: Mirafur†; *Jpn*: Mifurol†.

Carmustine *(BAN, USAN, rINN)*

BCNU; BiCNU; Carmustin; Carmustina; Carmustinum; Karmustiini; Karmustin; Karmustinas; Karmusztin; NSC-409962; WR-139021; Кармустин.

1,3-Bis(2-chloroethyl)-1-nitrosourea.

$C_5H_9Cl_2N_3O_2$=214.0

CAS — 154-93-8.

ATC — L01AD01.

ATC Vet — QL01AD01.

UNII — U68WG3173Y.

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

Ph. Eur. 8: (Carmustine). A yellowish, granular powder. Very slightly soluble in water; freely soluble in dehydrated alcohol; very soluble in dichloromethane. It melts at about 31 degrees with decomposition. Store at a temperature of 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Carmustine). Light yellow powder. Freely soluble in ether. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Stability. Licensed product information states that, when reconstituted, resulting carmustine solutions (undiluted or further diluted in sodium chloride 0.9% or glucose 5%) are stable for 8 hours at room temperature, or 24 hours at 2 degrees to 8 degrees, when protected from light. Carmustine is adsorbed onto PVC giving sets and containers, and polyethylene or glass should be used.

A study has indicated that diluted solutions of carmustine undergo increased degradation in the presence of sodium bicarbonate, with only 73% of the original concentration of carmustine remaining after 90 minutes, much of the loss being in the first 15 minutes.[1]

1. Colvin M, *et al.* Stability of carmustine in the presence of sodium bicarbonate. *Am J Hosp Pharm* 1980; 37: 677–8.

Uses and Administration

Carmustine is a cell-cycle phase non-specific antineoplastic belonging to the nitrosourea group of compounds, which are considered to function as alkylating agents. It is believed to alkylate DNA and RNA, and may also inhibit enzymatic processes by carbamoylation of amino acids in proteins. Carmustine is used in the treatment of brain tumours, and in combination chemotherapy for multiple myeloma. It may be given as second-line therapy in Hodgkin's disease, non-Hodgkin's lymphoma, and some other malignancies (see below).

Carmustine is licensed for use as a single agent either as a single dose of 150 to 200 mg/m^2 or divided into doses of 75 to 100 mg/m^2 given on 2 successive days. Doses are given by intravenous infusion over 1 to 2 hours in sodium chloride 0.9% or glucose 5%. Lower doses are usually given in combination therapy. Doses may be repeated every 6 weeks provided that blood counts have returned to acceptable levels. Subsequent doses must be adjusted according to the haematological response (see also Bone-marrow Depression, p. 730.3).

Polymer implants containing carmustine have been developed for implantation into the brain in the localised treatment of high-grade malignant glioma or recurrent glioblastoma multiforme. Each implant contains 7.7 mg of carmustine: up to 8 such implants are inserted into the cavity left by surgical removal of the tumour.

Amyloidosis. For mention of chemotherapy with epirubicin, cyclophosphamide, and carmustine to suppress amyloidosis after cardiac transplantation, see p. 819.3.

Malignant neoplasms. Carmustine has been used in chemotherapeutic regimens for several malignancies. Because of its ability to pass the blood-brain barrier it has been extensively used in malignant neoplasms of the brain (p. 701.2). As an extension of such use, carmustine-releasing wafers have been implanted directly into the brain.[1-3] In a multicentre study[4] in patients with recurrent malignant glioma, biodegradable poly(carboxyphenoxypropane/sebacic acid)anhydride polymer wafers containing carmustine implanted into the brain after tumour resection produced a median survival of 31 weeks compared with 23 weeks for placebo. A subsequent small cohort study[5] failed to find a clear survival benefit associated with wafer implantation in recurrent glioma, and reported a higher rate of complications including seizures, cerebral oedema, CSF leaks, sepsis, and wound infections. The limitations of this small study were acknowledged by the authors, and a review[6] that included these studies concluded that despite limited data, carmustine wafers do provide some survival benefit. A randomised study in 240 patients found that treatment with carmustine wafers reduced the risk of death by 28% compared with placebo;[7] this survival advantage was maintained at 1, 2, and 3 years, with statistical significance at 3 years.[8] The adverse effect profile was similar for carmustine and placebo groups,[7] and retrospective reviews[2,9] found carmustine wafers to be well tolerated with a low incidence of surgical complications such as infection. However, it was noted that, in some patients, neurological symptoms developed during an attempted tapering of dexamethasone dosage after carmustine with radiotherapy and that close supervision of patients is warranted. Treatment effects or necrosis can radiographically mimic recurrent tumour in a proportion of patients;[9] implantation of wafers caused morphological changes of the brain immediately adjacent to the implants.[10] There is considerable interest in multimodal therapy, using adjuvant temozolomide and radiotherapy after surgery and implantation of carmustine wafers.[3]

Other conditions in which carmustine has been used include malignant melanoma (p. 714.3) and Hodgkin's disease (p. 696.1).

1. Lin SH, Kleinberg LR. Carmustine wafers: localized delivery of chemotherapeutic agents in CNS malignancies. *Expert Rev Anticancer Ther* 2008; 8: 343–59.
2. Attenello FJ, *et al.* Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann Surg Oncol* 2008; 15: 2887–93.
3. La Rocca RV, Mehdorn HM. Localized BCNU chemotherapy and the multimodal management of malignant glioma. *Curr Med Res Opin* 2009; 25: 149–60.
4. Brem H, *et al.* Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 1995; 345: 1008–12.
5. Subach BR, *et al.* Morbidity and survival after 1,3-bis(2-chloroethyl)-1-nitrosourea wafer implantation for recurrent glioblastoma: a retrospective case-matched cohort series. *Neurosurgery* 1999; 45: 17–23.
6. Engelhard HH. The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. *Surg Neurol* 2000; 53: 458–64.
7. Westphal M, *et al.* A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-oncol* 2003; 5: 79–88.
8. Westphal M, *et al.* Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; 148: 269–75.
9. Kleinberg LR, *et al.* Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest* 2004; 22: 1–9.
10. Giese A, *et al.* Pattern of recurrence following local chemotherapy with biodegradable carmustine (BCNU) implants in patients with glioblastoma. *J Neurooncol* 2004; 66: 351–60.

Mycosis fungoides. Topical application of carmustine has been used successfully[1-5] in early mycosis fungoides (p. 698.3). Erythema and telangiectasia were the most frequent adverse effects.

1. Zackheim HS, *et al.* Topical carmustine (BCNU) for mycosis fungoides and related disorders: a 10-year experience. *J Am Acad Dermatol* 1983; 9: 363–74.
2. Zackheim HS, *et al.* Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. *J Am Acad Dermatol* 1990; 22: 802–10.
3. Zackheim HS. Topical carmustine (BCNU) for patch/plaque mycosis fungoides. *Semin Dermatol* 1994; 13: 202–6.
4. Heald PW, Glusac EJ. Unilesional cutaneous T-cell lymphoma: clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. *J Am Acad Dermatol* 2000; 42: 283–5.
5. Zackheim HS. Topical carmustine (BCNU) in the treatment of mycosis fungoides. *Dermatol Ther* 2003; 16: 299–302.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2. Delayed and cumulative bone-marrow depression is the most frequent and serious adverse effect of intravenous carmustine. Platelets and leucocytes are mainly affected, with platelet nadirs occurring at 4 to 5 weeks after a dose and leucocyte nadirs at 5 to 6 weeks; although thrombocytopenia is usually more severe, leucopenia may also be dose-limiting. Other adverse effects include pulmonary fibrosis (mainly but not exclusively at high cumulative doses—see also Effects on the Lungs, p. 729.1), renal and hepatic damage, and neuroretinitis. Nausea and vomiting, beginning up to 2 hours after a dose, is common but can be reduced by prophylactic antiemetic therapy. Venous irritation may follow intravenous injection and transient hyperpigmentation has been noted after contact of a solution with the skin. Flushing of the skin and suffusion of the conjunctiva may occur on rapid intravenous infusion. Hypotension, tachycardia, chest pain, headache, and hypersensitivity reactions have been reported.

Convulsions, cerebral oedema, and various neurological symptoms have been reported in patients given carmustine-containing polymer implants; abnormalities of wound

healing at the site of implantation, and an increased incidence of intracranial infection have also been reported.

As with other alkylating agents, carmustine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the eyes. Ocular toxicity has been reported in patients given carmustine,[1,2] and seems to be more likely when given into the carotid artery,[1,2] although it was also seen with high-dose intravenous therapy. There is some evidence that the alcohol diluent used to prepare carmustine solutions may contribute to the retinopathy.[2]

1. Shingleton BJ, *et al.* Ocular toxicity associated with high-dose carmustine. *Arch Ophthalmol* 1982; 100: 1766–72.
2. Greenberg HS, *et al.* Intra-arterial BCNU chemotherapy for treatment of malignant gliomas of the central nervous system. *J Neurosurg* 1984; 61: 423–9.

Effects on the lungs. Studies have found a high incidence of fatal pulmonary fibrosis (see also Effects on the Lungs, p. 729.1) in patients treated with carmustine for gliomas during childhood; patients who were treated before 5 or 6 years of age were more likely to die of pulmonary fibrosis than those treated at a later age.[1,2] However, there are reports of pulmonary toxicity and upper lobe pulmonary fibrosis occurring in adults given carmustine and high-dose chemotherapy.[3]

1. O'Driscoll BR, *et al.* Late carmustine lung fibrosis: age at treatment may influence severity and survival. *Chest* 1995; 107: 1355–7.
2. Lohani S, *et al.* 25-year study of lung fibrosis following carmustine therapy for brain tumor in childhood. *Chest* 2004; 126: 1007.
3. Parish JM, *et al.* Upper lobe pulmonary fibrosis associated with high-dose chemotherapy containing BCNU for bone marrow transplantation. *Mayo Clin Proc* 2003; 78: 630–4.

Extravasation. For mention of the use of sodium bicarbonate as a specific antidote after carmustine extravasation, see under Treatment of Adverse Effects of Antineoplastics, p. 731.3.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2. Carmustine should be used with extreme caution in children, who are at particular risk of severe delayed pulmonary toxicity. It should also be used with caution in patients with reduced lung function. Lung function should be monitored before and frequently during therapy. Blood counts should be monitored weekly during therapy, and for at least 6 weeks after the last dose. Renal and hepatic function should also be monitored periodically.

Patients undergoing craniotomy for malignant glioma and implantation of carmustine wafers should be monitored closely for complications, including seizures, intracranial infections, abnormal wound healing, and brain oedema. Brain oedema and compression (intracerebral mass effect) due to tumour recurrence, infection, or necrosis, may require further surgery or the removal of carmustine wafers.

Handling and disposal. Carmustine has been shown to permeate latex, PVC, and rubber gloves, the degree of permeation tending to increase with time,[1-3] up to an equilibrium value.[2] The permeation rate appears not to depend solely on glove thickness and material, and may be different for different gloves made from the same material.[2] The time for initial penetration was reported to vary between 4.7 and 66.0 minutes in one study,[2] and gloves could be chosen accordingly depending on the anticipated length of exposure. Double-gloving, particularly with thicker PVC[1] or ethylmethacrylate[3] gloves, may offer some additional protection.

1. Connor TH, *et al.* Permeability of latex and polyvinyl chloride gloves to carmustine. *Am J Hosp Pharm* 1984; 41: 676–9.
2. Thomas PH, Fenton-May V. Protection offered by various gloves to carmustine exposure. *Pharm J* 1987; 238: 775–7.
3. Mellström GA, *et al.* Barrier effect of gloves against cytostatic drugs. *Curr Probl Dermatol* 1996; 25: 163–9.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Cimetidine. Reductions in white cell counts and platelet counts well below those normally attributed to treatment with carmustine alone were seen in 6 of 8 patients receiving their first course of carmustine and corticosteroids with cimetidine given prophylactically,[1] and in 9 patients in a further study.[2] Cimetidine was also reported to exacerbate the neutropenia and leucopenia in a patient receiving lomustine.[3]

1. Selker RG, *et al.* Bone-marrow depression with cimetidine plus carmustine. *N Engl J Med* 1978; 299: 834.
2. Volkin RL, *et al.* Potentiation of carmustine-cranial irradiation-induced myelosuppression by cimetidine. *Arch Intern Med* 1982; 142: 243–5.
3. Hess WA, Kornblith PL. Combination of lomustine and cimetidine in the treatment of a patient with malignant glioblastoma: a case report. *Cancer Treat Rep* 1985; 69: 733.

Pharmacokinetics

Intravenous carmustine is rapidly metabolised, and no intact drug is detectable after 15 minutes; metabolites have a much longer half-life and are presumed to be responsible for its activity. It is mainly excreted in the urine; some is also excreted as carbon dioxide, via the lungs. Carmustine readily crosses the blood-brain barrier, appearing in CSF in substantial concentrations almost immediately after intravenous injection. Carmustine diffuses from polymer implants into surrounding brain tissue; however, tissue and plasma concentrations after implantation have not been determined.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: BiCNU; *Austral.*: BiCNU; Gliadel; *Austria*: Carmubris; *Braz.*: Becenun; *Canad.*: BiCNU; *Chile*: BiCNU; *Cz.*: BiCNU; *Fr.*: BiCNU; Gliadel; *Ger.*: Carmubris†; Gliadel; *Gr.*: BiCNU; Carmubris; Gliadel; Nitrumon; *Hung.*: BiCNU; *Irl.*: BiCNU†; Gliadel; *Israel*: Gliadel; *Ital.*: Gliadel; *Jpn*: Gliadel; *Malaysia*: Gliadel; *Mex.*: BiCNU; *Neth.*: Gliadel; *NZ*: BiCNU; *Philipp.*: BiCNU†; *Port.*: Gliadel; *S.Afr.*: BiCNU†; Gliadel; *Singapore*: BiCNU; Gliadel; *Spain*: Gliadel; *Thai.*: Gliadel†; *Turk.*: Nitrumon; *UK*: Gliadel; *USA*: BiCNU; Gliadel; *Venez.*: BiCNU.

Pharmacopoeial Preparations
USP 36: Carmustine for Injection.

Catumaxomab *(rINN)*

Catumaxomabum; Катумаксомаб.

Immunoglobulin G2a, anti-(human antigen 17-1A) (mouse monoclonal Ho-3/TP-A-01/TPBs01 heavy chain), disulfide with mouse monoclonal Ho-3/TP-A-01/TPBs01 light chain, disulfide with immunoglobulin G2b anti-(human CD3 (antigen)) (rat monoclonal 26/II/6-1.2/TPBs01 heavy chain), bidisulfide with rat monoclonal 26/II/6-1.2/TPBs01 light chain.

CAS — 509077-98-9.
ATC — L01XC09.
ATC Vet — QL01XC09.

Uses and Administration

Catumaxomab is a rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule EpCAM, which is overexpressed in most carcinomas, and the CD3 antigen; a third binding site enables interaction with accessory immune cells. These binding properties induce a reaction against tumour cells which includes T-cell activation, antibody-dependent cell mediated cytotoxicity, complement-dependent cytotoxicity, and phagocytosis.

Catumaxomab is used for the intraperitoneal treatment of malignant ascites in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible. Catumaxomab is diluted with sodium chloride 0.9% in polypropylene syringes before infusion via a constant infusion pump system. Four intraperitoneal infusions are given:

- first dose (day 0): 10 micrograms in 10 mL sodium chloride (total volume 10.1 mL)
- second dose (day 3): 20 micrograms in 20 mL sodium chloride (total volume 20.2 mL)
- third dose (day 7): 50 micrograms in 49.5 mL sodium chloride (total volume 50 mL)
- fourth dose (day 10): 150 micrograms in 48.5 mL sodium chloride (total volume 50 mL)

At least 2 days must elapse between infusions; this interval can be prolonged in the event of adverse reactions, but the overall treatment period should not exceed 20 days.

Catumaxomab is also under investigation for the treatment of gastric cancer.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Infusion-related reactions characteristic of a cytokine release syndrome (including fever, nausea, vomiting, chills, dyspnoea, and hypotension or hypertension) occur commonly with catumaxomab. A systemic inflammatory response syndrome (SIRS) may also occur; this generally develops within 24 hours of infusion, and manifests as fever, tachycardia, tachypnoea, and leucocytosis. Premedication with analgesics, antipyretics, or NSAIDs is recommended as prophylaxis for both syndromes.

Myelosuppression is common with catumaxomab. Other common adverse effects include tachycardia, vertigo, gastrointestinal disturbances, hyperbilirubinaemia, hepatitis, electrolyte imbalances (hyponatraemia, hypocalcaemia, hypokalaemia), hyperglycaemia, arthralgia, myalgia, headache, dizziness, anxiety, insomnia, and renal disorders such as proteinuria and haematuria. Ileus and abdominal pain may be serious. Skin and subcutaneous reactions are also common, and may be severe. Uncommon adverse effects which may be serious, include pulmonary embolism, pleural effusion, acute renal failure, convulsions, intestinal obstruction, gastric haemorrhage, and extravasation. Infections are common, and can be severe; use of catumaxomab is not recommended during acute infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Removab; *Cz.*: Removab; *Denm.*: Removab; *Fr.*: Removab; *Ger.*: Removab; *Irl.*: Removab; *Israel*: Removab; *Neth.*: Removab; *Norw.*: Removab; *Pol.*: Removab; *Port.*: Removab; *Swed.*: Removab; *UK*: Removab.

Cediranib *(BAN, rINN)*

AZD-2171; Cédiranib; Cediranibum; Цедираниб.

4-[(4-Fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline.

$C_{25}H_{27}FN_4O_3$=450.5

CAS — 288383-20-0.
UNII — NQU9IPY4K9.

NOTE. The name Recentin has been used as a trade mark for cediranib.

Cediranib Maleate *(BANM, USAN, rINNM)*

AZD-2171 maleate; Cédiranib, Maléate de; Cediranibi Maleas; Maleato de cediranib; Цедираниба Малеат.

4-[(4-Fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline(2*Z*)-but-2-enedioate.

$C_{25}H_{27}FN_4O_3.C_4H_4O_4$=566.6

CAS — 857036-77-2.
UNII — 68AYS9A614.

Profile

Cediranib is an inhibitor of tyrosine kinase associated with the vascular endothelial growth factor (VEGF) receptor. It is under investigation for the treatment of recurrent glioblastoma. It has been investigated for metastatic colorectal cancer and non-small cell lung cancer but results were disappointing. Adverse effects include hypertension and proteinuria.

References.

1. Robertson JD, *et al.* Phase III trial of FOLFOX plus bevacizumab or cediranib (AZD2171) as first-line treatment of patients with metastatic colorectal cancer: HORIZON III. *Clin Colorectal Cancer* 2009; 8: 59–60.
2. Langenberg MH, *et al.* Effective strategies for management of hypertension after vascular endothelial growth factor signaling inhibition therapy: results from a phase II randomized, factorial, double-blind study of cediranib in patients with advanced solid tumors. *J Clin Oncol* 2009; 27: 6152–9.
3. Dietrich J, *et al.* Cediranib: profile of a novel anti-angiogenic agent in patients with glioblastoma. *Expert Opin Invest Drugs* 2009; 18: 1549–57.
4. Robinson ES, *et al.* Rapid development of hypertension and proteinuria with cediranib, an oral vascular endothelial growth factor receptor inhibitor. *Clin J Am Soc Nephrol* 2010; 5: 477–83.
5. Goss GD, *et al.* Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small-cell lung cancer: NCIC clinical trials group BR24 study. *J Clin Oncol* 2010; 28: 49–55.
6. Batchelor TT, *et al.* Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. *J Clin Oncol* 2010; 28: 2817–23.

Cetuximab *(USAN, rINN)*

C-225; Cétuximab; Cetuximabum; IMC-C225; Цетуксимаб.

Immunoglobulin G1 (human-mouse monoclonal C225 γ1-chain anti-human epidermal growth factor receptor) disulfide with human-mouse monoclonal C225 κ-chain dimer.

CAS — 205923-56-4.
ATC — L01XC06.
ATC Vet — QL01XC06.
UNII — PQX0D8J21J.

Stability. Cetuximab 2 mg/mL was physically stable when stored for 14 days at 4 degrees in either PVC infusion bags or the opened original glass vial.[1]

1. Ikesue H, *et al.* Stability of cetuximab and panitumumab in glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2010; 67: 223–6.

Uses and Administration

Cetuximab is a chimeric monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). Signal transduction through the EGFR results in activation of the protein expressed by the wild-type *KRAS* gene (Kirsten rat sarcoma 2 viral oncogene homologue), which plays a role in cell growth regulation and angiogenesis. In patients with

KRAS gene mutations, activation of the *KRAS* protein is independent of EFGR regulation and cetuximab is ineffective. It is, however, used in the treatment of EGFR-expressing, *KRAS* wild-type, metastatic colorectal cancer (p. 706.3). Cetuximab may be used first-line with fluorouracil-based combinations such as the FOLFOX (infusional fluorouracil, folinic acid, and oxaliplatin) or FOLFIRI (fluorouracil, folinic acid, and irinotecan) regimens. It is also used with irinotecan in patients refractory to irinotecan-based chemotherapy, or as monotherapy in patients intolerant to irinotecan-based regimens or after failure of both oxaliplatin- and irinotecan-based regimens. Cetuximab with radiotherapy may be used for the treatment of locally advanced squamous cell cancer of the head and neck (p. 708.1). It is also used with platinum-based chemotherapy for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck, and as monotherapy in those for whom prior platinum-based therapy has failed. It is under investigation for non-small cell lung cancer and other solid tumours.

For all indications, cetuximab 400 mg/m^2 is given as a loading dose by intravenous infusion over 2 hours. This is followed by once weekly maintenance doses of 250 mg/m^2 given over 1 hour. The maximum infusion rate is 10 mg/min. Premedication with a histamine H_1-antagonist and corticosteroids is recommended, and patients should be closely monitored for at least 1 hour after the end of the cetuximab infusion. A low-protein-binding 0.22-micrometre in-line filter should be used, and the infusion given via an infusion or syringe pump.

In combined therapy for colorectal cancer, chemotherapy should not be given for at least 1 hour after the end of cetuximab infusion. In head and neck carcinoma, cetuximab therapy is started one week before radiation therapy and continued until the end of the radiation therapy period. Cetuximab is usually given 1 hour before radiation therapy. When used as monotherapy, cetuximab is continued until disease progression or unacceptable toxicity occurs.

The infusion rate should be permanently reduced in patients who have had a mild to moderate infusion reaction, and cetuximab should be immediately and permanently stopped if a severe reaction has occurred (see Adverse Effects and Precautions, below). When a severe acneform rash has occurred, the next dose should be delayed by 1 to 2 weeks. After the first occurrence, the full maintenance dose may be given if there has been improvement in the rash; after a second occurrence the next dose should be delayed and reduced to 200 mg/m^2; after a third occurrence the next dose should be delayed and reduced to 150 mg/m^2. If there is no improvement in the rash when therapy has been delayed, or if the rash has occurred 4 times, cetuximab should be stopped.

References.

1. NICE. Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck (issued June 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA145Guidance.pdf (accessed 03/09/09)
2. NICE. Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck (issued June 2009). Available at: http://www.nice.org.uk/nicemedia/live/12179/44644/44644.pdf (accessed 14/11/12)
3. NICE. Cetuximab for the first-line treatment of metastatic colorectal cancer (issued August 2009). Available at: http://www.nice.org.uk/nicemedia/live/12216/45198/45198.pdf (accessed 14/11/12)
4. Gerber DE, Choy H. Cetuximab in combination therapy: from bench to clinic. *Cancer Metastasis Rev* 2010; 29: 171–80.
5. Frampton JE. Cetuximab: a review of its use in squamous cell carcinoma of the head and neck. *Drugs* 2010; 70: 1987–2010.
6. Broadbridge VT, *et al.* Cetuximab in metastatic colorectal cancer. *Expert Rev Anticancer Ther* 2012; 12: 555–65.
7. Carillio G, *et al.* Cetuximab in non-small-cell lung cancer. *Expert Rev Anticancer Ther* 2012; 12: 163–75.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Adverse effects associated with cetuximab include skin reactions, asthenia, and gastrointestinal disturbances. Skin reactions present mainly as an acneform rash, and, if severe, require dosage adjustment (see Uses and Administration, p. 762.3). Sun exposure should be limited. Infusion reactions suggestive of a cytokine release syndrome can occur, usually with the first dose. Mild reactions include chills, fever, and dyspnoea; severe reactions include bronchospasm, urticaria, hypotension or hypertension, and loss of consciousness, and fatalities have occurred. Premedication with a histamine H_1-antagonist and corticosteroids is recommended, and dose adjustment may be necessary (see Uses and Administration, p. 762.3). Cardiopulmonary arrest and/or sudden death has been reported in patients treated with cetuximab and radiation therapy, and cetuximab should be given with caution to head and neck cancer patients with coronary artery disease, congestive cardiac failure, or arrhythmias. Radiation dermatitis has also been reported with cetuximab. Cardiotoxicity may be increased when cetuximab is used with fluorouracil. When used with platinum compounds, the frequency of severe leucopenia or severe neutropenia may be increased, leading to infectious complications such as febrile neutropenia, pneumonia, and sepsis. Hypomagnesaemia can occur; patients should be monitored for this and accompanying hypocalcaemia and hypokalaemia before, during, and for up to 8 weeks after stopping therapy. Interstitial lung disease, pulmonary embolism, deep-vein thrombosis, and renal failure have been reported rarely. Common adverse effects include headache, increases in liver enzyme concentrations, and conjunctivitis.

Effects on the nervous system. A 54-year-old man had a generalised seizure within 15 minutes of starting his first infusion of cetuximab;[1] he had been pretreated with ondansetron, ranitidine, diphenhydramine, and dexamethasone. The authors considered the seizure to be an infusion reaction.

1. McClellan NH, Bell WA. Seizure activity during cetuximab infusion in a patient with metastatic colorectal cancer. *Am J Health-Syst Pharm* 2012; 69: 1881–4.

Effects on the skin, hair, and nails. Acneform follicular rashes have been reported with cetuximab therapy;[1,2] lesions were pustular and papular,[2-4] and commonly occurred on the face, scalp, chest, and upper back.[1-5] The relative risk of developing high-grade rash was estimated to be over 20 times greater in patients given cetuximab than in controls; the incidence was higher in patients with colorectal cancer (12.6%) than in those with other malignancies (6.6%).[6] It has been suggested that there is a relationship between rash and response to therapy or survival, i.e. that rash might be a surrogate marker of cetuximab activity;[7,8] doubling the cetuximab dose in patients without severe initial skin reactions is reported to increase their response rate to therapy.[9] A few cases of lengthening eyelash and eyebrow hair[10] and abnormal growth of chest hair[11] have been described. Paronychia has also been reported,[1,5,12] as have intraoral aphthous ulcers.[1]

Treatment with oral isotretinoin 500 micrograms/kg daily has been reported to successfully clear acneform skin lesions in 2 patients; topical therapy with metronidazole 0.75% gel or erythromycin 1% was also used.[13] Prophylactic oral minocycline 100 mg daily, started on the same day as cetuximab and given for 8 weeks, significantly reduced total facial lesion counts in the first 4 weeks when compared with placebo; this difference tapered by the end of 8 weeks of treatment. Topical tazarotene showed no clinical benefit and caused local irritation that forced tazarotene to be stopped in many patients.[14]

Some have suggested that the clinical findings of papulopustular rash, nail and periungual abnormalities, alterations in hair texture and growth, and dry skin and pruritus, constitute a syndrome unique to the epidermal growth factor receptor (EGFR) inhibitors, believed to be due to EGFR inhibition in the epidermis, hair follicle, and nail matrix.[15] A retrospective study[16] of patients treated with EGFR inhibitors (erlotinib, cetuximab, or panitumumab) for more than 6 months found that all patients had cutaneous adverse effects. However, the frequency of skin changes arising from long-term use was different to effects seen soon after treatment; the incidence of folliculitis diminished over time, whereas paronychia, skin dryness, and hair modifications became more predominant.

Erythema and focal epidermolysis, progressing to severe radiation dermatitis with necrosis, has been reported in patients given radiation therapy with cetuximab.[17]

1. Busam KJ, *et al.* Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol* 2001; 144: 1169–76.
2. Walon L, *et al.* Éruptions acnéiformes indultes par le cétuximab. *Ann Dermatol Venereol* 2003; 130: 443–6.
3. Kimyai-Asadi A, Jih MH. Follicular toxic effects of chimeric anti-epidermal growth factor receptor antibody cetuximab used to treat human solid tumors. *Arch Dermatol* 2002; 138: 129–31.
4. Jacot W, *et al.* Acneiform eruption induced by epidermal growth factor receptor inhibitors in patients with solid tumours. *Br J Dermatol* 2004; 151: 238–41.
5. Monti M, *et al.* Cutaneous toxicity induced by cetuximab. *J Clin Oncol* 2003; 21: 4651–3.
6. Su X, *et al.* Risk of high-grade skin rash in cancer patients treated with cetuximab—an antibody against epidermal growth factor receptor: systemic [sic] review and meta-analysis. *Oncology* 2009; 77: 124–33.
7. Perét-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol* 2005; 23: 5235–46.
8. Gatzemeier U, *et al.* First-cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study. *Lancet Oncol* 2011; 12: 30–7.
9. Van Cutsem E, *et al.* Intrapatient cetuximab dose escalation in metastatic colorectal cancer according to the grade of early skin reactions: the randomized EVEREST study. *J Clin Oncol* 2012; 30: 2861–8.
10. Dueland S, *et al.* Epidermal growth factor receptor inhibition induces trichomegaly. *Acta Oncol* 2003; 42: 345–6.
11. Montagut C, *et al.* Abnormal hair growth in a patient with head and neck cancer treated with the anti-epidermal growth factor receptor monoclonal antibody cetuximab. *J Clin Oncol* 2005; 23: 5273–5.
12. Boucher KW, *et al.* Paronychia induced by cetuximab, an antiepidermal growth factor receptor antibody. *J Am Acad Dermatol* 2002; 47: 632–3.
13. Gutzmer R, *et al.* Successful treatment with oral isotretinoin of acneiform skin lesions associated with cetuximab therapy. *Br J Dermatol* 2005; 153: 849–51.
14. Scope A, *et al.* Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol* 2007; 25: 5390–6.
15. Lacouture ME, Lai SE. The PRIDE (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors) syndrome. *Br J Dermatol* 2006; 155: 852–4.
16. Osio A, *et al.* Cutaneous side-effects in patients on long-term treatment with epidermal growth factor receptor inhibitors. *Br J Dermatol* 2009; 161: 513–21.
17. Budach W, *et al.* Severe cutaneous reaction during radiation therapy with concurrent cetuximab. *N Engl J Med* 2007; 357: 514–5.

Hypersensitivity. For limited data pointing to a lack of cross-sensitivity between cetuximab and panitumumab, see Hypersensitivity, under Panitumumab, p. 843.2.

For a report of a generalised seizure considered to be an infusion reaction, see Effects on the Nervous System, above.

Hypomagnesaemia. A patient given cetuximab developed profound hypomagnesaemia, requiring intravenous supplementation with up to 10 g magnesium sulfate daily, throughout the duration of cetuximab therapy. This case prompted a review of 154 patients treated with cetuximab, of whom 34 had their magnesium concentrations measured at least once. Among these 34 patients, 6 had grade 3 and 2 had grade 4 hypomagnesaemia; this equated to an incidence of 24% of grade 3/4 hypomagnesaemia. In each of these cases the need for supplementation subsided after stopping cetuximab, with resolution of the hypomagnesaemia within several weeks.[1] However, it was not clear whether all patients had a normal magnesium concentration before treatment, nor was there any indication of the median time to development of hypomagnesaemia.

Another retrospective review of 114 patients did address these issues.[2] It found 48 patients had normal baseline magnesium concentrations before starting cetuximab. Of these 48 evaluable patients, 13 developed grade 3 or grade 4 hypomagnesaemia (27%); median time to onset of grade 3/4 hypomagnesaemia was 5.5 months. There was a significant association between duration of cetuximab therapy and grade of hypomagnesaemia. Magnesium replacement therapy was given to those patients with grade 3/4 toxicity. Initial attempts at oral replacement with up to 1.6 g magnesium oxide three times daily were ineffective, and intravenous supplementation was needed. However, the effects of infusion did not extend beyond 48 to 72 hours, with some patients requiring daily magnesium sulfate infusions of up to 10 g daily. Furthermore, in some patients, magnesium supplementation became less effective with continued cetuximab treatment. Of 3 patients evaluable for recovery from hypomagnesaemia after stopping cetuximab, 2 were found to correct their magnesium concentrations without supplementation after 1 month. However, 1 patient required prolonged and ongoing supplementation for more than 5 months, at 4 g infused 3 times weekly (having received 8 g daily while on cetuximab).[2] A prospective study[3] found that a progressive decrease in serum magnesium concentrations was seen in 97% of patients after treatment with cetuximab, panitumumab, or matuzumab. The authors concluded that magnesium wasting was specifically due to inhibition of the epidermal growth factor receptor (EGFR), and suggested hypomagnesaemia might be a class effect of the monoclonal antibodies directed against EGFR. However, incidence and severity may vary between products. There was also high interindividual variability; increasing age was associated with more severe hypomagnesaemia.

1. Schrag D, *et al.* Cetuximab therapy and symptomatic hypomagnesemia. *J Natl Cancer Inst* 2005; 97: 1221–4.
2. Fakih MG, *et al.* Cetuximab-induced hypomagnesemia in patients with colorectal cancer. *Clin Colorectal Cancer* 2006; 6: 152–6.
3. Tejpar S, *et al.* Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. *Lancet Oncol* 2007; 8: 387–94.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cetuximab 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 29/09/11)

Pharmacokinetics

The pharmacokinetics of cetuximab have been reported to be non-linear and dose-dependent. Steady-state concentrations are reached after 3 weeks. Cetuximab has a long elimination half-life of about 70 to 100 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Erbitux; *Austral.*: Erbitux; *Austria*: Erbitux; *Belg.*: Erbitux; *Braz.*: Erbitux; *Canad.*: Erbitux; *Chile*: Erbitux; *China*: Erbitux (爱必妥); *Cz.*: Erbitux; *Denm.*: Erbitux; *Fin.*: Erbitux; *Fr.*: Erbitux; *Ger.*: Erbitux; *Gr.*: Erbitux; *Hong Kong*: Erbitux; *Hung.*: Erbitux; *India*: Erbitux;

Indon.: Erbitux; ***Irl.***: Erbitux; ***Israel***: Erbitux; ***Ital.***: Erbitux; ***Malaysia***: Erbitux; ***Mex.***: Erbitux; ***Neth.***: Erbitux; ***Norw.***: Erbitux; ***NZ***: Erbitux; ***Philipp.***: Erbitux; ***Pol.***: Erbitux; ***Port.***: Erbitux; ***Rus.***: Erbitux (Эрбитукс); ***S.Afr.***: Erbitux; ***Singapore***: Erbitux; ***Spain***: Erbitux; ***Swed.***: Erbitux; ***Switz.***: Erbitux; ***Thai.***: Erbitux; ***UK***: Erbitux; ***Ukr.***: Erbituks (Эрбитукс); ***USA***: Erbitux.

Chlorambucil *(BAN, rINN)*

CB-1348; Chlorambucilis; Chlorambucilum; Chlorambucyl; Chloraminophene; Chlorbutinum; Clorambucilo; Klorambucil; Klórambucil; Klorambusilil; Klorambusil; NSC-3088; WR-139013; Хлорамбуцил.

4-[4-Bis(2-chloroethyl)aminophenyl]butyric acid.

$C_{14}H_{19}Cl_2NO_2$=304.2

CAS — 305-03-3.

ATC — L01AA02.

ATC Vet — QL01AA02.

UNII — 18D0SL7309.

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

Ph. Eur. 8: (Chlorambucil). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone. Protect from light.

USP 36: (Chlorambucil). An off-white, slightly granular powder. M.p. 65 degrees to 69 degrees. Very slightly soluble in water; soluble 1 in 2 of acetone; soluble in dilute alkali. Store in airtight containers. Protect from light.

Storage. Licensed product information recommends that tablets of chlorambucil should be stored at 2 degrees to 8 degrees and kept dry.

Uses and Administration

Chlorambucil is an oral antineoplastic derived from chlormethine (p. 765.1) and has a similar mode of action. It acts on lymphocytes and to a lesser extent on neutrophils and platelets. Chlorambucil is most valuable in those conditions associated with the proliferation of white blood cells, especially lymphocytes, and is used in the treatment of chronic lymphocytic leukaemia and lymphomas, including Hodgkin's disease. It is also used in Waldenström's macroglobulinaemia and has been given in gestational trophoblastic tumours. Although formerly widely used in the management of polycythaemia vera it has largely been superseded.

Chlorambucil also has immunosuppressant properties and has been given in auto-immune disorders including amyloidosis, Behçet's syndrome, glomerular kidney disease, primary biliary cirrhosis, polymyositis, rheumatoid arthritis, and sarcoidosis.

The use of chlorambucil in these disorders is discussed under the individual headings below.

Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

Chlorambucil is better tolerated than chlormethine hydrochloride and serious bone-marrow toxicity is not usually a problem with normal doses. When used as a single-agent antineoplastic for chronic lymphocytic leukaemia and lymphomas, chlorambucil is licensed for oral use in usual initial doses of 100 to 200 micrograms/kg daily (usually 4 to 10 mg once daily), for 3 to 8 weeks. A dose of 100 micrograms/kg daily may be adequate for the treatment of non-Hodgkin's lymphoma; 150 micrograms/kg daily until the total leucocyte count falls below 10 000 cells/mm^3 may be used in chronic lymphocytic leukaemia; and in Hodgkin's disease, 200 micrograms/kg daily is usually required. Lower doses may be given as part of a combination regimen. If lymphocytic infiltration of the bone marrow is present or if the bone marrow is hypoplastic, the daily dose should not exceed 100 micrograms/kg. Alternatively, high-dose chlorambucil may be given intermittently. For example, in chronic lymphocytic leukaemia it may be given in an initial single dose of 400 micrograms/kg increased by 100 micrograms/kg at each 2- or 4-week dose interval until control of lymphocytosis is achieved or toxicity occurs.

Once a remission has been established the patient may receive continuous maintenance with 30 to 100 micrograms/kg daily. However, short intermittent courses appear to be safer and are generally preferred for maintenance.

In patients with Waldenström's macroglobulinaemia chlorambucil is licensed in an initial oral dose of 6 to 12 mg daily until leucopenia develops. Maintenance therapy with doses of 2 to 8 mg daily may then be given indefinitely.

Total and differential white cell counts and haemoglobin and platelet examinations are recommended each week during treatment with chlorambucil.

Amyloidosis. Chlorambucil may be of use in preserving kidney function and improving survival in patients with amyloidosis secondary to rheumatic disease,[1-4] the management of which is discussed in more detail on p. 819.3.

1. Berglund K, *et al.* Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease. *Ann Rheum Dis* 1987; 46: 757–62.
2. Berglund K, *et al.* Results, principles and pitfalls in the management of renal AA-amyloidosis: a 10-21 year followup of 16 patients with rheumatic disease treated with alkylating cytostatics. *J Rheumatol* 1993; 20: 2051–7.
3. David J, *et al.* Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study. *Clin Exp Rheumatol* 1993; 11: 85–90.
4. Savolainen HA. Chlorambucil in severe juvenile chronic arthritis: longterm followup with special reference to amyloidosis. *J Rheumatol* 1999; 26: 898–903.

Blood disorders, non-malignant. Chlorambucil may produce a response in cold auto-immune haemolytic anaemia (p. 1122.2).

Connective tissue and muscular disorders. Chlorambucil has been used as a corticosteroid-sparing agent in patients with Behçet's syndrome (p. 1601.1). It has occasionally been tried in polymyositis (p. 1611.1). In both these conditions, the potential benefits must be weighed against the possibility of toxicity.

Kidney disorders, non-malignant. Chlorambucil has been used in some forms of glomerular kidney disease (p. 1604.3). Minimal change nephropathy occurs mainly in young children and is the most common cause of childhood nephrotic syndrome. Treatment with cytotoxics is reserved for the most severe cases because of fears about toxicity; cyclophosphamide is generally preferred to chlorambucil because it is perceived as entailing somewhat less risk although chlorambucil has been used successfully in cyclophosphamide-resistant disease.[1] Although not licensed for use in children with relapsing corticosteroid-sensitive nephrotic syndrome, the *BNFC* suggests that children from 3 months of age may be given an oral dose of 200 micrograms/kg once daily for 8 weeks. Chlorambucil has been used with corticosteroids in patients with membranous nephropathy,[2-4] but again cyclophosphamide may be better tolerated.

1. Ueda N, *et al.* Beneficial effect of chlorambucil in steroid-dependent and cyclophosphamide-resistant minimal change nephrotic syndrome. *J Nephrol* 2009; 22: 610–5.
2. Ponticelli C, *et al.* Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. *N Engl J Med* 1992; 327: 599–603.
3. Reichert LJM, *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; 121: 328–33.
4. Ponticelli C, *et al.* A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int* 1995; 48: 1600–4.

Liver disorders, non-malignant. No treatment has proven unequivocally successful in the management of primary biliary cirrhosis (p. 2638.3). Chlorambucil is one of several drugs for which reports of benefit exist.[1]

1. Hoofnagle JH, *et al.* Randomized trial of chlorambucil for primary biliary cirrhosis. *Gastroenterology* 1986; 91: 1327–34.

Malignant neoplasms. Chlorambucil is used in the management of haematological malignancies such as chronic lymphocytic leukaemia (p. 693.3), Hodgkin's disease (p. 696.1), indolent low-grade non-Hodgkin's lymphomas (p. 696.3), and Waldenström's macroglobulinaemia (p. 699.1). It was formerly used in polycythaemia vera (p. 695.2) but is now largely superseded.

Ocular disorders, non-malignant. Chlorambucil is one of the immunosuppressants that may be considered for patients with uveitis (p. 1615.1) unresponsive to corticosteroids in tolerable doses.[1-3]

1. Mudun AB, *et al.* Short-term chlorambucil for refractory uveitis in Behcet's disease. *Ocul Immunol Inflamm* 2001; 9: 219–29.
2. Miserocchi E, *et al.* Efficacy and safety of chlorambucil in intractable noninfectious uveitis. *Ophthalmology* 2002; 109: 137–42.
3. Goldstein DA, *et al.* Long-term follow-up of patients treated with short-term high-dose chlorambucil for sight-threatening ocular inflammation. *Ophthalmology* 2002; 109: 370–7.

Pemphigus and pemphigoid. Chlorambucil with prednisone or prednisolone has been reported[1,2] to be effective in the treatment of pemphigus and pemphigoid (p. 1687.1).

1. Shah N, *et al.* The use of chlorambucil with prednisone in the treatment of pemphigus. *J Am Acad Dermatol* 2000; 42: 85–8.
2. Chave TA, *et al.* Chlorambucil as a steroid-sparing agent in bullous pemphigoid. *Br J Dermatol* 2004; 151: 1107–8.

Rheumatoid arthritis. Chlorambucil has been used for its immunosuppressant properties in a few patients with severe rheumatoid arthritis (p. 13.2), especially with vasculitis, who have failed to respond to other drugs. However, the use of cytotoxic immunosuppressants other than methotrexate is considered debatable.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p. 1612.2), corticosteroids are the usual treatment. Chlorambucil is one of several cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

A reversible progressive lymphocytopenia tends to develop during treatment with chlorambucil. Neutropenia may continue to develop up to 10 days after the last dose. Irreversible bone-marrow depression can occur particularly when the total dosage for the course approaches 6.5 mg/kg.

Other reported adverse effects include gastrointestinal disturbances, hepatotoxicity, skin rashes (rarely Stevens-Johnson syndrome or toxic epidermal necrolysis), peripheral neuropathy, and central neurotoxicity, including seizures. Interstitial pneumonia and pulmonary fibrosis have occurred; the latter is usually reversible but fatalities have been recorded. Chlorambucil in high doses may produce azoospermia and amenorrhoea; sterility has developed particularly when chlorambucil has been given to boys at or before puberty.

Overdosage may result in pancytopenia and in neurotoxicity, including agitation, ataxia, and grand mal seizures.

Like other alkylating agents, chlorambucil is potentially mutagenic, teratogenic, and carcinogenic, and an increased incidence of acute leukaemias and other secondary malignancies has been reported in patients who have received the drug.

Effects on the bladder. Chlorambucil-induced cystitis was reported in a 73-year-old woman given 2 mg daily for over 2 years for the treatment of lymphocytic lymphoma.[1]

1. Daoud D, *et al.* Sterile cystitis associated with chlorambucil. *Drug Intell Clin Pharm* 1977; 11: 491.

Effects on the eyes. Visual impairment and optic atrophy in a patient who had been receiving chlorambucil for 5 years to control non-Hodgkin's lymphoma were thought to be due to the drug,[1] although ocular effects are extremely rare with chlorambucil.

1. Yiannakis PH, Larner AJ. Visual failure and optic atrophy associated with chlorambucil therapy. *BMJ* 1993; 306: 109.

Effects on the nervous system. There have been a few reports of seizures in patients given chlorambucil. A review[1] of these suggested that in adults, patients with a history of seizures, or those given high doses of chlorambucil may be at increased risk. The reports in children consisted mainly of patients being treated for nephrotic syndrome, possibly because the condition may alter the pharmacokinetics of chlorambucil.

1. Salloum E, *et al.* Chlorambucil-induced seizures. *Cancer* 1997; 79: 1109–13.

Hypersensitivity. Drug fever, characterised by high temperature, rigors, and malaise, may occur in patients within hours or days of starting chlorambucil, often after a drug-free interval. In 3 patients who developed symptoms of chlorambucil-induced drug fever, desensitisation, beginning with an oral dose of 500 micrograms daily, increased about every 5 days by 500 micrograms up to 2 mg was successful. In one patient the dose was successfully increased to 4 mg daily by continuing to increase by 500 micrograms every 7 days.[1]

1. Weber E, *et al.* Rapid desensitization for chlorambucil drug fever. *Haematologica* 2007; 92: e77.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2. Chlorambucil should be avoided, or given with great care and at reduced doses, for at least 4 weeks after treatment with radiotherapy or other antineoplastics (unless only low doses of radiation have been given to parts remote from the bone marrow and the neutrophil and platelet counts are not depressed). The dose should be reduced if there is lymphocytic involvement of the bone marrow or if it is hypoplastic. Chlorambucil should be given with care to patients with impaired renal function; consideration should also be given to dose reduction in patients with gross hepatic dysfunction. Children with nephrotic syndrome, patients receiving high-dose pulse therapy with chlorambucil, and those with a history of seizures, may be at increased risk of seizures. Regular blood counts are required during therapy.

Handling and disposal. Chlorambucil is irritant; avoid contact with skin and mucous membranes.

Urine produced for up to 48 hours after a dose of chlorambucil should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorambucil 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 28/09/11)

Pregnancy. A patient with chronic lymphocytic leukaemia who was taking low-dose chlorambucil was found to be pregnant with a viable 20-week fetus during the third month of chlorambucil treatment. Treatment was stopped, and a healthy child without apparent congenital anomaly was delivered at 36 weeks by caesarean section. Development and growth had remained normal at 3 months of age.[1]

1. Ali R, *et al.* Pregnancy in chronic lymphocytic leukemia: experience with fetal exposure to chlorambucil. *Leuk Res* 2009; 33: 567–9.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Pharmacokinetics

Chlorambucil is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses and is reported to have a terminal half-life in plasma of about 1.5 hours. It is extensively metabolised in the liver, mainly to active phenylacetic acid mustard, which has a slightly longer plasma half-life of about 1.8 to 2.5 hours, and which like chlorambucil also undergoes some spontaneous degradation to further derivatives. Chlorambucil and its metabolites are extensively protein bound. It is excreted in the urine almost entirely as metabolites with less than 1% unchanged.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Leukeran; *Austral.*: Leukeran; *Austria*: Leukeran; *Belg.*: Leukeran; *Braz.*: Leukeran; *Canad.*: Leukeran; *Chile*: Leukeran; *China*: Leukeran (留可然); *Cz.*: Leukeran; *Denm.*: Leukeran; *Fin.*: Leukeran; *Ger.*: Leukeran; *Gr.*: Leukeran; *Hong Kong*: Leukeran; *India*: Clokeran; Leukeran; *Irl.*: Leukeran; *Israel*: Leukeran; *Ital.*: Leukeran; *Malaysia*: Leukeran; *Mex.*: Leukeran; *Neth.*: Leukeran; *Norw.*: Leukeran; *NZ*: Leukeran; *Philipp.*: Leukeran; *Pol.*: Leukeran; *Port.*: Leukeran; *Rus.*: Leukeran (Лейкеран); *S. Afr.*: Leukeran; *Singapore*: Leukeran; *Spain*: Leukeran; *Swed.*: Leukeran; *Switz.*: Leukeran; *Thai.*: Leukeran; *Turk.*: Leukeran; *UK*: Leukeran.

Pharmacopoeial Preparations
BP 2014: Chlorambucil Tablets;
USP 36: Chlorambucil Tablets.

Chlormethine Hydrochloride

(BANM, rINNM)

Chlorethazine Hydrochloride; Chlorméthine, Chlorhydrate de; Chlormethini Hydrochloridum; Clormetina, hidrocloruro de; Hidrocloruro de clormetina; HN2 (chlormethine); Klormetin Hidroklorür; Mechlorethamine Hydrochloride; Mecloretamina (chlormethine); Mustin Hidroklorür; Mustine Hydrochloride; Nitrogen Mustard (chlormethine); NSC-762; WR-147650; Хлорметина Гидрохлорид.

Bis(2-chloroethyl)methylamine hydrochloride; 2,2′-Dichloro-*N*-methyldiethylamine hydrochloride.

$C_5H_{11}Cl_2N,HCl=192.5$

CAS — 51-75-2 (chlormethine); 55-86-7 (chlormethine hydrochloride).

ATC — L01AA05.

ATC Vet — QL01AA05.

UNII — L0MR697HHL

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

BP 2014: (Chlormethine Hydrochloride). A white or almost white, hygroscopic, vesicant, crystalline powder or mass. Very soluble in water. Store at a temperature of 8 degrees to 15 degrees.

USP 36: (Mechlorethamine Hydrochloride). A white, hygroscopic, crystalline powder. A 0.2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Stability. Solutions of chlormethine hydrochloride lose their activity very rapidly, particularly at neutral or alkaline pH.

A study[1] using an assay specific for chlormethine found that a 0.1% solution in Water for Injections or sodium chloride 0.9% injection underwent a loss of about 10% when stored for 6 hours at room temperature, and of about 4 to 6% when stored for the same period at 4 degrees; similar results were obtained whether the solution was stored in glass vials or plastic syringes. Solutions in 500 mL of sodium chloride or glucose 5% injection and stored in PVC infusion bags were still less stable, with 15% and 10% degradation respectively after 6 hours at room temperature.

Chlormethine hydrochloride has been used in extemporaneous ointment preparations in the treatment of mycosis fungoides.[2] One formulation of chlormethine hydrochloride, dissolved in acetone and worked into white soft paraffin, was reported[3] to be stable for at least 84 days when stored at 4 degrees, and for at least 40 days at 37 degrees.

1. Kirk B. Stability of reconstituted Mustine Injection BP during storage. *Br J Parenter Ther* 1986; 7: 86–92.
2. Price NM, *et al.* Ointment-based mechlorethamine treatment for mycosis fungoides. *Cancer* 1983; 52: 2214–19.
3. Cummings J, *et al.* The long term stability of mechlorethamine hydrochloride (nitrogen mustard) ointment measured by HPLC. *J Pharm Pharmacol* 1993; 45: 6–9.

Uses and Administration

Chlormethine belongs to the group of antineoplastic drugs described as alkylating agents. It also possesses weak immunosuppressant properties.

Chlormethine hydrochloride has been used in the treatment of advanced Hodgkin's disease (p. 696.1), historically with a vinca alkaloid, procarbazine, and prednisone or prednisolone (the MOPP regimen). Chlormethine has also been tried in non-Hodgkin's lymphomas, notably mycosis fungoides (p. 698.3), and some other malignancies including chronic leukaemias, tumours of the breast, ovary, and lung, and in polycythaemia vera. Chlormethine has been used in the management of malignant effusions but is not the agent of choice.

In the MOPP regimen chlormethine hydrochloride has been given in doses of 6 mg/m^2. However, when licensed for use as a single agent, the usual dose of chlormethine hydrochloride is 400 micrograms/kg, preferably as a single dose, although it may be divided into 2 or 4 equal doses on successive days. It is given by intravenous injection in a strength of 1 mg/mL in Water for Injections or sodium chloride 0.9%. Injection over 2 minutes into the tubing of a fast running intravenous infusion of sodium chloride 0.9% or glucose 5% may reduce the incidence of thrombophlebitis and the risk of extravasation.

The response should be assessed by the trend of the blood counts. Treatment with chlormethine may be repeated when the bone-marrow function has recovered.

Intracavitary injections of 200 to 400 micrograms/kg have been given in the treatment of malignant, especially pleural, effusions.

For topical treatment of mycosis fungoides, see below.

Histiocytic syndromes. Dilute solutions of chlormethine (200 micrograms/mL) have been applied topically for the cutaneous symptoms of Langerhans-cell histiocytosis (p. 692.1).[1,2] Such therapy was reported to effectively clear skin lesions in most patients, and be well tolerated. However, although no malignant skin disease developed during the follow-up of one group of children, the long-term effects of topical chlormethine are of concern in young patients.[2]

1. Sheehan MP, *et al.* Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. *J Pediatr* 1991; 119: 317–21.
2. Roeger PH, *et al.* Long term follow up of topical mustine treatment for cutaneous Langerhans cell histiocytosis. *Arch Dis Child* 2000; 82: 483–7.

Mycosis fungoides. Chlormethine is used topically in the management of mycosis fungoides (p. 698.3). A retrospective cohort analysis[1] of 203 patients treated with chlormethine found a partial response rate of 33% and a complete response rate of 50%. The median time to achieve complete response was 12 months and the time to relapse was also 12 months. Mild disease of limited skin involvement responded better than generalised patch/plaque disease, and more patients with mild disease obtained long-term remission. Maintenance therapy was used in some patients, but on cessation the relapse rate was similar to patients who did not receive maintenance therapy. Although unlicensed in the UK, guidelines[2] suggest chlormethine as a treatment option for early-stage mycosis fungoides, applied in a concentration of 0.01% or 0.02%, either as an aqueous solution in sodium chloride 0.9% or in an ointment base such as emulsifying ointment.

1. Kim YH, *et al.* Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003; 139: 165–73.
2. Whittaker SJ, *et al.* Joint British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003; 149: 1095–1107. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Cutaneous%20T%20Cell%20Lymphoma.pdf (accessed 22/04/10)

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Chlormethine hydrochloride is extremely toxic and its use is invariably accompanied by adverse effects. Severe nausea and vomiting may begin within an hour of injection of the drug and last for some hours; antiemetics should be given before treatment. It causes varying degrees of bone-marrow depression depending on the dose. In heavily pretreated patients, or when the total dose for a single course exceeds 400 micrograms/kg, there is a risk of severe and possibly fatal depression with anaemia, lymphocytopenia, granulocytopenia, and thrombocytopenia with consequent haemorrhage. Depression of lymphocytes may be apparent within 24 hours of a dose and maximum suppression of granulocytes and platelets occurs within 7 to 21 days; haematological recovery may be adequate after 4 weeks.

Tinnitus, vertigo, deafness, headache, drowsiness, and other neurological symptoms have been reported, as have episodes of jaundice. Skin reactions to chlormethine hydrochloride include maculopapular rashes. Hypersensitivity is frequent when topical preparations are used.

Chlormethine hydrochloride has a powerful vesicant action on the skin and mucous membranes and great care must be taken to avoid contact with the eyes. Thrombophlebitis is a potential hazard of chlormethine particularly if it is not sufficiently diluted. Extravasation of the injection causes severe irritation and even sloughing. If extravasation occurs during injection, it has been suggested that the involved area should be infiltrated with an isotonic 4% solution of sodium thiosulfate, followed by the application of an ice compress intermittently for 6 to 12 hours, although the role of specific antidotes in antineoplastic extravasation is somewhat contentious (see p. 731.3).

Chlormethine hydrochloride may produce temporary or permanent inhibition of fertility. There is some evidence of mutagenicity, teratogenicity, and carcinogenicity.

Effects on the nervous system. Severe immediate neurotoxicity developed[1] in 14 of 21 evaluable patients who underwent bone marrow transplantation after preparation with cytotoxic regimens including chlormethine 0.3 to 2 mg/kg. Symptoms developed a median of 4 days after treatment and included headache, hallucinations, confusion, convulsions, paraplegia, and tremor. Symptoms resolved in most, although in some they had not done so before their death. Six of the patients who recovered from acute toxicity developed a delayed neurotoxicity, beginning a median of 169 days after the first chlormethine injection and characterised by symptoms including confusion, somnolence, personality change, dementia, focal motor seizures, and hydrocephalus. Patients older than 21 years, those who had received CNS irradiation, and those treated concomitantly with other cytotoxic agents were at increased risk of neurotoxicity.

1. Sullivan KM, *et al.* Immediate and delayed neurotoxicity after mechlorethamine preparation for bone marrow transplantation. *Ann Intern Med* 1982; 97: 182–9.

Handling and disposal. Chlormethine hydrochloride is a strong vesicant; avoid contact with skin and mucous membranes.

The manufacturers state that *unused injection* solutions of chlormethine hydrochloride may be neutralised by mixing with an equal volume of a solution containing sodium thiosulfate 5% and sodium bicarbonate 5% and allowing to stand for 45 minutes. Equipment used in the preparation and administration of such solutions may be treated similarly. Alternatively a solution containing sodium carbonate 2.5% or sodium hydroxide in a mixture of industrial methylated spirit and water has been suggested for the decontamination of equipment.

Urine produced for up to 48 hours after a dose of chlormethine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlormethine 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 28/09/11)

Pharmacokinetics

On intravenous injection, chlormethine is rapidly converted to a reactive ethyleneimmonium ion. It usually disappears from the blood in a few minutes. A very small proportion is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Mustargen†; *Fr.*: Caryolysine†; *Gr.*: Caryolysine; *Israel*: Mustargen; *Switz.*: Mustargen†; *USA*: Mustargen; Valchlor.

Pharmacopoeial Preparations
BP 2014: Chlormethine Injection;
USP 36: Mechlorethamine Hydrochloride for Injection.

Cilengitide *(USAN, rINN)*

Cilengitida; Cilengitidum; EMD-121974; Циленгитид.
Cyclo(L-arginylglycyl-L-α-aspartyl-D-phenylalanyl-*N*-methyl-L-valyl).
$C_{27}H_{40}N_8O_7$=588.7
CAS — 188968-51-6.
UNII — 4EDF46E4GL

Profile

Cilengitide is an integrin inhibitor with anti-angiogenic actions, under investigation in the treatment of glioma, squamous cell carcinoma of the head and neck, and non-small cell lung cancer.

References.

1. Friess H, *et al.* A randomized multi-center phase II trial of the angiogenesis inhibitor cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer. *BMC Cancer* 2006; 6: 285.
2. Hariharan S, *et al.* Assessment of the biological and pharmacological effects of the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptor antagonist, cilengitide (EMD 121974), in patients with advanced solid tumors. *Ann Oncol* 2007; 18: 1400–7.
3. MacDonald TJ, *et al.* Phase I clinical trial of cilengitide in children with refractory brain tumors: Pediatric Brain Tumor Consortium Study PBTC-012. *J Clin Oncol* 2008; 26: 919–24.
4. Reardon DA, *et al.* Cilengitide: an integrin-targeting arginine-glycine-aspartic acid peptide with promising activity for glioblastoma multiforme. *Expert Opin Invest Drugs* 2008; 17: 1225–35.

Cintredekin Besudotox *(USAN, rINN)*

Cintredekina besudotox; Cintrédékine Bésudotox; Cintredekinum Besudotoxum; IL13-PE38; IL13-PE38QQR; NK-408; Pseudomonas Exotoxin (domains II/III)-Interleukin 13 Chimeric Protein; Toxin hIL 13-PE38QQR (plasmid phuIL 13-Tx); Tredekincept Sudotox; Цинтредекин Безудотокс.
CAS — 372075-36-0.
UNII — ZL04JX89M7

Profile

Cintredekin besudotox is a recombinant fusion protein of interleukin-13 and a bacterial toxin derived from *Pseudomonas aeruginosa*. It is under investigation for the treatment of malignant gliomas.

References.

1. Kunwar S, *et al.* Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group. *J Clin Oncol* 2007; 25: 837–44.
2. Vogelbaum MA, *et al.* Convection-enhanced delivery of cintredekin besudotox (interleukin-13-PE38QQR) followed by radiation therapy with and without temozolomide in newly diagnosed malignant gliomas: phase 1 study of final safety results. *Neurosurgery* 2007; 61: 1031–7.
3. Mut M, *et al.* Cintredekin besudotox in treatment of malignant glioma. *Expert Opin Biol Ther* 2008; 8: 805–12.

Cisplatin *(BAN, USAN, rINN)*

CDDP; *cis*-DDP; Cisplatina; Cisplatine; Cisplatino; Cisplatinum; Cis-platinum; Cisplatyna; Ciszplatin; DDP; Diaminodicloruro de platino (II); NSC-119875; Peyrone's Salt; Platinum Diamminodichloride; Sisplatiini; Sisplatin; Цисплатин.
cis-Diamminedichloroplatinum.
$(NH_3)_2PtCl_2$=300.0
CAS — 15663-27-1.
ATC — L01XA01.
ATC Vet — QL01XA01.
UNII — Q20Q21Q62J.

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

Ph. Eur. 8: (Cisplatin). A yellow powder or yellow or orange-yellow crystals. Slightly soluble in water; practically insoluble in alcohol; sparingly soluble in dimethylformamide. A 0.1% solution in sodium chloride 0.9% has a pH of 4.5 to 6.0 immediately after preparation. Store in airtight containers. Protect from light.

USP 36: (Cisplatin). Store in airtight containers. Protect from light.

Incompatibility. Cisplatin is rapidly degraded in the presence of bisulfite or metabisulfite,[1,2] and admixture with preparations containing these as preservatives may result in loss of activity.[2] Sodium bicarbonate may also increase the loss of cisplatin from solution, and in some cases may cause precipitation.[3] The stability of cisplatin when mixed with fluorouracil is reported to be limited, with 10% loss of cisplatin in 1.2 to 1.5 hours.[4] Mixtures with etoposide[5] in sodium chloride 0.9% injection formed a precipitate if mannitol and potassium chloride were present as additives, but not when the diluent was glucose 5% with sodium chloride 0.45%. Turbidity has been reported[6] within 4 hours of mixing 0.1% solutions of cisplatin and thiotepa in glucose 5%. Cisplatin exhibits variable incompatibility with paclitaxel, depending on the paclitaxel concentration and the temperature.[7]

Cisplatin reacts with aluminium causing loss of potency and precipitate formation. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving cisplatin.

1. Hussain AA, *et al.* Reaction of cis-platinum with sodium bisulfite. *J Pharm Sci* 1980; 69: 364–5.
2. Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; 24: 91–9.
3. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; 33: 107–16.
4. Stewart CF, Fleming RA. Compatibility of cisplatin and fluorouracil in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1990; 47: 1373–7.
5. Stewart CF, Hampton EM. Stability of cisplatin and etoposide in intravenous admixtures. *Am J Hosp Pharm* 1989; 46: 1400–4.
6. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; 53: 1041–5.
7. Zhang Y, *et al.* Compatibility and stability of paclitaxel combined with cisplatin and with carboplatin in infusion solutions. *Ann Pharmacother* 1997; 31: 1465–70.

Stability. Decomposition of cisplatin in aqueous solutions is mainly due to reversible substitution of water for chloride, and its stability is enhanced in sodium chloride solutions because of the excess of chloride ions available.[1,2] A solution in sodium chloride 0.9% injection has been reported to lose 3% of the drug in less than one hour and to remain stable at this equilibrium value for 24 hours at room temperature.[1] Stability is decreased if exposed to intense light, but the effect of normal lighting conditions is apparently smaller.[1,2] It has been recommended that admixtures of cisplatin with mannitol and magnesium sulfate (in glucose 5% with sodium chloride 0.45%) stored at room temperature in PVC bags should be used within 48 hours, but may be stored for 4 days at 4 degrees or frozen and stored at -15 degrees for up to 30 days.[3] However, solutions containing 600 micrograms/mL or more of cisplatin precipitate out when refrigerated and are slow to redissolve.[1]

1. Greene RF, *et al.* Stability of cisplatin in aqueous solution. *Am J Hosp Pharm* 1979; 36: 38–43.
2. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; 33: 107–16.
3. LaFollette JM, *et al.* Stability of cisplatin admixtures in polyvinyl chloride bags. *Am J Hosp Pharm* 1985; 42: 2652.

Uses and Administration

The antineoplastic cisplatin is a platinum-containing complex that may act similarly to the alkylating agents. Its antineoplastic actions are cell-cycle non-specific and are dependent upon its *cis* configuration; they appear to be related to its hydrolysis in the body to form reactive aquated species. Although it causes immunosuppression, stimulation of the host immune response against the tumour has been suggested as contributing to cisplatin's antineoplastic action.

Cisplatin is of value in the treatment of tumours of the testis, usually as a major component of combination chemotherapy regimens, and particularly with bleomycin and etoposide (BEP), or with bleomycin and a vinca alkaloid. It is also used in metastatic ovarian tumours, cervical tumours, lung cancer, advanced bladder cancer, and squamous cell carcinoma of the head and neck. It has been reported to be active against many other solid tumours, as indicated by the cross references given under Malignant Neoplasms, p. 767.1.

Cisplatin is given by intravenous infusion in sodium chloride 0.9% or in a mixture of sodium chloride and glucose. In monotherapy, it is usually given as a single dose of 50 to 120 mg/m² every 3 to 4 weeks. Alternatively, 15 to 20 mg/m² is given daily for 5 days, every 3 to 4 weeks. Lower doses are generally used for combination chemotherapy regimens than for single agent therapy; 20 mg/m² or more is given once every 3 to 4 weeks. A dose of 20 mg/m² daily for 5 days every 3 to 4 weeks has been used in combination chemotherapy of testicular tumours.

Licensed product information recommends that cisplatin is given in 2 litres of chloride-containing infusion fluid. In practice, volumes of less than 2 litres have been used in expert centres. The infusion may be given over 1 to 2 hours, although licensed product information generally recommends a longer infusion time of 6 to 8 hours in order to reduce renal and gastrointestinal toxicities.

To aid diuresis and protect the kidneys, 37.5 g of mannitol (e.g. 375 mL of mannitol 10%) is usually added to the infusion or is infused separately immediately before cisplatin. In order to begin diuresis the patient is usually hydrated by the infusion of 1 to 2 litres of a suitable fluid over several hours before giving cisplatin. Adequate hydration must also be maintained for up to 24 hours after a dose. Renal, haematological, auditory, and neurological function should be monitored during therapy, and dosage adjusted accordingly.

Cisplatin has also been given by the intra-arterial and intraperitoneal routes, and by instillation into the bladder. It is being investigated as a liposomal formulation, and as a collagen-based injectable gel containing cisplatin and adrenaline (MPI-5010) to localise the effect. An oral formulation of cisplatin is also under investigation.

Various analogues of cisplatin have been developed or investigated including those with fewer adverse effects e.g. carboplatin, p. 759.1; nedaplatin, p. 834.3), an altered spectrum of activity (oxaliplatin, p. 838.1), or activity on oral dosage (satraplatin, p. 856.3).

Administration. Adjustments to the way in which cisplatin is given have been suggested in an attempt to improve efficacy while reducing toxicity.

Hydration before and after a dose of cisplatin, together with the use of mannitol to promote diuresis, is now standard (see Uses and Administration, above). Higher doses of cisplatin (up to 200 mg/m² per treatment cycle) have been successfully given by infusion in hypertonic sodium chloride, accompanied by intensive hydration.[1,2] Sodium chloride 3% infusion solution has been used.[3] However, while such a regimen may limit nephrotoxicity, other toxic effects, such as peripheral neuropathy, are not prevented;[1,2,4,5] myelosuppression may be less if the total dose is given in 2 divided doses rather than divided over 5 days.[2] High-dose cisplatin has been given once weekly; haematological toxicity may be dose-limiting with this regimen.[3]

Toxicity has been reported to be reduced when cisplatin was given by continuous intra-arterial[6] or intravenous[7] infusion. It has also been suggested that giving cisplatin in the evening rather than the morning results in less damage to renal function, apparently because of circadian variations in urine production.[8] However, another study[9] found that morning, rather than evening, doses of cisplatin resulted in less renal damage. Noting the inconsistency with previous reports, the authors concluded that use of a prolonged hydration protocol and concomitant furosemide might have been responsible for these results (see also under Interactions, Cardiovascular Drugs, p. 768.3). It was also found that morning dosage of cisplatin may be more emetogenic than evening dosage, although the use of prophylactic ondansetron before cisplatin reduced this apparent circadian effect on vomiting.

A suggested alternative way to increase the platinum dose without producing incapacitating toxicity has been the combination of cisplatin and carboplatin.[10] Formulation as liposomal cisplatin is also under investigation.[11]

Various drugs have been investigated to reduce toxicity, including amifostine, glutathione, and thiosulfate, as discussed under Effects on the Ears, p. 767.2 Effects on the Kidneys, p. 767.2 and Effects on the Nervous System, p. 767.3.

A retrospective study of patients with bladder cancer found that calculation of creatinine clearance (CC) by mathematical formulas was inadequate in determining renal eligibility for treatment with cisplatin, especially in patients over 65 years of age; up to 44% of patients who were treated with cisplatin based on measured CC would have been deemed ineligible using mathematical calculations.[12] The value of therapeutic drug monitoring has been reviewed.[13]

1. Ozols RF, *et al.* High-dose cisplatin in hypertonic saline. *Ann Intern Med* 1984; 100: 19–24.
2. Gandara DR, *et al.* Cisplatin dose intensity in non-small cell lung cancer: phase II results of a day 1 and day 8 high-dose regimen. *J Natl Cancer Inst* 1989; 81: 790–4.
3. de Jongh FE, *et al.* Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. *Br J Cancer* 2003; 88: 1199–1206.
4. Bagley CM, *et al.* High-dose cisplatin therapy for cancer of the ovary: neurotoxicity. *Ann Intern Med* 1985; 102: 719.
5. Ozols RF, Young RC. High-dose cisplatin therapy for cancer of the ovary: neurotoxicity. *Ann Intern Med* 1985; 102: 719.
6. Jacobs SC, *et al.* Intraarterial cisplatin infusion in the management of transitional cell carcinoma of the bladder. *Cancer* 1989; 64: 388–9.
7. Salem P, *et al.* Cis-diamminedichloroplatinum (II) by 5-day continuous infusion: a new dose schedule with minimal toxicity. *Cancer* 1984; 53: 837–40.
8. Hrushesky WJM, *et al.* Circadian time dependence of cisplatin urinary kinetics. *Clin Pharmacol Ther* 1982; 32: 330–9.
9. Kobayashi M, *et al.* Cisplatin-induced vomiting depends on circadian timing. *Chronobiol Int* 2001; 18: 851–63.
10. Piccart MJ, *et al.* Cisplatin combined with carboplatin: a new way of intensification of platinum dose in the treatment of advanced ovarian cancer. *J Natl Cancer Inst* 1990; 82: 703–7.
11. Stathopoulos GP. Liposomal cisplatin: a new cisplatin formulation. *Anticancer Drugs* 2010; 21: 732–6.
12. Raj GV, *et al.* Formulas calculating creatinine clearance are inadequate for determining eligibility for cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol* 2006; 24: 3095–3100.
13. Hulin A, *et al.* Suivi thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique du cisplatine. *Therapie* 2011; 66: 151–5.

Administration in the elderly. Despite receiving less chemotherapy than their younger counterparts, selected

elderly patients have been shown to benefit from adjuvant cisplatin-based chemotherapy and studies have concluded that chemotherapy should not be withheld from patients on the basis of age.[1,2] A review[3] considered cisplatin to be a viable treatment option in selected elderly patients; renal function and the high incidence of age-related hearing loss should, however, be taken into consideration. The authors recommended that cisplatin be used at the lower range of dosage, and preferably at a reduced infusion rate (for example, over 24 hours) to avoid excessive toxicity in the elderly; hydration should be monitored to prevent fluid overload and concomitant use of nephrotoxic drugs should be avoided.

Use of mathematical formulas to determine renal eligibility for cisplatin treatment has been deemed to be inadequate, especially in patients over 65 years of age, see Administration, p. 766.3.

1. Pepe C, *et al.* Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. *J Clin Oncol* 2007; **25**: 1553–61.
2. Früh M, *et al.* Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. *J Clin Oncol* 2008; **26**: 3573–81.
3. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25**: 1832–43.

Administration in renal impairment. Licensed product information generally contra-indicates the use of cisplatin in patients with renal impairment. However, there are reports of the use of cisplatin with peritoneal dialysis[1] or haemodialysis[2,3] in a few patients.

1. Sebestyen J, *et al.* Cisplatin pharmacokinetics in a child receiving peritoneal dialysis. *Pediatr Nephrol* 2010; **25**: 1185–9.
2. Matsumoto K. Pharmacokinetics of cisplatin and methotrexate after M-VAC chemotherapy for advanced urothelial cancer in hemodialysis patients. *Int J Urol* 2008; **15**: 949–50.
3. Zahra MA, *et al.* Concurrent weekly cisplatin chemotherapy and radiotherapy in a haemodialysis patient with locally advanced cervix cancer. *Clin Oncol (R Coll Radiol)* 2008; **20**: 6–11.

Malignant neoplasms. Cisplatin is used in the management of many solid malignancies, notably those of the bladder, cervix, lung, ovary, and testis, as discussed on p. 700.2, p. 704.2, p. 710.2, p. 711.2, and p. 715.1 respectively. Other malignancies where cisplatin may be employed, as discussed in the introduction to this chapter, include non-Hodgkin's lymphomas (p. 696.3), tumours of brain (p. 701.2), endometrium (p. 704.3), oesophagus, stomach, and anus (p. 705.3, p. 706.1, and p. 708.1), head and neck (p. 708.1), and thymus (p. 715.3), neuroblastoma (p. 716.2), and sarcoma of bone and soft tissue (p. 717.3 and p. 718.2).

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

Severe nausea and vomiting occur in most patients during treatment with cisplatin; nausea may persist for up to a week.

Serious toxic effects on the kidneys, bone marrow, and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative.

Damage to the renal tubules may be evident during the second week after a dose of cisplatin and renal function must return to normal before further cisplatin is given. Adequate hydration, and use of osmotic diuretics such as mannitol to increase urine volume and thus decrease the urinary concentration of platinum, can reduce the incidence of nephrotoxicity. Electrolyte disturbances, particularly hypomagnesaemia and hypocalcaemia, may occur, possibly as a result of renal tubular damage. Hyperuricaemia is also seen.

Bone-marrow depression may be severe with higher doses of cisplatin. Nadirs in platelet and leucocyte counts occur between days 18 and 23 and most patients recover by day 39; anaemia is common and may be partly related to decreased production of erythropoietin after renal damage.

Ototoxicity may be more severe in children. It can manifest as tinnitus, loss of hearing in the high frequency range, and occasionally deafness or vestibular toxicity. Other neurological effects reported include peripheral neuropathies, loss of taste, seizures, and encephalopathy including reversible posterior leukoencephalopathy. Ocular toxicities include optic neuritis, papilloedema, and cerebral blindness.

Anaphylactoid reactions and cardiac abnormalities have occurred. Injection site reactions, including localised oedema, pain, erythema, skin ulceration and phlebitis may occur. Extravasation may lead to tissue cellulitis, fibrosis, and necrosis. Intra-arterial use of cisplatin has been associated with hepatobiliary disorders, including cholecystitis, biloma, and liver abscesses.

Platinum derivatives are potentially mutagenic and teratogenic, and there is some evidence they may be associated with the development of secondary leukaemias—see Carcinogenicity, p. 726.2.

Effects on the blood. Cisplatin-induced anaemia appears to be disproportionate to the effects on other blood cells, and to correlate with renal tubular dysfunction.[1] It may therefore be due to an erythropoietin deficiency state resulting from cisplatin-induced renal tubular damage. Haemolysis has also been reported.[2]

1. Wood PA, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome. *J Clin Invest* 1995; **95**: 1650–9.
2. Rothmann SA, Welck JK. Cisplatin toxicity for erythroid precursors. *N Engl J Med* 1981; **304**: 360.

THROMBOEMBOLISM. For discussion of thromboembolic events possibly associated with cisplatin-containing chemotherapy regimens see Effects on the Cardiovascular System, p. 727.2.

Effects on the ears. Ototoxicity is a well-established adverse effect of cisplatin.[1] It appears to be due to generation of reactive oxygen species that cause apoptosis of hair cells in the cochlea,[1] and results in hearing loss, particularly at high frequencies.[1,2] Risk factors include younger age,[1] larger cumulative doses[1] (one study[2] identified doses above 60 mg/m^2 as risk factors), pre-existing hearing loss or renal disease,[1] and irradiation of the brain or base of the skull.[1,3] Various substances including thiols, amifostine, ebselen, allopurinol, and salicylates have been investigated in *animals* for their protective effect against cisplatin-induced neurotoxicity[1] but although some promising results have been seen, benefit is yet to be shown in large clinical studies, and there is some concern about the risk of reducing the antineoplastic effect of cisplatin as well. However, a small study comparing cisplatin chemoradiation with or without sodium thiosulfate tentatively concluded that thiosulfate did seem to offer some protection against hearing loss.[4] Another study[5] in young patients with average-risk medulloblastoma found that amifostine, given before and during cisplatin infusion, significantly reduced the risk of severe ototoxicity. It was noted[6] that the cisplatin dose and schedule used for this study were different to those commonly used in other paediatric malignancies, and that amifostine might not necessarily be protective in other settings.

1. Rybak LP, *et al.* Mechanisms of cisplatin-induced ototoxicity and prevention. *Hear Res* 2007; **226**: 157–67.
2. Rademaker-Lakhai JM, *et al.* Relationship between cisplatin administration and the development of ototoxicity. *J Clin Oncol* 2006; **24**: 918–24.
3. Low WK, *et al.* Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. *J Clin Oncol* 2006; **24**: 1904–9.
4. Zuur CL, *et al.* Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol* 2007; **25**: 3759–65.
5. Fouladi M, *et al.* Amifostine protects against cisplatin-induced ototoxicity in children with average-risk medulloblastoma. *J Clin Oncol* 2008; **26**: 3749–55.
6. Freyer DR, *et al.* Prevention of hearing loss in children receiving cisplatin chemotherapy. *J Clin Oncol* 2009; **27**: 317–18.

Effects on electrolytes. Renal-magnesium wasting and, less commonly, symptomatic hypomagnesaemia occurs with cisplatin therapy.[1,2] Adding magnesium to the pre- and posthydration fluids has been suggested.[2] When hypocalcaemia is also present, tetany may result,[1,3] although this has responded to electrolyte infusion without the need to interrupt chemotherapy.[1] Cisplatin therapy may also be associated with significant hypokalaemia,[1] and salt-wasting,[4] and hyponatraemia.[5,6]

See also Effects on the Kidneys, below.

1. Winkler CF, *et al.* Cisplatin and renal magnesium wasting. *Ann Intern Med* 1979; **91**: 502.
2. Lajer H, Daugaard G. Cisplatin and hypomagnesemia. *Cancer Treat Rev* 1999; **25**: 47–58.
3. Stuart-Harris R, *et al.* Tetany associated with cis-platin. *Lancet* 1980; **ii**: 1303.
4. Hamdi T, *et al.* Cisplatin-induced renal salt wasting syndrome. *South Med J* 2010; **103**: 793–9.
5. Hutchison FN, *et al.* Renal salt wasting in patients treated with cisplatin. *Ann Intern Med* 1988; **108**: 21–5.
6. Mariette X, *et al.* Cisplatin and hyponatremia. *Ann Intern Med* 1988; **108**: 770–1.

Effects on the heart. Cases of cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia, sinus tachycardia, sinus bradycardia, and third-degree heart block) have been reported following the use of cisplatin and other platinum-based antineoplastic drugs.[1,2] It was proposed that this may be due to either direct arrhythmogenicity, hypersensitivity, or electrolyte imbalances (see also Effects on Electrolytes, above).

1. Tassinari D, *et al.* Cardiac arrhythmias after cisplatin infusion: three case reports and a review of the literature. *Ann Oncol* 1997; **8**: 1263–7.
2. Zakaria S, *et al.* Atrial flutter associated with carboplatin administration. *Ann Pharmacother* 2011; **45**: e59.

Effects on the kidneys. Nephrotoxicity is a well-established adverse effect of cisplatin, may be dose-limiting, and can manifest as acute or chronic renal failure, polyuria, or chronic hypomagnesaemia.[1] The mechanism appears to involve mainly damage to the proximal renal tubule; selective magnesium loss may be due to a specific membrane or transport system abnormality. Sulfhydryl metabolism and oxidative stress play a role in toxicity, and measures that reduce glutathione depletion and scavenge intracellular free oxygen radicals have been tried in an attempt to modulate nephrotoxicity.[1-3] However, the primary measures for reducing renal damage have been aggressive hydration with chloride-containing solutions, and the use of mannitol (see also Prophylaxis, below). It has been suggested that cisplatin may mobilise lead accumulated in bone and cause temporary accumulation in the kidney, with concomitant toxicity,[4] but this has been vigorously disputed.[5-7]

See also under Effects on Electrolytes, above.

1. Anand AJ, Bashey B. Newer insights into cisplatin nephrotoxicity. *Ann Pharmacother* 1993; **27**: 1519–25.
2. Meyer KB, Madias NE. Cisplatin nephrotoxicity. *Miner Electrolyte Metab* 1994; **20**: 201–13.
3. Kuhlmann MK, *et al.* Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. *Nephrol Dial Transplant* 1997; **12**: 2478–80.
4. El-Sharkawi AM, *et al.* Unexpected mobilisation of lead during cisplatin chemotherapy. *Lancet* 1986; **ii**: 249–50.
5. Tothill P, *et al.* Is lead mobilised by cisplatin? *Lancet* 1989; **ii**: 333.
6. Tothill P, *et al.* Mobilisation of lead by cisplatin. *Lancet* 1989; **ii**: 1342.
7. Hainsworth IR, Morgan WD. Plasma lead and cisplatin. *Lancet* 1989; **ii**: 624.

PROPHYLAXIS. Hydration with 1 to 2 litres of fluid before treatment, and infusion of cisplatin in a further 2 litres of infusion fluid containing an osmotic diuretic such as mannitol reduces the nephrotoxicity of cisplatin, but does not abolish it. Maintaining adequate hydration and urinary output post-treatment is also important. It has been recommended[1] that urinary output be maintained at 3 to 4 litres daily for 2 to 3 days after a dose of cisplatin. Giving cisplatin over 6 to 8 hours rather than 1 to 2 hours may also decrease renal toxicity.

Sulfur-containing nucleophiles can inactivate cisplatin, and have therefore been investigated for their chemoprotective potential. Amifostine is a prodrug that is selectively activated by normal tissue, and has been shown to protect normal tissue (principally the kidney) against the cytotoxicity of cisplatin without affecting antitumour activity (for references, see Cytoprotection, p. 1539.3). Glutathione (p. 1555.2) is a similar agent, which may be selectively taken up by kidney and neural tissue. Sodium thiosulfate (p. 1576.1) does not show selective activation or uptake, and its use is therefore limited to situations where cisplatin is given locally (e.g. intraperitoneal[2,3]) or directly (e.g. intra-arterial[4]).

1. Launay-Vacher V, *et al.* Prevention of cisplatin nephrotoxicity: state of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care. *Cancer Chemother Pharmacol* 2008; **61**: 903–9.
2. Malmstrom H, *et al.* Intraperitoneal high-dose cisplatin and etoposide with systemic thiosulfate protection in second-line treatment of advanced ovarian cancer. *Gynecol Oncol* 1993; **49**: 166–71.
3. van Rijswijk RE, *et al.* Experience with intraperitoneal cisplatin and etoposide and i.v. sodium thiosulphate protection in ovarian cancer patients with either pathologically complete response or minimal residual disease. *Ann Oncol* 1997; **8**: 1235–41.
4. Rohde S, *et al.* Intra-arterial high-dose chemotherapy with cisplatin as part of a palliative treatment concept in oral cancer. *Am J Neuroradiol* 2005; **26**: 1804–9.

Effects on the nervous system. The features of cisplatin-induced peripheral neuropathy are consistent with damage mainly to sensory fibres, with numbness, tingling, and decreased vibratory sensation and deep tendon reflexes, progressing in severe cases to disabling sensory ataxia.[1] The toxicity is dose-dependent, with symptoms usually appearing in patients who have received cumulative doses of 300 to 600 mg/m^2, although individuals vary in susceptibility. Neuropathy is reversible but recovery may take a year or more. The pathophysiology is unknown. Peripheral neuropathy can be a dose-limiting toxicity for cisplatin and agents such as Org-2766 (a corticotropin analogue) and amifostine (p. 1539.2) have been investigated for their potential in protecting peripheral nerves.[1-3] Vitamin E has been reported to be effective in reducing cisplatin-induced peripheral neuropathy.[4,5] Glutathione is also under investigation for the prevention of neurotoxicity (see p. 1555.2). Other drugs that have been tried include oxcarbazepine and ditiocarb sodium.[6] However, a systematic review considered that the evidence for most of the interventions intended to reduce cisplatin neurotoxicity was insufficient to show benefit.[6] Autonomic neuropathy, with, in some cases, consequent orthostatic hypotension, has also been described after treatment with cisplatin-containing regimens.[7] Apart from ototoxicity (see above), cisplatin has also been associated with central neurotoxicity, including leukoencephalopathy or focal encephalopathy, seizures, aphasia, confusion, agitation, and cortical blindness.[8-12] It has been suggested that the mechanism of focal encephalopathy may be vascular,[8] although this is uncertain.

1. Mollman JE. Cisplatin neurotoxicity. *N Engl J Med* 1990; **322**: 126–7.
2. Alberts DS, Noel JK. Cisplatin-associated neurotoxicity: can it be prevented? *Anticancer Drugs* 1995; **6**: 369–83.

3. Cavaletti G, *et al.* Neuroprotectant drugs in cisplatin neurotoxicity. *Anticancer Res* 1996; 16: 3149–59.
4. Pace A, *et al.* Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003; 21: 927–31.
5. Pace A, *et al.* Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. *Neurology* 2010; 74: 762–6.
6. Albers JW, *et al.* Interventions for preventing neuropathy caused by cisplatin and related compounds. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 22/03/11).
7. Richardson P, Cantwell BMJ. Autonomic neuropathy after cisplatin based chemotherapy. *BMJ* 1990; 300: 1466–7.
8. Lindeman G, *et al.* Cisplatin neurotoxicity. *N Engl J Med* 1990; 323: 64–5.
9. Philip PA, *et al.* Convulsions and transient cortical blindness after cisplatin. *BMJ* 1991; 302: 416.
10. Higa GM, *et al.* Severe, disabling neurologic toxicity following cisplatin retreatment. *Ann Pharmacother* 1995; 29: 134–7.
11. Ito Y, *et al.* Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. *AJNR Am J Neuroradiol* 1998; 19: 415–17.
12. Steeghs N, *et al.* Cisplatin-induced encephalopathy and seizures. *Anticancer Drugs* 2003; 14: 443–6.

Extravasation. For discussion of the management of extravasation, including methods to manage cisplatin extravasation, see under Treatment of the Adverse Effects of Antineoplastics, p. 731.3.

Hypersensitivity. Anaphylactoid reactions to intravenous cisplatin generally appear within a few minutes of dosage and have manifested as facial oedema, wheezing, tachycardia, and hypotension.[1] A high incidence of anaphylactoid reaction has also been seen after intravesical instillation in patients with bladder cancer,[2] but intraperitoneal or intrapleural use does not seem to be associated with an enhanced risk of hypersensitivity,[3] although anaphylactoid reactions have occurred when cisplatin is given intraperitoneally.[4] Anaphylactoid symptoms and ischaemia of the hands accompanied severe exfoliative dermatitis in one patient on the second cycle of cisplatin-based chemotherapy;[5] she had earlier had exfoliative dermatitis associated with carboplatin. However, it is unclear to what extent cross-sensitivity exists between platinum compounds; cisplatin has been successfully used after a hypersensitivity reaction to oxaliplatin.[6] Palmar-plantar erythrodysesthesia (p. 730.1) has also occurred with cisplatin.[7]

1. Von Hoff DD, *et al.* Allergic reactions to cis platinum. *Lancet* 1976; i: 90.
2. Denis L. Anaphylactic reactions to repeated intravesical instillation with cisplatin. *Lancet* 1983; i: 1378–9.
3. Markman M. No increase in allergic reactions with intracavitary administration of cisplatin. *Lancet* 1984; ii: 1164.
4. Hebert MB, *et al.* Anaphylactoid reactions with intraperitoneal cisplatin. *Ann Pharmacother* 1995; 29: 260–3.
5. Lee TC, *et al.* Severe exfoliative dermatitis associated with hand ischemia during cisplatin therapy. *Mayo Clin Proc* 1994; 69: 80–2.
6. Elligers KT, *et al.* Rechallenge with cisplatin in a patient with pancreatic cancer who developed a hypersensitivity reaction to oxaliplatin. Is skin test useful in this setting? *JOP* 2008; 9: 197–202.
7. Vakalis D, *et al.* Acral erythema induced by chemotherapy with cisplatin. *Br J Dermatol* 1998; 139: 750–1.

Nausea and vomiting. For discussion of the management of chemotherapy-induced nausea and vomiting, see under Nausea and Vomiting, p. 1814.3.

Overdosage. Fatalities have occurred with a total intravenous cisplatin dose of 640 mg given over 4 days and 750 mg given over 1 day; overdoses ranging from 180 to 480 mg/m^2 have been reported without fatalities, although significant toxicities are expected to occur. Immediate effects, in the first hours or days include nausea and vomiting, and rarely, diarrhoea. These may be followed by acute renal failure, electrolyte disturbances, hepatotoxicity, and rarely, pancreatitis, respiratory failure, and seizures. Later adverse effects that occur after days or weeks include chronic renal failure, myelosuppression, ototoxicity, peripheral neuropathy, and retinopathy. Key management strategies for a cisplatin overdose involve renal protection and enhancing drug elimination. Aggressive intravenous hydration with at least 3 to 6 litres daily is essential for reducing nephrotoxicity (for prophylaxis of nephrotoxicity with therapeutic doses, see p. 767.3). The osmotic diuretic mannitol (25 to 50 g intravenously, diluted in 250 to 500 mL of a suitable infusion fluid and given over 60 minutes) may be used to achieve a urine output of 1 to 3 mL/kg per hour for 6 to 24 hours. Sodium thiosulfate may be considered, particularly within the first 2 hours, although the optimum dose regimen has not been established. It is thought to bind free platinum thereby limiting renal tubular necrosis, and may protect against renal magnesium wasting. Plasmapheresis has been used successfully in some cases; haemodialysis, although useful for acute renal failure, is not effective at removing cisplatin from the circulation. Investigational therapies include amifostine, ditiocarb sodium, acetylcysteine, fosfomycin, and colestipol.[1]

1. Tsang RY, *et al.* Cisplatin overdose: toxicities and management. *Drug Safety* 2009; 32: 1109–22.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2. Cisplatin is generally contra-indicated in patients with renal or hearing impairment, or bone-marrow depression. Renal and neurological function and hearing should be monitored during treatment, and regular blood counts performed. Electrolytes should be measured before starting therapy, and before each subsequent course. Adequate hydration and urinary output must be maintained before, and for 24 hours after, a dose.

Patients are recommended to use appropriate contraceptive measures during treatment and for 6 months after stopping treatment.

Breast feeding. Platinum concentrations in a patient receiving cisplatin were 900 nanograms/mL in breast milk and 800 nanograms/mL in plasma.[1] Although most of the platinum in breast milk is probably protein-bound the authors considered that a mother should not breast feed while receiving cisplatin. However, in another report,[2] cisplatin was undetectable in breast milk and the American Academy of Pediatrics[3] considers its use to be compatible with breast feeding.

1. de Vries EGE, *et al.* Excretion of platinum into breast milk. *Lancet* 1989; i: 497. Correction. *ibid.*; 798.
2. Egan PC, *et al.* Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep* 1985; 69: 1387–9.
3. 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 29/06/04)

Handling and disposal. Methods for the destruction of *cisplatin wastes* by reduction with zinc powder under acidic conditions or by reaction with ditiocarb sodium have been described.[1] Residue produced by the degradation of cisplatin by either method showed no mutagenicity *in vitro*.

Urine produced for up to 7 days after a dose of cisplatin should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cisplatin 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 26/08/11)

Pregnancy. Cisplatin was given with etoposide and bleomycin to a pregnant woman at 26 weeks of gestation for carcinoma of uncertain primary origin. At 27 weeks of gestation, she developed profound neutropenia followed by septicaemia and went into premature labour. The infant had profound leucopenia and neutropenia by day 3, which was attributed to chemotherapy given 6 days before delivery; prophylactic antibacterials including gentamicin were given. Hair loss at the age of 10 days was attributed to etoposide. At 1 year of age, the child had moderate bilateral sensorineural hearing loss; this was considered to be either due to cisplatin exposure *in utero* or to gentamicin use.[1] However, there are other reports of cisplatin use during the second or third trimester of pregnancy with no subsequent apparent adverse effects on the infant.[2-5] In most cases, cisplatin had been given with cyclophosphamide,[2-4] although in one instance it was given with paclitaxel.[5] In one report, cisplatin-induced maternal ototoxicity led to it being replaced after 2 courses by carboplatin.[4]

1. Raffles A, *et al.* Transplacental effects of maternal cancer chemotherapy: case report. *Br J Obstet Gynaecol* 1989; 96: 1099–1100.
2. Malfetano JH, Goldkrand JW. Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma. *Obstet Gynecol* 1990; 75: 545–7.
3. King LA, *et al.* Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy. *Gynecol Oncol* 1991; 41: 78–80.
4. Henderson CE, *et al.* Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary. *Gynecol Oncol* 1993; 49: 92–4.
5. Sood AK, *et al.* Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. *Gynecol Oncol* 2001; 83: 599–600.

Radiotherapy. Enhanced ototoxicity has been reported in patients given cisplatin with cranial irradiation.[1,2]

1. Granowetter L, *et al.* Enhanced cis-platinum neurotoxicity in pediatric patients with brain tumors. *J Neurooncol* 1983; 1: 293–7.
2. Mahoney DH, *et al.* Ototoxicity with cisplatin therapy. *J Pediatr* 1983; 103: 1006.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Use with other myelosuppressive, nephrotoxic or ototoxic drugs may exacerbate the adverse effects of cisplatin. The effects of cisplatin on renal function may also affect the pharmacokinetics of other drugs excreted by the renal route.

Antibacterials. Although the use of cisplatin with other nephrotoxic or ototoxic drugs requires great caution, there is some evidence that *aminoglycosides* can be used in patients who have recently received cisplatin if appropriate supportive care is available.[1]

1. Cooper BW, *et al.* Renal dysfunction during high-dose cisplatin therapy and autologous hematopoietic stem cell transplantation: effect of aminoglycoside therapy. *Am J Med* 1993; 94: 497–504.

Antineoplastics. The ototoxicity of cisplatin was reportedly enhanced by *ifosfamide*,[1] a drug that is not ototoxic when given alone, although it does have nephrotoxic potential, making reports of increased nephrotoxicity in patients who have received both unsurprising.[2,3]

For a report of increased toxicity with *etoposide*, see p. 792.1. Cisplatin may reduce the clearance of *paclitaxel*, see p. 842.2.

1. Meyer WH, *et al.* Ifosfamide and exacerbation of cisplatin-induced hearing loss. *Lancet* 1993; 341: 754–5.
2. Rossi R, Ehrich JHH. Partial and complete de Toni-Debré-Fanconi syndrome after ifosfamide chemotherapy of childhood malignancy. *Eur J Clin Pharmacol* 1993; 44 (suppl 1): S43–S45.
3. Martinez F, *et al.* Ifosfamide nephrotoxicity: deleterious effect of previous cisplatin administration. *Lancet* 1996; 348: 1100–1.

Cardiovascular drugs. A patient whose renal function was unaffected by cisplatin alone developed nephrotoxicity when given cisplatin and antihypertensive therapy with *furosemide, hydralazine, diazoxide,* and *propranolol*.[1] Previous results in *animals* suggest that furosemide may aggravate cisplatin nephrotoxicity, while the other antihypertensives might have contributed to a transient fall in renal-blood flow with resultant increased renal-tubular cisplatin concentration.

1. Markman M, Trump DL. Nephrotoxicity with cisplatin and antihypertensive medications. *Ann Intern Med* 1982; 96: 257.

Gastrointestinal drugs. For mention of 2 retrospective studies, one showing a decreased area under the plasma-concentration time curve of high-dose cisplatin with *ondansetron* and the other an increase, see p. 773.3.

Pharmacokinetics

After intravenous doses cisplatin disappears from the plasma in a biphasic manner and half-lives of 25 to 49 minutes and 3 to 4 days have been reported for total platinum. More than 90% of the platinum from a dose is protein bound within 2 to 4 hours; only the unbound fraction has significant antineoplastic activity. Cisplatin is concentrated in the liver, kidneys, and large and small intestines. Penetration into the CNS appears to be poor. Excretion is mainly in the urine but is incomplete and prolonged: up to about 50% of a dose has been reported to be excreted in urine over 5 days, and platinum may be detected in tissue for several months afterwards. The unbound fraction, which is more rapidly cleared, may be actively secreted by the renal tubules. Cisplatin is well-absorbed on intraperitoneal use. Cisplatin may be distributed into breast milk (see Breast Feeding, above).

References.

1. Loh GW, *et al.* A systematic review of limited sampling strategies for platinum agents used in cancer chemotherapy. *Clin Pharmacokinet* 2007; 46: 471–94.
2. Jehn CF, *et al.* Pharmacokinetics of liposomal cisplatin (lipoplatin in combination with 5-FU in patients with advanced head and neck cancer: first results of a phase III study. *Anticancer Res* 2007; 27: 471–5.
3. Royer B, *et al.* Population pharmacokinetics and dosing recommendations for cisplatin during intraperitoneal perioperative administration: development of a limited sampling strategy for toxicity risk assessment. *Clin Pharmacokinet* 2009; 48: 169–80.
4. Cotte E, *et al.* Population pharmacokinetics and pharmacodynamics of cisplatinum during hyperthermic intraperitoneal chemotherapy using a closed abdominal procedure. *J Clin Pharmacol* 2011; 51: 9–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ciskebir†; Elvecis; Platamine†; Platanovag; Platino II; Sicatem; *Belg.*: Platosin†; *Braz.*: C-Platin; Cisplatex†; Citoplax; Fauldcispla; Incel; Platiran; Platistine; Tecnoplatin; *Chile*: Blastolem; *China*: Fangtan (方坦); Jin Shun (金顺); Nuo Xin (诺欣); Yi Jiu Bo (益久博); *Cz.*: Platidiam; Platosin†; *Fin.*: Platinol†; *Fr.*: Cisplatyl†; *Ger.*: Cis-Gry†; Platinex†; *Gr.*: Cisplamin; Cisplamol; Cisplasan; Cisplatyl; Oncoplat; Platamine; Platinol; Platosin; *Hung.*: Platidiam; *India*: Blastolem; Cadiplat; Cisget; Cisplan; Cisplat; Cisteen; Cistriz; Cytoplatin; Duplat; Kemoplat; Neoplat; Oncoplatin; Platin; *Indon.*: Platinox; Platosin; *Israel*: Abiplatin; *Ital.*: Platamine; Pronto Platamine; *Jpn*: Platosin; Randa; *Malaysia*: Platosin; *Mex.*: Accocit; Blastolem; Noveldexis; Platinol; Tecnoplatin; *Neth.*: Platosin; *NZ*: Platinol†; *Philipp.*: Ciplexal†; Cisplagen; Cisteen; Cytosplat; Docistin; Kemoplat; Oncotin; Placitin; Platamine†; Platin; Platinol†; Platinoxan†; Platosin; *Pol.*: Platidiam; *Port.*: Faulplatin†; *Rus.*: Blastolem (Бластолем)†; Kemoplat (Кемоплат); Platidiam (Платидиам); Platinol (Платинол); *S.Afr.*: Abiplatin; Platosin; *Singapore*: Abiplatin; *Spain*: Neoplatin†;

Switz.: Platiblastin-S†; Platinol†; *Thai.*: Abiplatin†; Blastolem†; Kemoplat†; Placis; Platinol†; Platosin; *Turk.*: Oncoplatin†; Placis; Platosin-S; *USA*: Platinol†; *Venez.*: Cytoplatin.

Pharmacopoeial Preparations
BP 2014: Cisplatin Injection;
USP 36: Cisplatin for Injection.

Cladribine *(BAN, USAN, rINN)*

2-Chlorodeoxyadenosine; Cladribin; Cladribina; Cladribinum; Kladribiini; Kladribin; Kladrybina; RWJ-26251-000; RWJ-26251; Кладрибин.
2-Chloro-2′-deoxyadenosine.
$C_{10}H_{12}ClN_5O_3$=285.7
CAS — 4291-63-8.
ATC — L01BB04.
ATC Vet — QL01BB04.
UNII — 47M74X9YT5.

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

Ph. Eur. 8: (Cladribine). A white or almost white crystalline powder. It exhibits polymorphism. Slightly soluble in water and in methyl alcohol; soluble in dimethyl sulfoxide; practically insoluble in acetonitrile. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Cladribine). Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Stability. Cladribine shows increased degradation in glucose 5%, therefore this diluent should not be used. Cladribine in sodium chloride 0.9% is stable for at least 24 hours at room temperature and ambient lighting in PVC infusion containers.

Licensed product information states that cladribine should be stored at 2 degrees to 8 degrees and protected from light.

Uses and Administration

Cladribine is a chlorinated purine nucleoside analogue that inhibits DNA synthesis and repair, particularly in lymphocytes and monocytes. It is used as an antimetabolite antineoplastic for the treatment of lymphoid malignancies including hairy-cell leukaemia (p. 694.3) and chronic lymphocytic leukaemia (p. 693.3). It has also been used in histiocytic syndromes (p. 692.1) and in Waldenström's macroglobulinaemia (p. 699.1).

The recommended intravenous dose of cladribine in **hairy-cell leukaemia** is a single course of 90 micrograms/kg (3.6 mg/m²) daily for 7 days by continuous infusion. If the patient does not respond to the initial course, they are unlikely to respond to further doses. Cladribine is also given subcutaneously in a dose of 140 micrograms/kg (5.6 mg/m²) daily for 5 consecutive days.

For the treatment of **chronic lymphocytic leukaemia** the recommended intravenous dose is 120 micrograms/kg (4.8 mg/m²) daily for 5 consecutive days of a 28-day cycle; the infusion is given over 2 hours. Response should be determined every 2 cycles, and once maximum response has occurred a further 2 cycles of treatment are recommended, up to a maximum of 6 cycles. Patients who do not respond with a lymphocyte reduction of 50% or more after 2 cycles should not receive further therapy. Cladribine is also given subcutaneously in a dose of 100 micrograms/kg (4 mg/m²) daily for 5 consecutive days. This dose of subcutaneous cladribine is also licensed in some countries for the treatment of indolent **non-Hodgkin's lymphoma** and **Waldenström's macroglobulinaemia**.

Reviews.
1. Belani R, Saven A. Cladribine in hairy cell leukemia. *Hematol Oncol Clin North Am* 2006; **20**: 1109–23.
2. Sigal DS, Saven A. Cladribine in indolent non-Hodgkin's lymphoma. *Expert Rev Anticancer Ther* 2008; **8**: 535–45.
3. Huynh E, *et al.* Cladribine in the treatment of hairy cell leukemia: initial and subsequent results. *Leuk Lymphoma* 2009; **50** (suppl 1): 12–17.
4. Spurgeon S, *et al.* Cladribine: not just another purine analogue? *Expert Opin Invest Drugs* 2009; **18**: 1169–81.
5. Sigal DS, *et al.* Beyond hairy cell: the activity of cladribine in other hematologic malignancies. *Blood* 2010; **116**: 2884–96.

Multiple sclerosis. Cladribine has been investigated for the treatment of multiple sclerosis (p. 996.3).

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2.

Cladribine produces severe myelosuppression, including neutropenia, anaemia, and thrombocytopenia, especially at high doses. Transfusion of blood products may be required. Prolonged CD4 lymphopenia with a nadir at 4 to 6 months also develops. Prolonged bone-marrow hypocellularity may also occur, although it is not clear if this is due to the drug or underlying disease. Haemolytic anaemia has also been reported. Severe infections can occur, and may be fatal. Myelodysplastic syndrome has been reported rarely.

Other adverse effects include fever, chills, diaphoresis, fatigue, malaise, mild nausea and gastrointestinal disturbances, rashes, pruritus, purpura, headache, anxiety, dizziness, abnormal breath and/or chest sounds, cough, dyspnoea, oedema, tachycardia, hypotension, arthralgia, and myalgia. Reversible, mild increases in bilirubin and hepatic transaminases are common. Rare adverse events include hepatic, renal, or cardiac failure, atrial fibrillation, and hypereosinophilia; tumour lysis syndrome can occur, and may be fatal.

Very high doses of cladribine have been associated with severe renal and nervous system toxicity as well as myelosuppression. Severe neurotoxicity is rare at currently recommended doses, but confusion, neuropathy, ataxia, insomnia, and somnolence have occurred.

Carcinogenicity. As with some other antimetabolites (see p. 726.2), Epstein-Barr virus-related lymphoma has been reported after cladribine therapy.[1] A study found that in patients with chronic lymphocytic leukaemia, treatment with cladribine did not increase the risk of secondary malignancies when compared with treatment with alkylating agents and combination therapy. However, lung cancers occurred more frequently with cladribine treatment.[2]

1. Niesvizky R, *et al.* Epstein-Barr virus-associated lymphoma after treatment of macroglobulinemia with cladribine. *N Engl J Med* 1999; **341**: 55.
2. Robak T, *et al.* Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. *Eur J Cancer* 2004; **40**: 383–9.

Precautions

For the precautions necessary with antineoplastics, see p. 732.2. Careful haematological monitoring is recommended, especially during the first 4 to 8 weeks of therapy. Renal and hepatic function should also be monitored periodically.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cladribine 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 29/09/11)

Interactions

Lamivudine. A patient with chronic lymphocytic leukaemia had no decrease in lymphocyte count when cladribine was given with lamivudine, the latter being to prevent reactivation of hepatitis B. Lamivudine was stopped and, after another course of cladribine, the lymphocyte count responded. Study *in-vitro* found that lamivudine inhibited the phosphorylation of cladribine, rendering it inactive.[1]

1. Chtioui H, *et al.* Concomitant treatment with lamivudine renders cladribine inactive by inhibition of its phosphorylation. *Br J Haematol* 2009; **144**: 136–7.

Pharmacokinetics

Plasma-cladribine concentrations after intravenous infusion show either a biphasic or triphasic decline, with terminal half-lives ranging from 3 to 22 hours. A bi-exponential decline has been reported after subcutaneous injection, with an initial and terminal half-life of about 2 and 11 hours, respectively. Cladribine is extensively distributed and penetrates into the CNS. It is about 20% bound to plasma proteins. Cladribine is phosphorylated within cells by deoxycytidine kinase to form 2-chlorodeoxyadenosine-5′-monophosphate which is further phosphorylated to the diphosphate by nucleoside monophosphate kinase and to the active metabolite 2-chlorodeoxyadenosine-5′-triphosphate (CdATP) by nucleoside diphosphate kinase.

References.
1. Lillemark J. The clinical pharmacokinetics of cladribine. *Clin Pharmacokinet* 1997; **32**: 120–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hemobine; Intocel; Leustat; *Austral.*: Leustatin; Litak; *Austria*: Leustatin; Litak; *Belg.*: Leustatin; *Braz.*: Leustatin; *Canad.*: Leustatin; *China*: Ai Bo Ding (艾博定); *Cz.*: Leustatin†; Litak; *Denm.*: Litak; *Fin.*: Leustatin; Litak; *Fr.*: Leustatine; Litak; *Ger.*: Leustatin; Litak; *Gr.*: Leustatin; Litak; *Hong Kong*: Leustatin; *Irl.*: Litak; *Israel*: Leustatin†; Litak; *Ital.*: Leustatin; *Neth.*: Leustatin; Litak; *Norw.*: Leustatin; Litak; *NZ*: Leustatin; *Philipp.*: Leustatin†; *Pol.*: Biodribin; Litak; *Port.*: Leustatin; Litak; *Rus.*: Leicladin (Лейкладин); Movectro (Мовектро); *S.Afr.*: Leustatin; Litak; *Singapore*: Leustatin†; *Spain*: Leustatin; Litak; *Swed.*: Leustatin; Litak; *Switz.*: Leustatin; Litak; *UK*: Leustat; Litak; *USA*: Leustatin; *Venez.*: Leustatin.

Clofarabine *(BAN, USAN, rINN)*

Cl-F-Ara-A; Clofarabina; Clofarabinum; Клюфарабин.
2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine.
$C_{10}H_{11}ClFN_5O_3$=303.7
CAS — 123318-82-1.
ATC — L01BB06.
ATC Vet — QL01BB06.
UNII — 762RDY0Y2H.

Uses and Administration

Clofarabine, a purine nucleoside analogue, is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory acute lymphoblastic leukaemia (p. 692.3) in patients aged 1 to 21 years. A dose of 52 mg/m² is given daily for 5 days, by intravenous infusion (see Administration, below) over 2 hours. A longer infusion time should be considered in children weighing less than 20 kg to reduce anxiety and irritability, and to avoid high clofarabine concentrations. The course may be repeated every 2 to 6 weeks, depending on the patient's recovery from bone-marrow depression and other adverse effects (see Administration in Subsequent Cycles, p. 770.1). Treatment is usually assessed after 2 treatment cycles.

For doses in hepatic and renal impairment, see below and p. 770.1, respectively.

Clofarabine is also under investigation for the treatment of acute myeloid leukaemia. An oral formulation is under investigation for the treatment of patients with myelodysplastic syndromes.

References.
1. Hamed TM, Gaynon PS. Treating refractory leukemias in childhood, role of clofarabine. *Ther Clin Risk Manag* 2008; **4**: 327–36.
2. McGregor BA, *et al.* The use of higher dose clofarabine in adults with relapsed acute lymphoblastic leukemia. *Am J Hematol* 2009; **84**: 228–30.
3. Larson ML, Venugopal P. Clofarabine: a new treatment option for patients with acute myeloid leukemia. *Expert Opin Pharmacother* 2009; **10**: 1353–7.
4. Lech-Maranda E, *et al.* Clofarabine as a novel nucleoside analogue approved to treat patients with haematological malignancies: mechanism of action and clinical activity. *Mini Rev Med Chem* 2009; **9**: 805–12.
5. Zhenchuk A, *et al.* Mechanisms of anti-cancer action and pharmacology of clofarabine. *Biochem Pharmacol* 2009; **78**: 1351–9.
6. Sampat K, *et al.* Clofarabine: emerging role in leukemias. *Expert Opin Invest Drugs* 2009; **18**: 1559–64.
7. Jeha S. Recent progress in the treatment of acute lymphoblastic leukemia: clofarabine. *Hematol Oncol Clin North Am* 2009; **23**: 1137–44.
8. Thomas X, *et al.* Clofarabine for the treatment of adult acute myeloid leukemia. *Future Oncol* 2009; **5**: 1197–1210.
9. Paderi S, *et al.* Oral clofarabine in the treatment of patients with higher-risk myelodysplastic syndrome. *J Clin Oncol* 2010; **28**: 2755–60.
10. Tiu RV, *et al.* Clofarabine for myelodysplastic syndromes. *Expert Opin Invest Drugs* 2011; **20**: 1005–14.
11. Majda K, *et al.* Clofarabine (2-chloro-2′-fluoro-2′-deoxyarabinosyladenine)—biochemical aspects of anticancer activity. *Acta Pol Pharm* 2011; **68**: 459–66.
12. O'Connor D, *et al.* Early UK experience in the use of clofarabine in the treatment of relapsed and refractory paediatric acute lymphoblastic leukaemia. *Br J Haematol* 2011; **154**: 482–5.
13. Tran H, Yang D. Clofarabine in the treatment of newly diagnosed acute myeloid leukemia in older adults. *Ann Pharmacother* 2012; **46**: 89–96.

Administration. Instructions for dilution of clofarabine for intravenous use may vary according to country. US licensed product information recommends to filter clofarabine through a 0.2 micrometre syringe filter and then dilute with either glucose 5% or sodium chloride 0.9%, to obtain a final concentration between 150 and 400 micrograms/mL. However, UK licensed product information states that, after filtration (as above), clofarabine should be diluted with sodium chloride 0.9%; total volumes are based on body-surface area as follows:
- ⩽1.44 m²: 100 mL
- 1.45 to 2.4 m²: 150 mL
- 2.41 to 2.5 m²: 200 mL

UK licensed product information also states that if the use of a 0.2 micrometre syringe filter is unfeasible, then the concentrate may be filtered with a 5 micrometre filter, diluted as above, and then given through a 0.22 micrometre in-line filter.

Administration in children. Clofarabine is licensed for use in patients aged 1 to 21 years, see Uses and Administration, above.

Administration in hepatic impairment. Clofarabine should be used with caution in hepatic impairment, because data are limited, and there is a potential for hepatotoxicity (see Adverse Effects, p. 770.1). UK licensed product information states that use in severe hepatic impairment is therefore contra-indicated. US licensed product information states that if grade 3 (or higher) increases in bilirubin are seen, clofarabine dosage should be withheld; it may be restarted at a dose reduced by 25% once organ function has recovered (see also Administration in Subsequent Cycles, p. 770.1).

Administration in renal impairment. Clofarabine should be used with caution in renal impairment, because data are limited, and there is a potential for accumulation in patients with decreased creatinine clearance. In patients with moderate impairment (creatinine clearance 30 to 60 mL/min), a dose reduction of 50% is recommended. No dosage recommendations are made for patients with severe impairment and UK licensed product information contra-indicates its use in such patients.

If grade 3 (or higher) increases in creatinine are seen, clofarabine dosage should be withheld; it may be restarted at a dose reduced by 25% once organ function has recovered (see also Administration in Subsequent Cycles, below).

Administration in subsequent cycles. Dosage of clofarabine is determined by body-surface (see Uses and Administration, p. 769.3), based on the actual height and weight before the start of each cycle.

- Treatment cycles are repeated after recovery or return to baseline organ function, about every 2 to 6 weeks.
- Subsequent cycles should not be given sooner than 14 days from the starting day of the previous cycle.
  The absolute **neutrophil** count (ANC) should be ≥ 750 cells/mm^3 before a dose is given.
  If the ANC has not recovered after 6 weeks from the start of a cycle, a bone marrow aspirate should be performed to determine possible refractory disease; if this is not evident, and once the ANC has recovered to the above concentration, the dose for the next cycle should be reduced by 25% (of the previous dose given).
  If a patient has severe neutropenia, defined as ANC < 500 cells/mm^3, that lasts ≥ 4 weeks, the dose for the next cycle should be reduced by 25%.
- Clofarabine should be withheld in the event of a clinically significant **infection**; once controlled, treatment may be restarted at the full dose. However, if a second significant infection occurs, treatment may be restarted at a dose reduced by 25% once the infection is controlled.
- If **other** severe toxicities occur (grade 3 toxicities excluding nausea and vomiting), then clofarabine should be withheld until recovery, and restarted at a dose reduced by 25%. If the same toxicity recurs on a second occasion, treatment is withheld until recovery and a *further* 25% dose reduction is recommended.

If a severe toxicity recurs on a third occasion, or does not resolve within 14 days, or is life-threatening or disabling, then clofarabine treatment should be stopped.

Adverse Effects, Treatment, and Precautions

As for Fludarabine Phosphate, p. 794.3, although neurotoxicity is less severe. Febrile neutropenia is very common with clofarabine, as are anxiety, headache, flushing, mucosal inflammation, pruritus, and palmar-plantar erythrodysesthesia syndrome. Other common adverse effects include pain, myalgia, arthralgia, hypersensitivity reactions, haematuria, skin exfoliation, alopecia, erythema (which can be generalised), petechiae, dry skin, hyperhidrosis, dizziness, tremor, hearing loss, and epistaxis. Hypertension has also been reported. Hepatotoxicity is also common and can include hyperbilirubinaemia, jaundice, and veno-occlusive disease; patients who have received a haematopoietic stem cell transplant may be at higher risk for hepatotoxicity.

Patients should be monitored for signs and symptoms of cytokine release (including tachypnoea, tachycardia, hypotension, and pulmonary oedema) that could develop into systemic inflammatory response syndrome (SIRS) or capillary leak syndrome, which can be fatal. Symptoms of the latter include respiratory distress, hypotension, pleural and pericardial effusions, and multi-organ failure. Prophylactic corticosteroids may be useful, but clofarabine must be stopped immediately if signs or symptoms of SIRS, capillary leak syndrome, or hypotension develop; further treatment, at a lower dose (see Uses and Administration, p. 769.3), can be considered once patients are stabilised and organ function has returned to baseline. Patients with cardiac disease should be closely monitored. Enterocolitis, including neutropenic enterocolitis and *Clostridium difficile* colitis have been reported, usually within a month of treatment with clofarabine, and usually when given with other chemotherapy.

Renal and hepatic function, and complete blood counts, should be monitored during clofarabine therapy. Hydration should be maintained during treatment to minimise the risk of tumour lysis syndrome and other adverse effects.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clofarabine 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 29/09/11)

Interactions

Patients taking drugs that affect blood pressure or cardiac function should be closely monitored during clofarabine therapy. Drugs that are eliminated by renal tubular secretion might interfere with the excretion of clofarabine and should be avoided.

Pharmacokinetics

Clofarabine is about 47% bound to plasma proteins, mainly to albumin. About 50 to 60% of a dose is excreted unchanged in the urine and it has a terminal half-life of about 5 hours.

References.
1. Bonate PL, *et al.* Population pharmacokinetics of clofarabine and its metabolite 6-ketoclofarabine in adult and pediatric patients with cancer. *Cancer Chemother Pharmacol* 2011; 67: 875–90.
2. Long-Boyle J, *et al.* Pharmacokinetics of clofarabine in patients with high-risk inherited metabolic disorders undergoing brain-sparing hematopoietic cell transplantation. *J Clin Pharmacol* 2011; 51: 679–86.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Evoltra; *Austria*: Evoltra; *Belg.*: Evoltra; *Canad.*: Clolar; *Cz.*: Evoltra; *Denm.*: Evoltra; *Fr.*: Evoltra; *Ger.*: Evoltra; *Gr.*: Evoltra; *Irl.*: Evoltra; *Israel*: Evoltra; *Ital.*: Evoltra; *Jpn*: Evoltra; *Neth.*: Evoltra; *Norw.*: Evoltra; *NZ*: Evoltra; *Pol.*: Evoltra; *Port.*: Evoltra; *Spain*: Evoltra; *Swed.*: Evoltra; *UK*: Evoltra; *USA*: Clolar.

Corynebacterium parvum

C. parvum; NSC-220537; *Propionibacterium acnes*.
UNII — TRZ1AA965O.

Profile

Inactivated *Corynebacterium parvum* has been used in the treatment of malignant effusions, and has been tried as an adjuvant to cancer chemotherapy for its immunostimulant properties. It has also been used in the treatment of musculoskeletal and joint disorders.

Fever and pain have occurred after intracavitary injection. There have been reports of nephrotoxicity after intravenous use.

Crizotinib *(USAN rINN)*

Crizotinibum; PF-02341066; Кризотиниб.
3-[(1*R*)-1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridine-2-amine.
$C_{21}H_{22}Cl_2FN_5O$=450.3
CAS — 877399-52-5.
UNII — 53AH36668S.

Uses and Administration

Crizotinib is an inhibitor of receptor tyrosine kinases, including ALK (anaplastic lymphoma kinase) and hepatocyte growth factor receptor (HGFR; c-Met). Crizotinib is used for the treatment of patients with locally advanced, metastatic, or advanced and refractory non-small cell lung cancer (p. 711.1) that is ALK-positive. The recommended dose is 250 mg orally twice daily; capsules should be swallowed whole. Treatment is continued until patients no longer benefit, or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* If a daily dose of crizotinib is missed, no catch-up dose is recommended if it is less than 6 hours before the next dose. Doses may need to be reduced or treatment interrupted for toxicity (see Administration in Subsequent Cycles, below).

Crizotinib is also under investigation for the treatment of other solid tumours and non-Hodgkin's lymphoma.

References.
1. Kwak EL, *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010; 363: 1693–1703.
2. Rodig SJ, Shapiro GI. Crizotinib, a small-molecule dual inhibitor of the c-Met and ALK receptor tyrosine kinases. *Curr Opin Investig Drugs* 2010; 11: 1477–90.
3. Gadgeel SM, Bepler G. Crizotinib: an anaplastic lymphoma kinase inhibitor. *Future Oncol* 2011; 7: 947–53.

Administration in subsequent cycles. The oral dose of crizotinib may need to be reduced or therapy withheld if toxicities occur. Licensed product information gives the following guidelines:

for haematological toxicities

- grade 3: withhold until recovery $\leq$ grade 2, then resume at the same dose schedule
- grade 4: withhold until recovery $\leq$ grade 2, then resume at 200 mg twice daily; in the case of recurrence, withhold again until recovery $\leq$ grade 2, then resume at 250 mg once daily. For further grade 4 recurrence, permanently stop crizotinib

for non-haematological toxicities

- any grade pneumonitis (that is not due to disease progression, other pulmonary disease, infection, or effects of radiation): permanently stop crizotinib
- grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with total bilirubin $\leq$ grade 1: withhold until recovery to $\leq$ grade 1 or baseline, then resume at 200 mg twice daily; in the case of recurrence, withhold again until recovery $\leq$ grade 1, then resume at 250 mg once daily. For further grade 3 or 4 recurrence, permanently stop crizotinib
- grade 2, 3, or 4 ALT or AST elevation with concurrent grade 2, 3, or 4 total bilirubin elevation (without evidence of cholestasis or haemolysis): permanently stop crizotinib
- grade 3 QTc prolongation: withhold until recovery to $\leq$ grade 1, then resume at 200 mg twice daily; in the case of recurrence, withhold again until recovery $\leq$ grade 1, then resume at 250 mg once daily. For further grade 3 recurrence, permanently stop crizotinib
- grade 4 QTc prolongation: permanently stop crizotinib

Adverse Effects, Treatment, and Precautions

Crizotinib has been associated with severe pneumonitis and fatalities have been reported. Patients should be monitored for pulmonary symptoms and crizotinib should be permanently stopped in those diagnosed with treatment-related pneumonitis. Other respiratory adverse effects associated with fatalities have included hypoxia, acute respiratory distress syndrome, dyspnoea, empyema, and pulmonary haemorrhage. Pulmonary embolism can occur. Increases in liver transaminases have been seen, and liver function tests should be monitored monthly, or more frequently if needed. While most patients were asymptomatic, some may require dose interruption or for therapy to be permanently stopped. QTc prolongation can occur and crizotinib should be avoided in patients with congenital long QT syndrome. Monitoring (using ECGs and electrolyte concentrations) should be considered in those with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking drugs known to prolong the QT interval. Bradycardia can occur with crizotinib therapy. Severe neutropenia, thrombocytopenia, and lymphopenia have been reported and dose modifications may be needed. For details of dose delay, dose reductions, or stoppage of therapy for adverse effects, see Administration in Subsequent Cycles, above.

The most common adverse effects associated with crizotinib are visual disorders, gastrointestinal disturbances and oedema. Visual disorders include visual impairment, blurred vision, diplopia, photopsia, photophobia, and vitreous floaters; events have generally been reported within 2 weeks of starting crizotinib. Gastrointestinal disturbances include nausea, diarrhoea, vomiting, constipation, oesophageal disorders, abdominal pain, and stomatitis. Other common adverse effects include fatigue, decreased appetite, hypophosphataemia, dizziness, headache, dysgeusia, insomnia, upper respiratory-tract infection, dyspnoea, cough, arthralgia, and rash. Neuropathy is also common and can include burning sensations, dysaesthesia, hypoaesthesia or hyperaesthesia, neuralgia, and paraesthesia; peripheral neuropathy can be sensory or motor. Pain (in the chest or back) and fever can occur. Renal cysts without evidence of abnormal urinalysis or renal impairment, have been reported.

Interactions

Crizotinib is metabolised by cytochrome P450 isoenzyme CYP3A4/5. Strong CYP3A inhibitors (such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole) can increase crizotinib plasma concentrations and concomitant use should be avoided; grapefruit juice should also be avoided. Caution is advised with concomitant use of moderate CYP3A inhibitors. Strong CYP3A inducers (such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St John's Wort) can decrease crizotinib plasma concentration and concomitant use should be avoided. Crizotinib also inhibits CYP3A and dose reduction may be needed for drugs that are mainly metabolised by CYP3A. Use of crizotinib with CYP3A substrates with narrow therapeutic indices (such as alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be avoided.

Pharmacokinetics

Peak plasma concentrations occur between 4 to 6 hours after a single oral dose of crizotinib. Mean bioavailability is about 43%. Exposure is reduced by a high-fat meal; however, crizotinib can be given with or without food. Steady-state concentrations are reached within 15 days. Plasma protein binding is about 90%. *In-vitro* data suggest that crizotinib is a substrate for P-glycoprotein, tha

metabolism is mainly via the cytochrome P450 isoenzymes CYP3A4 and CYP3A5. The main metabolic pathways are oxidation (to crizotinib lactam) and *O*-dealkylation. The mean apparent plasma terminal half-life has been reported to be about 42 hours after a single dose of crizotinib. About 63% and 22% of a single dose is recovered in faeces and urine, respectively (of which unchanged drug is about 53% and 2.3%, respectively).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Xalkori; *Denm.*: Xalkori; *Fr.*: Xalkori; *Israel*: Xalkori; *Jpn*: Xalkori; *Neth.*: Xalkori; *Norw.*: Xalkori; *Switz.*: Xalkori; *UK*: Xalkori; *USA*: Xalkori.

Cyclophosphamide *(BAN, rINN)*

B-518; Ciclofosfamida; Ciklofosfamidas; Ciklofoszfamid; Cyclophosphamid; Cyclophosphamidum; Cyclophosphamidum Monohydricum; Cyclophosphanum; Cyklofosfamid; Cyklofosfamid monohydrát; NSC-26271; Siklofosfamid; Syklofosfamidi; WR-138719; Циклофосфамид.

2-[Bis(2-chloroethyl)amino]perhydro-1,3,2-oxazaphosphorinan 2-oxide monohydrate.

$C_7H_{15}Cl_2N_2O_2P,H_2O$=279.1

CAS — 6055-19-2 (cyclophosphamide monohydrate); 50-18-0 (anhydrous cyclophosphamide).

ATC — L01AA01.

ATC Vet — QL01AA01.

UNII — 8N3DW7272P (cyclophosphamide); 6UXW23996M (anhydrous cyclophosphamide).

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

Ph. Eur. 8: (Cyclophosphamide). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. A freshly prepared 2% solution in water has a pH of 4.0 to 6.0.

USP 36: (Cyclophosphamide). A white, crystalline powder. It liquefies upon loss of its water of crystallisation. Soluble in water and in alcohol. A 1% solution in water has a pH of 3.9 to 7.1 when determined 30 minutes after preparation. Store in airtight containers at 2 degrees to 30 degrees.

Uses and Administration

Cyclophosphamide is an antineoplastic that is converted in the body to active alkylating metabolites with properties similar to those of chlormethine (p. 765.2). It also possesses marked immunosuppressant properties.

Cyclophosphamide is widely used, often with other agents, in the treatment of malignant diseases. It is given for Burkitt's and other non-Hodgkin's lymphomas, multiple myeloma, and mycosis fungoides. It is also used in gestational trophoblastic tumours and malignancies of the brain, breast, endometrium, lung, and ovary; in childhood malignancies such as neuroblastoma, retinoblastoma, Wilms' tumour; and in sarcomas and some leukaemias.

The immunosuppressant properties of cyclophosphamide have been used in organ and tissue transplantation. It has also been used in the management of disorders thought to have an auto-immune component including amyloidosis, Behçet's syndrome, glomerular kidney disease, immune thrombocytopenia, aplastic anaemia, idiopathic pulmonary fibrosis, polymyositis, scleroderma, SLE, and vasculitic syndromes including the Churg-Strauss syndrome, polyarteritis nodosa, and Wegener's granulomatosis.

The use of cyclphosphamide is these disorders is further discussed under the headings below.

Cyclophosphamide is usually given orally or by intravenous injection.

In the BP 2014 the content of Cyclophosphamide Injection is expressed in terms of the equivalent amount of anhydrous cyclophosphamide whereas the content of Cyclophosphamide Tablets is given in terms of the monohydrate; the USP 36 expresses content in terms of anhydrous cyclophosphamide for both injection and tablets. Confusion has arisen when patients were changed from a preparation in which the content was expressed as the monohydrate to one in which it was expressed as the anhydrous substance (see Effects on the Bladder, p. 772.3). 53.45 mg of cyclophosphamide monohydrate is equivalent to 50 mg of anhydrous cyclophosphamide. *Doses below are given in terms of anhydrous cyclophosphamide.*

The dosage of cyclophosphamide given may vary considerably depending on the disease being treated, the condition of the patient including the state of the bone marrow, and use with radiotherapy or other chemotherapy. The white cell count is usually used to guide the dose. Every effort should be made to establish that the dose is appropriate according to the above factors. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

In the UK, examples of regimens given, generally without specific indications, in licensed product information are:

- *low-dose*: cyclophosphamide 2 to 6 mg/kg weekly as a single intravenous dose or in divided oral doses
- *moderate-dose*: 10 to 15 mg/kg weekly as a single intravenous dose.
- *high-dose*: 20 to 40 mg/kg as a single intravenous dose every 10 to 20 days, although higher doses have been used

Alternative regimens include:

- 100 to 300 mg daily in divided oral doses
- 50 to 250 mg/m² daily orally
- 80 to 300 mg/m² daily as a single intravenous dose, or daily in divided oral doses
- 300 to 600 mg/m² weekly as a single intravenous dose
- 600 to 1500 mg/m² as a single intravenous dose or short infusion at 10- to 20-day intervals

Alternative regimens used in some other European countries include:

- 3 to 6 mg/kg (about 120 to 240 mg/m²) daily intravenously
- 10 to 15 mg/kg (about 400 to 600 mg/m²) every 2 to 5 days intravenously

In the UK, the use of mesna is generally recommended with single doses of cyclophosphamide over 2 g, but it is used with cyclophosphamide doses as low as 10 mg/kg in some countries.

In the USA, an initial dose of 40 to 50 mg/kg has been licensed for single agent therapy of malignancy, given intravenously in divided doses over 2 to 5 days although in practice treatment of malignancy will generally be with combination regimens. Other licensed regimens include:

- 3 to 5 mg/kg twice weekly intravenously
- 10 to 15 mg/kg every 7 to 10 days intravenously
- 1 to 5 mg/kg daily orally

In patients who are to undergo haematopoietic stem cell transplantation, intravenous doses of 20 to 40 mg/kg (about 800 to 1600 mg/m²) and higher are given, at intervals of 21 to 28 days. Alternatively, very high doses of cyclophosphamide such as 60 mg/kg daily for 2 days may be given as part of the conditioning regimen.

Cyclophosphamide has also been given intramuscularly, intraperitoneally, and intrapleurally, as well as intra-arterially, and by local perfusion (but passage through the liver is required for its activation—see Pharmacokinetics, p. 774.1). A liquid preparation of cyclophosphamide for oral use may be prepared using the powder for injection.

Regular blood counts are essential during therapy with cyclophosphamide and treatment should be withdrawn or delayed if leucopenia or thrombocytopenia becomes severe (see also Bone-marrow Depression, p. 730.3). Patients should be adequately hydrated and urine output maintained.

Administration in the elderly. Despite some suggestion that cyclophosphamide metabolism may be slower in the elderly, there appear to be no pharmacokinetic differences based on age alone. A review concluded that healthy older patients should not be denied adjuvant chemotherapy on an age basis, and that there is no solid evidence for dose reduction of cyclophosphamide based on age alone.[1]

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25**: 1832–43.

Amyloidosis. Although there is no unequivocally effective treatment for amyloidosis (p. 819.3), cyclophosphamide may reduce the decline in renal function and prolong survival;[1-3] it has also been used with epirubicin and carmustine to suppress the disease in a patient who had undergone heart transplantation for cardiac amyloid.[4] Good responses have also been reported to cyclophosphamide given in a regimen with thalidomide and dexamethasone.[5]

1. Berglund K, *et al.* Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease. *Ann Rheum Dis* 1987; **46**: 757–62.
2. Berglund K, *et al.* Results, principles and pitfalls in the management of renal AA-amyloidosis: a 10-21 year followup of 16 patients with rheumatic disease treated with alkylating cytostatics. *J Rheumatol* 1993; **20**: 2051–7.
3. Chevret G, *et al.* Renal type AA amyloidosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide. *Rheumatology (Oxford)* 2001; **40**: 821–5.
4. Hall R, *et al.* Cardiac transplantation for AL amyloidosis. *BMJ* 1994; **309**: 1135–7.
5. Wechalekar AD, *et al.* Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; **109**: 457–64.

Blood disorders, non-malignant. Cyclophosphamide has been used in patients with immune thrombocytopenia (p. 1606.1), but cytotoxic immunosuppressants tend to be a second-line treatment option. Responses generally occur within 8 weeks.[1] In patients with refractory life-threatening disease, high-dose cyclophosphamide[1] may be tried. Combination chemotherapy including cyclophosphamide has also produced responses in a few patients.[2]

In the management of warm auto-immune haemolytic anaemia (p. 1122.2) low-dose cyclophosphamide may be used in patients refractory to corticosteroids and splenectomy. A small number of patients with severe refractory disease have been treated with high-dose cyclophosphamide with some success.[3]

Cyclophosphamide is often used in preparation for bone marrow transplantation in patients with aplastic anaemia (p. 1121.3), and complete remission has also been reported with high-dose cyclophosphamide alone.[4,5] However, a randomised study[6] of high-dose cyclophosphamide plus ciclosporin compared with conventional immunosuppression was stopped early when a higher mortality was seen in those given cyclophosphamide. Further follow-up[7] also found that relapse rates were no different.

Cyclophosphamide with a corticosteroid has been tried in the rare condition of acquired haemophilia (p. 1126.3).

1. McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997; **126**: 307–14.
2. Figueroa M, *et al.* Combination chemotherapy in refractory immune thrombocytopenic purpura. *N Engl J Med* 1993; **328**: 1226–9.
3. Moyo VM, *et al.* High-dose cyclophosphamide for refractory autoimmune hemolytic anemia. *Blood* 2002; **100**: 704–6.
4. Brodsky RA, *et al.* Durable treatment-free remission after high-dose cyclophosphamide therapy for previously untreated severe aplastic anemia. *Ann Intern Med* 2001; **135**: 477–83.
5. Savage WJ, *et al.* Treatment of hepatitis-associated aplastic anemia with high-dose cyclophosphamide. *Pediatr Blood Cancer* 2007; **49**: 947–51.
6. Tisdale JF, *et al.* High-dose cyclophosphamide in severe aplastic anaemia: a randomised trial. *Lancet* 2000; **356**: 1554–9.
7. Tisdale JF, *et al.* Late complications following treatment for severe aplastic anemia (SAA) with high-dose cyclophosphamide (Cy): follow-up of a randomized trial. *Blood* 2002; **100**: 4668–70.

Cogan's syndrome. For reference to the use of cyclophosphamide with corticosteroids for Cogan's syndrome, see p. 1603.2.

Connective tissue and muscular disorders. Cyclophosphamide is one of several immunosuppressants that have been tried for disease control in Behçet's syndrome (p. 1601.1); such drugs may permit a reduction in the use of corticosteroids, although they carry their own risks of toxicity. In polymyositis (p. 1611.1) cyclophosphamide may have a role where there is lung disease; the role of immunosuppressants other than azathioprine or methotrexate is poorly defined. In patients with SLE (p. 1613.3), cyclophosphamide has been used with some success for severe disease or disease refractory to corticosteroids alone, and appears to be more effective than corticosteroids for lupus nephritis; the evidence for its use has been critically assessed.[1,2]

1. Houssiau F. Thirty years of cyclophosphamide: assessing the evidence. *Lupus* 2007; **16**: 212–16.
2. Bargman JM. How did cyclophosphamide become the drug of choice for lupus nephritis? *Nephrol Dial Transplant* 2009; **24**: 381–4.

Kidney disorders, non-malignant. Cyclophosphamide is used with corticosteroids in the treatment of some forms of glomerular kidney disease (p. 1604.3). In children with nephrotic syndrome, oral cyclophosphamide 2 to 3 mg/kg daily for 8 weeks may be added to a course of corticosteroid therapy in relapsing disease; intravenous cyclophosphamide 500 mg/m² monthly for 6 months also substantially reduces the risk of relapse.[1] Addition of cyclophosphamide to corticosteroid therapy also improves the prospect of remission in focal glomerulosclerosis. Oral cyclophosphamide helps to stabilise progressive disease in patients with membranous nephropathy[2] although intermittent intravenous pulses are reported to be ineffective.[3] Such treatment is usually reserved for those whose disease is severe and progressive enough to justify it, but is probably better tolerated than other alkylating agents such as chlorambucil.[4] Cyclophosphamide has been given with methylprednisolone for rapidly progressive glomerulonephritis,[5] and has been used as part of the aggressive management of renal lesions in Goodpasture's syndrome. A systematic review[6] concluded that pulse cyclophosphamide, which allows for a reduced dose, results in good remission rates in rapidly progressive glomerulonephritis, but has an increased risk of relapse when compared with continuous use.

1. Hodson EM *et al.* Non-corticosteroid treatment for nephrotic syndrome in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 20/07/10).
2. Falk RJ, *et al.* Treatment of progressive membranous glomerulopathy: a randomized trial comparing cyclophosphamide and corticosteroids with corticosteroids alone. *Ann Intern Med* 1992; **116**: 438–45.
3. Reichert LJM, *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; **121**: 328–33.
4. Schieppati A, *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 22/07/09).
5. Bruns FJ, *et al.* Long-term follow-up of aggressively treated idiopathic rapidly progressive glomerulonephritis. *Am J Med* 1989; **86**: 400–6.
6. Walters G, *et al.* Interventions for renal vasculitis in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 22/07/09).

Liver disorders, non-malignant. For mention of the use of cyclophosphamide in auto-immune hepatitis inadequately

controlled by corticosteroids and azathioprine see Chronic Active Hepatitis, p. 1602.3.

Lung disorders, non-malignant. Cyclophosphamide has been used with corticosteroids in patients with idiopathic pulmonary fibrosis as mentioned under Interstitial Lung Disease, p. 1607.1.

Malignant neoplasms. Cyclophosphamide is one of the most widely used drugs for the chemotherapy of malignancy, and mention of its role may be found in the discussions of the management of gestational trophoblastic tumours (p. 691.2); the non-Hodgkin's lymphomas, including AIDS-related lymphoma, Burkitt's lymphoma, and mycosis fungoides (p. 696.3, p. 697.2, p. 697.3, p. 698.3); malignancies of the brain (p. 701.2), breast (p. 702.1), lung (p. 710.2), ovary (p. 711.2) and thymus (p. 715.3); multiple myeloma (p. 699.2); Wilms' tumour, neuroblastoma, and retinoblastoma (p. 709.1, p. 716.2, and p. 717.2 respectively); and sarcomas of bone (p. 717.3) and rhabdomyosarcoma (see Soft-tissue Sarcoma, p. 718.2). Cyclophosphamide is also used in the management of acute lymphoblastic leukaemia (p. 692.3) and chronic lymphocytic leukaemia (p. 693.3).

Neuromuscular disorders. Cyclophosphamide has been tried in myasthenia gravis (p. 684.1) in patients who require immunosuppressants but are intolerant of or unresponsive to corticosteroids and azathioprine. Cyclophosphamide has also been tried in regimens for the management of multiple sclerosis (p. 996.3), but the reported benefits have generally been slight and outweighed by toxicity, such that it is usually reserved for patients with severe disease resistant to standard therapies.

References.

1. De Feo LG, *et al.* Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. *Muscle Nerve* 2002; 26: 31–6.
2. Drachman DB, *et al.* Treatment of refractory myasthenia: 'rebooting' with high-dose cyclophosphamide. *Ann Neurol* 2003; 53: 29–34.
3. Portaccio E, *et al.* Safety and tolerability of cyclophosphamide 'pulses' in multiple sclerosis: a prospective study in a clinical cohort. *Multiple Sclerosis* 2003; 9: 446–50.
4. Zephir H, *et al.* Treatment of progressive forms of multiple sclerosis by cyclophosphamide: a cohort study of 490 patients. *J Neurol Sci* 2004; 218: 73–7.
5. La Mantia L, *et al.* Cyclophosphamide for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Ocular disorders, non-malignant. Immunosuppressive agents, including cyclophosphamide, have been used in scleritis and uveitis (see p. 1612.3 and p. 1615.1) unresponsive to corticosteroids in tolerable doses.

Organ and tissue transplantation. Cyclophosphamide is used in high doses, usually with busulfan or irradiation, in conditioning regimens for bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1937.1). It has been tried as part of immunosuppressant regimens after transplantation of heart grafts (p. 1938.2).

Paraquat poisoning. For reference to the use of cyclophosphamide in paraquat poisoning, see p. 2159.2.

Pemphigus and pemphigoid. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p. 1687.1). Immunosuppressive therapy, including cyclophosphamide,[1,2] has been used with corticosteroids to permit a reduction in corticosteroid dosage. Cyclophosphamide with a corticosteroid is also reported to be of value in ocular mucous membrane pemphigoid,[3] although treatment may not completely prevent cicatrisation.[4] Oral cyclophosphamide is considered an alternative to azathioprine in pemphigus vulgaris and pulsed intravenous doses might be considered in severe or recalcitrant cases.[5] There is less support for cyclophosphamide in bullous pemphigoid and it should only be considered if other treatments have failed or are contra-indicated.[6] However, oral or intravenous cyclophosphamide with corticosteroids may be considered for first-line treatment of severe or rapidly progressive mucous membrane pemphigoid.[7]

1. Pandya AG, Sontheimer RD. Treatment of pemphigus vulgaris with pulse intravenous cyclophosphamide. *Arch Dermatol* 1992; 128: 1626–30.
2. Itoh T, *et al.* Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. *Br J Dermatol* 1996; 134: 931–3.
3. Kirtschig G, *et al.* Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol* 2002; 138: 380–4.
4. Elder MJ, *et al.* Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* 1995; 79: 264–6.
5. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; 149: 926–37. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Pemphigus%20Vulgaris.pdf (accessed 20/07/10)
6. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; 147: 214–21. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Bullous%20Pemphigoid.pdf (accessed 20/07/10)
7. Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol* 2005; 6: 93–103.

Retroperitoneal fibrosis. There are reports[1,2] of success with cyclophosphamide, with or without corticosteroids, in the treatment of retroperitoneal fibrosis (p. 1612.1). In one study,[2] severe or refractory disease was treated with monthly intravenous pulses of cyclophosphamide 15 mg/kg, for 6 months, followed by azathioprine; all patients went into remission.

1. Fukuda W, *et al.* Multifocal fibrosclerosis: retroperitoneal fibrosis associated with a suprasellar tumor and pachymeningitis. *Intern Med* 2003; 42: 1006–10.
2. Warnatz K, *et al.* Immunosuppressive treatment of chronic periaortitis: a retrospective study of 20 patients with chronic periaortitis and a review of the literature. *Ann Rheum Dis* 2005; 64: 828–33.

Rheumatoid arthritis. Cyclophosphamide has been used as a disease-modifying antirheumatic drug in rheumatoid arthritis (p. 13.2), usually in patients with severe disease unresponsive to other drugs; its severe toxicity limits its usefulness.[1] It is of most value in controlling antibody-mediated systemic complications of the disease such as vasculitis[2] through inhibition of B-cell function.

1. Suarez-Almazor ME, *et al.* Cyclophosphamide for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 12/05/05).
2. Choy E, Kingsley G. How do second-line agents work? *Br Med Bull* 1995; 51: 472–92.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p. 1612.2), corticosteroids are the usual treatment. Cyclophosphamide is one of several cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy; its use has been limited by toxicity.

Scleroderma. As discussed on p. 1942.3 the role of drug treatment for scleroderma is not well determined, and it is unclear whether cyclophosphamide (with or without a corticosteroid) is useful for patients with lung involvement.

Vasculitic syndromes. Treatment of the systemic vasculitides has revolved around the use of corticosteroids and cyclophosphamide. The benefits are uncertain in polyarteritis nodosa (p. 1610.2) and Takayasu's arteritis (p. 1614.3), but the benefits of combined therapy are generally accepted in Churg-Strauss syndrome (p. 1603.1) and microscopic polyangiitis (p. 1610.2), and cyclophosphamide is the mainstay of effective treatment of Wegener's granulomatosis (p. 1615.2). Several cyclophosphamide regimens are used, with no major differences reported in outcome.[1] A pulsed regimen (intermittent high-dose intravenous therapy) was found to be as effective in antineutrophil cytoplasmic antibody-associated vasculitis as an oral daily regimen; pulsed therapy allowed for a reduced cumulative cyclophosphamide dose and caused fewer adverse effects.[2]

1. Richmond R, *et al.* Optimisation of cyclophosphamide therapy in systemic vasculitis. *Clin Pharmacokinet* 1998; 34: 79–90.
2. de Groot K, *et al.* EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670–80.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p. 726.1 and p. 730.2. The major dose-limiting effect is myelosuppression. After single doses the nadir of the white cell count may occur in around 1 to 2 weeks with full recovery usually in 3 to 4 weeks. Thrombocytopenia and anaemia may occur but tend to be less common and less severe.

Haemorrhagic cystitis may develop after high or prolonged dosage, and can be life-threatening. Adequate hydration to maintain urine output at 100 mL/hour and use of mesna (see p. 1557.2) are generally recommended in an attempt to reduce urotoxicity. If mesna is used, frequent emptying of the bladder should be avoided. Doses of cyclophosphamide should be given early in the day.

Alopecia occurs in about 20% of patients given low doses and in practically all patients given high doses. Hair loss starts after 3 weeks of treatment but regrowth is usually evident after 3 months, even with continued treatment. Hyperpigmentation of skin, especially that of the palms and soles, and of the nails, has been reported.

Nausea and vomiting commonly occur, and may be reduced by prophylactic antiemetics. Mucositis may also occur.

Other adverse effects include a syndrome resembling inappropriate secretion of antidiuretic hormone (which may require diuretic therapy), disturbances of carbohydrate metabolism, gonadal suppression (common and occasionally resulting in sterility), interstitial pulmonary fibrosis, and, especially at high doses, cardiotoxicity.

Cyclophosphamide, in common with other alkylating agents, has carcinogenic, mutagenic, and teratogenic potential and secondary malignancies have occurred in patients given previous antineoplastic therapy including cyclophosphamide—see p. 726.2.

Effects on the bladder. *Sterile haemorrhagic cystitis* (p. 2347.3) can occur after high-dose infusions of cyclophosphamide or after prolonged low-dose oral use.[1-4] It is believed to be secondary to renal excretion of alkylating metabolites, particularly the acrolein metabolite, that cause sloughing, thinning, and inflammation of the bladder wall. Damage ranges from minor bleeding to diffuse necrotic ulceration, and can lead to anaemia, constriction of the bladder, bladder perforation, and death.[2] Symptoms may be delayed, and have been reported to occur up to 6 months after stopping the drug.[3] An increased incidence of cystitis when patients on a high-dose cyclophosphamide regimen were transferred from one brand to another has been reported,[4] apparently because one was labelled in terms of the anhydrous substance and one as the monohydrate, resulting in a 6.4% difference in the content of active substance.[7]

Measures used to prevent haemorrhagic cystitis include intravenous hydration with diuresis, frequent voiding, or bladder catheterisation with irrigation, to increase urine output and dilute the excreted metabolites. Mesna may be used as a uroprotectant to reduce exposure to the metabolites.[2-4] If bleeding occurs, various drugs have been instilled intravesically, including sodium chloride 0.9%, alum, or prostaglandins.[2,3,8-11] Silver nitrate, formaldehyde, or phenol instillations have been used but are painful and patients require anaesthesia.[2] There is limited information to suggest that conjugated oestrogens given orally or intravenously may be effective;[2,12] oral pentosan polysulfate sodium may also be of benefit.[3] Nonpharmacological techniques are reserved for refractory cases and include arterial embolisation or surgery.[2]

In addition to the shorter term effects, cyclophosphamide has been reported to be associated with the development of *bladder carcinoma*.[1,4,13-16] A history of cyclophosphamide-induced cystitis may be associated with an increased risk of bladder carcinoma[1,4,13] but some studies have not found a link,[15] and bladder malignancies can develop in patients who have not experienced cystitis while receiving cyclophosphamide.[14] For a discussion of the carcinogenic effects of antineoplastics, including cyclophosphamide, see p. 726.2.

1. Talar-Williams C, *et al.* Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; 124: 477–84.
2. West NJ. Prevention and treatment of hemorrhagic cystitis. *Pharmacotherapy* 1997; 17: 696–706.
3. Mukhtar S, Woodhouse C. The management of cyclophosphamide-induced haematuria. *BJU Int* 2010; 105: 908–12.
4. Monach PA, *et al.* Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. *Arthritis Rheum* 2010; 62: 9–21.
5. Armstrong B, *et al.* Delayed cystitis due to cyclophosphamide. *N Engl J Med* 1979; 300: 45.
6. Shaw IC, *et al.* Difference in bioactivity between two preparations of cyclophosphamide. *Lancet* 1983; I: 709.
7. Hilgard P, *et al.* Bioactivity of cyclophosphamide preparations. *Lancet* 1983; I: 1436.
8. Mohiuddin J, *et al.* Treatment of cyclophosphamide-induced cystitis with prostaglandin E_2. *Ann Intern Med* 1984; 101: 142.
9. Miller LJ, *et al.* Treatment of cyclophosphamide-induced hemorrhagic cystitis with prostaglandins. *Ann Pharmacother* 1994; 28: 590–4.
10. Ippoliti C, *et al.* Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; 46: 811–15.
11. Laszlo D, *et al.* Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. *Haematologica* 1995; 80: 421–5.
12. Ordemann R, *et al.* Encouraging results in the treatment of haemorrhagic cystitis with estrogen – report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; 25: 981–5.
13. Wall RL, Clausen KP. Carcinoma of the urinary bladder in patients receiving cyclophosphamide. *N Engl J Med* 1975; 293: 271–3.
14. Plotz PH, *et al.* Bladder complications in patients receiving cyclophosphamide for systemic lupus erythematosus or rheumatoid arthritis. *Ann Intern Med* 1979; 91: 221–3.
15. Pedersen-Bjergaard J, *et al.* Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N Engl J Med* 1988; 318: 1028–32.
16. Travis LB, *et al.* Bladder cancer after chemotherapy for non-Hodgkin's lymphoma. *N Engl J Med* 1989; 321: 544–5.

Effects on the blood. Amifostine has been reported to protect against the myelosuppressive effects of cyclophosphamide, and may be used to reduce neutropenia-related infection associated with the combination of cyclophosphamide and cisplatin (see p. 1539.2).

Effects on carbohydrate metabolism. Acute onset type 1 diabetes occurred in a patient treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), and was thought to be due to the cyclophosphamide.[1]

1. Atlan-Gepner C, *et al.* A cyclophosphamide-induced autoimmune diabetes. *Lancet* 1998; 352: 373–4.

Effects on electrolytes. Water intoxication has been reported with cyclophosphamide,[1-4] usually in high doses (30 to 50 mg/kg or more) although symptoms have been reported after a dose of 20 mg/kg in a patient with renal disease,[5] and in another patient with SLE but apparently

normal renal function who received 10 mg/kg.[4] One case of severe hyponatraemia leading to convulsions and death has been reported.[5] Symptoms resemble the syndrome of inappropriate antidiuretic hormone secretion[5] but plasma concentrations of antidiuretic hormone do not appear to be raised in these patients.[3]

1. DeFronzo RA, *et al.* Water intoxication in man after cyclophosphamide therapy: time course and relation to drug activation. *Ann Intern Med* 1973; 78: 861–9.
2. Green TP, Mirkin BL. Prevention of cyclophosphamide-induced antidiuresis by furosemide infusion. *Clin Pharmacol Ther* 1981; 29: 634–42.
3. Bressler RB, Huston DP. Water intoxication following moderate-dose intravenous cyclophosphamide. *Arch Intern Med* 1985; 145: 548–9.
4. McCarron MO, *et al.* Water intoxication after low dose cyclophosphamide. *BMJ* 1995; 311: 292.
5. Harlow PJ, *et al.* A fatal case of inappropriate ADH secretion induced by cyclophosphamide therapy. *Cancer* 1979; 44: 896–8.

Effects on the eyes. Recurrent transient myopia, apparently due to increased hydration of the lens of the eye, was induced by an intravenous bolus of cyclophosphamide in an adolescent with SLE.[1]

CMV retinitis has occurred in patients during or after cyclophosphamide therapy; presenting symptoms included floaters and blurred or decreased vision.[2]

1. Arranz JA, *et al.* Cyclophosphamide-induced myopia. *Ann Intern Med* 1992; 116: 92–3.
2. Agrawal A, *et al.* Visual symptoms in patients on cyclophosphamide may herald sight threatening disease. *Br J Ophthalmol* 2003; 87: 122–3.

Effects on reproductive potential. Severe gonadal failure with transient or permanent azoospermia is common in men treated with cyclophosphamide. Suppression of germ-cell function with intramuscular testosterone in 5 men during cyclophosphamide therapy for nephrotic syndrome was associated with a more rapid return of spermatogenesis compared with 10 patients not given the androgen.[1] Others have also suggested that gonadal suppression using testosterone in men, and triptorelin in women, has some benefit in protecting against cyclophosphamide-induced damage.[2]

1. Masala A, *et al.* Use of testosterone to prevent cyclophosphamide-induced azoospermia. *Ann Intern Med* 1997; 126: 292–5.
2. Cigni A, *et al.* Hormonal strategies for fertility preservation in patients receiving cyclophosphamide to treat glomerulonephritis: a nonrandomized trial and review of the literature. *Am J Kidney Dis* 2008; 52: 887–96.

Effects on the skin. An erythematous pruritic rash, similar to the palmar-plantar erythrodysesthesia syndrome (p. 730.1) but occurring on the dorsal surfaces of the hands and feet, occurred 6 days after the first high dose of cyclophosphamide in a patient being prepared for bone marrow transplantation.[1] Previous cyclophosphamide-containing chemotherapy did not produce this reaction. The symptoms improved somewhat on treatment with triamcinolone ointment, and subsequently desquamation of the hands occurred with decreased purplish discoloration and oedema of the feet. There has also been a report of 2 patients who developed Stevens-Johnson syndrome, with some features suggestive of overlapping toxic epidermal necrolysis.[2]

For reports of subacute cutaneous lupus erythematosus after treatment with cyclophosphamide plus doxorubicin, see Effects on the Skin and Nails, under Doxorubicin, p. 784.3.

1. Matsuyama JR, Kwok KK. A variant of the chemotherapy-associated erythrodysesthesia syndrome related to high-dose cyclophosphamide. *DICP Ann Pharmacother* 1989; 23: 776–9.
2. Assier-Bonnet H, *et al.* Stevens-Johnson syndrome induced by cyclophosphamide: report of two cases. *Br J Dermatol* 1996; 135: 864–6.

Hypersensitivity. Occasional anaphylaxis has been reported with cyclophosphamide;[1] analysis of data by the Boston Collaborative Drug Surveillance Program detected only one allergic skin reaction among 210 patients given cyclophosphamide, resulting in a calculated incidence of 4.8 reactions per 1000 recipients.[2]

1. Jones JB, *et al.* Cyclophosphamide anaphylaxis. *DICP Ann Pharmacother* 1989; 23: 88–9.
2. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; 256: 3358–63.

Precautions

For reference to the precautions necessary with antineoplastics, see p. 732.2.

Cyclophosphamide should not be given to patients with bone-marrow aplasia, acute infection, or drug- or radiation-induced urothelial toxicity. It should be given with care to those with diabetes mellitus. Care is also needed in elderly or debilitated patients, or those with renal or hepatic impairment or who have undergone adrenalectomy. Liberal fluid intake and frequent micturition are advised to reduce the risk of cystitis but care must be taken to avoid water retention and intoxication. Urine should be examined regularly for red cells, which may precede haemorrhagic cystitis. The haematological profile should be monitored regularly.

The use of cyclophosphamide in pregnancy should be avoided where possible.

Breast feeding. Cyclophosphamide has been detected in breast milk,[1] and there are reports of neutropenia,[2] and leucopenia and thrombocytopenia,[3] in infants who have been breast fed by women receiving cyclophosphamide. The American Academy of Pediatrics considers[4] that cyclophosphamide may interfere with cellular metabolism, causing neutropenia and possibly immune suppression in the infant, and has unknown effects on growth, and an association with carcinogenesis.

1. Wiernik PH, Duncan JH. Cyclophosphamide in human milk. *Lancet* 1971; 1: 912.
2. Amato D, Niblett JS. Neutropenia from cyclophosphamide in breast milk. *Med J Aust* 1977; 1: 383–4.
3. Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. *J Natl Med Assoc* 1979; 71: 165–6.
4. 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 29/06/04)

Handling and disposal. *Residues* of cyclophosphamide or ifosfamide destroyed using alkaline hydrolysis in the presence of dimethylformamide showed no mutagenicity *in vitro*.[1] An alternative method, involving refluxing of cyclophosphamide with hydrochloric acid, neutralising, and then reacting with sodium thiosulfate, was effective for the degradation of cyclophosphamide, but residues from ifosfamide were still highly mutagenic *in vitro* and this second method should therefore not be used to degrade ifosfamide.

Urine and faeces produced for up to 72 hours and 5 days respectively after an oral dose of cyclophosphamide should be handled wearing protective clothing.[2] As cyclophosphamide was present in sweat and saliva, protective clothing was advised for 72 hours after a dose when bathing the patient or carrying out oral procedures.

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications* 73. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cyclophosphamide 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 28/09/11)

Pregnancy. For a report of a healthy infant born to a woman treated with a cyclophosphamide-containing regimen, see Pregnancy, under Teniposide, p. 867.2.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Since cyclophosphamide must undergo hepatic metabolism before it is active, interactions are possible with drugs that inhibit or stimulate the mixed function oxidase enzymes responsible. There may be an increased risk of cardiotoxicity in patients who have also received doxorubicin or other cardiotoxic drugs.

Allopurinol. Although the Boston Collaborative Drug Surveillance Program reported an increased incidence of bone-marrow depression in patients given allopurinol with cyclophosphamide than in those given cyclophosphamide without allopurinol (15 of 26 compared with only 6 of 32),[1] a subsequent study in patients given combination chemotherapy, including cyclophosphamide, for lymphomas failed to find any difference in the nadirs of the platelet and white blood cell counts in cycles in which allopurinol was given.[2] Although allopurinol pretreatment in 4 patients resulted in a longer cyclophosphamide half-life in a study in 26 patients given cyclophosphamide, urinary excretion of cyclophosphamide was unchanged.[3] A longer cyclophosphamide half-life was also seen in a study in children given allopurinol.[4]

1. Boston Collaborative Drug Surveillance Program. Allopurinol and cytotoxic drugs: interaction in relation to bone marrow depression. *JAMA* 1974; 227: 1036–40.
2. Stolbach L, *et al.* Evaluation of bone marrow toxic reaction in patients treated with allopurinol. *JAMA* 1982; 247: 334–6.
3. Bagley CM, *et al.* Clinical pharmacology of cyclophosphamide. *Cancer Res* 1973; 33: 226–33.
4. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; 41: 13–19.

Antibacterials. *Chloramphenicol* given before cyclophosphamide prolonged the mean cyclophosphamide serum half-life from 7.5 to 11.5 hours and reduced the peak activity in all of 5 subjects.[1] Giving *sulfaphenazole* before cyclophosphamide significantly inhibited the rate of biotransformation of cyclophosphamide in 2 of 7 subjects and enhanced it in 2; it remained unchanged in 3. A study in patients with non-Hodgkin's lymphoma found that giving *ciprofloxacin* before cyclophosphamide affected pharmacokinetic parameters of cyclophosphamide. The area under the concentration-time curve (AUC) of cyclophosphamide was increased and clearance was lower; AUC of the active metabolite of cyclophosphamide, 4-hydroxycyclophosphamide, was decreased and clearance increased.[2]

1. Faber OK, *et al.* The effect of chloramphenicol and sulphaphenazole on the biotransformation of cyclophosphamide in man. *Br J Clin Pharmacol* 1975; 2: 281–5.
2. Afsharian P, *et al.* The effect of ciprofloxacin on cyclophosphamide pharmacokinetics in patients with non-Hodgkin lymphoma. *Eur J Haematol* 2005; 75: 206–11.

Anticoagulants. For reference to the interaction of cyclophosphamide with *warfarin*, see p. 1532.2.

Antifungals. Analysis of cyclophosphamide metabolism in patients enrolled in a study comparing itraconazole with fluconazole found that those given itraconazole had higher exposure to toxic metabolites of cyclophosphamide. Both the antifungals appeared to alter cyclophosphamide metabolism and the authors cautioned against use of azole antifungals with antineoplastics that are metabolised via cytochrome P450 isoenzymes.[1]

1. Marr KA, *et al.* Cyclophosphamide metabolism is affected by azole antifungals. *Blood* 2004; 103: 1557–9.

Barbiturates. Although patients receiving cyclophosphamide developed higher peak plasma concentrations of active cyclophosphamide metabolites when given enzyme-inducing agents such as barbiturates, the active metabolites also disappeared rapidly.[1]

1. Bagley CM, *et al.* Clinical pharmacology of cyclophosphamide. *Cancer Res* 1973; 33: 226–33.

Chlorpromazine. The half-life of cyclophosphamide was about 200% greater in 2 children also taking chlorpromazine than in children not given the phenothiazine.[1]

1. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; 41: 13–19.

Ciclosporin. For reference to the effect of cyclophosphamide on ciclosporin concentrations, see Interactions, Antineoplastics, p. 1957.2.

Colony-stimulating factors. Fatal respiratory insufficiency associated with alveolar fibrosis developed in an infant given cyclophosphamide and doxorubicin followed by *filgrastim*.[1] Since pulmonary toxicity with cyclophosphamide is normally associated with high cumulative doses it was suggested that in this case the effects might have been exacerbated by the granulocyte colony-stimulating factor. (The pulmonary toxicity of bleomycin has also been suggested to be exacerbated by colony-stimulating factors, as discussed on p. 751.3).

1. van Woensel JBM, *et al.* Acute respiratory insufficiency during doxorubicin, cyclophosphamide, and G-CSF therapy. *Lancet* 1994; 344: 759–60.

Corticosteroids. Single doses of *prednisone* have been found to inhibit the activation of cyclophosphamide but after longer-term treatment the rate of activation has increased.[1] A study in children found that pretreatment with *dexamethasone* was associated with increased clearance of cyclophosphamide and a decrease in its half-life relative to children not given the corticosteroid.[2]

1. Faber OK, Mouridsen HT. Cyclophosphamide activation and corticosteroids. *N Engl J Med* 1974; 291: 211.
2. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; 41: 13–19.

Gastrointestinal drugs. In a retrospective study in patients receiving high-dose cyclophosphamide, cisplatin, and carmustine,[1] the area under the plasma-concentration time curve (AUC) for cyclophosphamide (measured as the parent compound) was 17% lower when *ondansetron* rather than prochlorperazine was added to the antiemetic regimen. In addition, the AUC for cisplatin was 10% higher with the ondansetron regimen. In a similar study,[2] the AUCs for both cyclophosphamide and cisplatin were lower in patients receiving an antiemetic regimen including ondansetron rather than prochlorperazine. The authors of both studies noted that the relevance of these findings to toxicity and antitumour effect of the antineoplastics remained to be determined.

1. Gilbert CJ, *et al.* Pharmacokinetic interaction between ondansetron and cyclophosphamide during high-dose chemotherapy for breast cancer. *Cancer Chemother Pharmacol* 1998; 42: 497–503.
2. Cagnoni PJ, *et al.* Modification of the pharmacokinetics of high-dose cyclophosphamide and cisplatin by antiemetics. *Bone Marrow Transplant* 1999; 24: 1–4.

NSAIDs. Acute life-threatening water intoxication was reported in a patient given low-dose cyclophosphamide with *indometacin*.[1] The patient had previously received

treatment with cyclophosphamide (for multiple myeloma) without significant adverse effect.

1. Webberley MJ, Murray JA. Life-threatening acute hyponatraemia induced by low dose cyclophosphamide and indomethacin. *Postgrad Med J* 1989; 65: 950–2.

Suxamethonium. For reference to a possible interaction between cyclophosphamide and suxamethonium, see under Suxamethonium Chloride, p. 2039.3.

Pharmacokinetics

After oral doses, cyclophosphamide is well absorbed from the gastrointestinal tract with a bioavailability greater than 75%. It is widely distributed in the tissues and crosses the blood-brain barrier. It undergoes activation by various cytochrome P450 isoenzymes (notably CYP2B6) in the liver. The initial metabolites are 4-hydroxycyclophosphamide and its acyclic tautomer, aldophosphamide, which both undergo further metabolism; aldophosphamide may undergo non-enzymatic conversion to active phosphoramide mustard. Acrolein is also produced and may be responsible for bladder toxicity. Cyclophosphamide is excreted principally in urine, as metabolites and some unchanged drug. It crosses the placenta, and is found in breast milk.

Reviews.

1. Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; 38: 291–304.
2. de Jonge ME, *et al.* Clinical pharmacokinetics of cyclophosphamide. *Clin Pharmacokinet* 2005; 44: 1135–64.

Absorption. Cyclophosphamide was detected in the urine of 5 patients after application to intact skin, showing that cyclophosphamide can be absorbed via this route.[1] Absorption continued after the site of application had been cleaned, suggesting that cyclophosphamide had penetrated subcutaneous lipid and was slowly released to the circulation from this depot. Cyclophosphamide was also identified in the urine of 2 oncology nurses but appeared more quickly than in patients, suggesting a faster route of absorption, perhaps by inhalation of aerosols generated during dissolution of the drug.

1. Hirst M, *et al.* Occupational exposure to cyclophosphamide. *Lancet* 1984; i: 186–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ciclokebir; *Austral.*: Cyclo-blastin; Endoxan; *Austria*: Endoxan; *Belg.*: Endoxan; *Braz.*: Evocicio; Genuxal; *Canad.*: Cytoxan†; Procytox; *Chile*: Endoxan; Ledoxina; *China*: Endoxan (安道生); *Cz.*: Endoxan; *Denm.*: Sendoxan; *Fin.*: Sendoxan; *Fr.*: Endoxan; *Ger.*: Endoxan; *Gr.*: Cyclolest; Endoxan; *Hong Kong*: Cycram; Endoxan; *Hung.*: Cytoxan†; Endoxan; *India*: Cycloxan; Cycrame; Cydoxan; Cyphos; Eldamide; Endoxan; Ledoxan; Neophos; Oncomide; Oncophos; Oncoxan; *Indon.*: Cyclovid; Endoxan; *Irl.*: Endoxana; *Israel*: Endoxan; *Ital.*: Endoxan; *Jpn*: Endoxan; *Mex.*: Cryofaxol; Formitex; Hidrofosmin; Ledoxina; *Neth.*: Endoxan; *Norw.*: Sendoxan; *NZ*: Cycloblastin; Cytoxan; Endoxan; *Philipp.*: Cytoxan†; Endoxan†; Ledoxan; Xydomed; *Pol.*: Endoxan; *Port.*: Endoxan; *Rus.*: Endoxan (Эндоксан); *S. Afr.*: Cycloblastin†; Endoxan; *Singapore*: Alkyloxan; Cycram; Endoxan; *Spain*: Genoxal; *Swed.*: Sendoxan; *Switz.*: Endoxan; *Thal.*: Endoxan; Ledoxan†; *Turk.*: Alkyloxan; Endoxan; *Venez.*: Biodoxan.

Pharmacopoeial Preparations

BP 2014: Cyclophosphamide Injection; Cyclophosphamide Oral Solution; Cyclophosphamide Tablets;
USP 36: Cyclophosphamide for Injection; Cyclophosphamide Tablets.

Cytarabine *(BAN, USAN, rINN)*

Ara-C; Arabinosylcytosine; Citarabin; Citarabina; Citarabinas; Citosina arabinósido; Cytarabin; Cytarabina; Cytarabine Liposome; Cytarabinum; Cytosine Arabinoside; Liposomal Cytarabine; NSC-63878 (cytarabine hydrochloride); Sitarabin; Sytarabiini; U-19920; U-19920A (cytarabine hydrochloride); WR-28453; Цитарабин.

1-β-D-Arabinofuranosylcytosine; 4-Amino-1-β-D-arabinofuranosylpyrimidin-2(1*H*)-one.

$C_9H_{13}N_3O_5$=243.2.

CAS — 147-94-4 (cytarabine); 69-74-9 (cytarabine hydrochloride).

ATC — L01BC01.

ATC Vet — QL01BC01.

UNII — 04079A1RDZ.

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

Chin. includes the hydrochloride.

Ph. Eur. 8: (Cytarabine). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Cytarabine). An odourless, white to off-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in chloroform. Protect from light.

Incompatibility. Although cytarabine has been stated in the literature to be incompatible with solutions of fluorouracil[1,2] and methotrexate[2] some studies have reported it to be stable for some hours when mixed with the latter.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; 33: 1010–13.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; 17: 532–8.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; 41: 1802–6.

Uses and Administration

Cytarabine, a pyrimidine nucleoside analogue, is an antimetabolite antineoplastic that inhibits DNA synthesis. Its actions are specific for the S phase of the cell cycle. It also has antiviral and immunosuppressant properties. Cytarabine is one of the mainstays of the treatment of acute myeloid leukaemia (p. 693.1), and is used in regimens for consolidation in patients with acute lymphoblastic leukaemia (p. 692.3). It has also been used for chronic myeloid leukaemia (p. 694.2) and the myelodysplasias (p. 694.3) (see also Low-dose Therapy, under Administration, below). It may be used in salvage regimens for Hodgkin's disease (p. 696.1), as part of the complex regimens sometimes employed in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p. 696.3 *et seq.*), and for meningeal leukaemia or lymphoma.

Cytarabine is usually given intravenously; it is also used subcutaneously. Higher doses can be tolerated when given by rapid intravenous injection rather than slow infusion, because of the rapid clearance of cytarabine, but there is little evidence of clinical advantage either way. Cytarabine (in a suitable formulation) may be given intrathecally for leukaemic or lymphomatous meningitis.

For the induction of remission in **acute leukaemias** many dosage regimens have been used: 100 mg/m² twice daily by rapid intravenous injection, or 100 mg/m² daily by continuous intravenous infusion, both for 7 days, are used in combination regimens for acute myeloid leukaemia. Cytarabine 200 mg/m² by continuous intravenous infusion for 5 days, at intervals of about 2 weeks, has also been used as monotherapy. Other recommended regimens include a continuous dosing regimen in which cytarabine 2 mg/kg daily is given by rapid intravenous injection for 10 days; thereafter, the dose may be increased if necessary to 4 mg/kg until a therapeutic response or toxicity is evident. Alternatively, 0.5 to 1 mg/kg may be infused daily (over 1 to 24 hours) for 10 days, increased thereafter to 2 mg/kg daily until toxicity or remission occurs. Intermittent regimens include intravenous cytarabine 3 to 5 mg/kg daily for 5 consecutive days, repeated after an interval of 2 to 9 days, until therapeutic response or toxicity occurs.

For maintenance 1 to 1.5 mg/kg once or twice weekly may be given intravenously or subcutaneously.

In the treatment of refractory non-Hodgkin's **lymphomas**, high-dose regimens have been used, with cytarabine given in doses of 3 g/m² every 12 hours for up to 12 doses. These doses should be given by intravenous infusion over 1 to 3 hours.

In the management of meningeal leukaemia and other **meningeal neoplasms**, cytarabine has been given by intrathecal injection in doses of 5 to 75 mg/m², or 30 to 100 mg, once every 2 to 7 days to once daily for 4 or 5 days. The dosage schedule is usually determined by the type and severity of CNS manifestations and the patient's response to prior therapy. A commonly used intrathecal cytarabine regimen is 10 to 30 mg/m² 3 times weekly, or 30 mg/m² once every 4 days, until CSF findings are normal; the latter regimen is followed by one additional dose. If systemic toxicity occurs with intrathecal cytarabine, modification of other therapy may be necessary. A liposomal formulation is available in some countries for intrathecal use, and permits less frequent dosing because of its longer duration of action: the recommended dose for lymphomatous meningitis is 50 mg intrathecally every 2 weeks for 5 doses then every 4 weeks for 5 doses. Oral or intravenous dexamethasone 4 mg twice daily for 5 days should be given, starting on the day of the liposomal cytarabine intrathecal injection. If neurotoxicity develops, the dose may be reduced to 25 mg; if this persists, liposomal cytarabine therapy should be stopped. For discussion of use of this formulation in children, see Administration in Children, below.

White cell and platelet counts should be determined regularly during treatment with cytarabine and therapy should be stopped or modified if platelets fall below 50 000 cells/mm³ or the polymorphonuclear granulocyte count falls below 1000 cells/mm³.

Cytarabine ocfosfate is an orally active prodrug o cytarabine under investigation for acute and chroni myeloid leukaemia.

Administration. *INTRATHECAL.* Intrathecal cytarabine ha been associated with neurotoxicity (see also Effects on the Nervous System, p. 775.2), some of which has been var iously attributed to preservatives, volume, osmolality, anc pH of the preparation;[1] common practice is to prepare intrathecal chemotherapy with preservative-free diluen and limit the volume of the final solution, usually to 5 mL A study[1] evaluated pH and osmolality for cytarabine intrathecal solutions (in various diluents) at concentrations of 2, 5, 10, and 25 mg/mL. Osmolality increased with increased concentrations but was within 10% of the physiological range of the CSF. However, the pH o cytarabine at 10 and 25 mg/mL was more than 10% high er than the upper limit of the physiological pH of CSF.

Intrathecal doses of the liposomal formulation o cytarabine result in prolonged drug exposure when compared with intrathecal doses of the conventiona formulation (see Pharmacokinetics, p. 775.3). In a randomised study,[2] the liposomal formulation given once every 2 weeks produced a higher response rate anc improved Karnofsky score compared with the conventiona formulation given twice a week in patients with lymphomatous meningitis secondary to lymphoma. The use of liposomal formulations intrathecally to trea leukaemic or lymphomatous meningitis has been reviewed.[3,4] For discussion of use of this formulation in children, see Administration in Children, below.

1. de Lemos ML, *et al.* Evaluation of osmolality and pH of various concentrations of methotrexate, cytarabine, and thiotepa prepared in normal saline, sterile water for injection, and lactated Ringer's solution for intrathecal administration. *J Oncol Pharm Pract* 2009; 15: 45–52.
2. Glantz MJ, *et al.* Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. *J Clin Oncol* 1999; 17: 3110–16.
3. Rueda Dominguez A, *et al.* Liposomal cytarabine (DepoCyte) for the treatment of neoplastic meningitis. *Clin Transl Oncol* 2005; 7: 232–8.
4. Benesch M, Urban C. Liposomal cytarabine for leukemic and lymphomatous meningitis: recent developments. *Expert Opin Pharmacother* 2008; 9: 301–9.

LOW-DOSE THERAPY. Because of initial suggestions that low doses of cytarabine might induce differentiation and maturation of leukaemic cells, low-dose therapy has been tried in patients with myelodysplastic syndrome and acute myeloid leukaemia. Although complete remission may occur in about 20% of patients with myelodysplastic syndromes a similar proportion succumb to treatment-related mortality, and remissions do not appear to be particularly long-lasting. Bone-marrow suppression may be marked even at these doses.[1] Low-dose subcutaneous cytarabine (20 mg twice daily for 10 days, at intervals of 4 to 6 weeks) was found to be superior to hydroxycarbamide (with or without all-trans retinoic acid) in elderly patients with acute myeloid leukaemia. Although the authors considered the prognosis for these patients to still be unsatisfactory, they suggested that therapy with low-dose cytarabine could represent a baseline against which other promising treatments might be compared.[2]

1. Aul C, Gattermann N. The role of low-dose chemotherapy in myelodysplastic syndrome. *Leuk Res* 1992; 16: 207–15.
2. Burnett AK, *et al.* The National Cancer Research Institute Haematological Oncology Study Group Adult Leukemia Working Party. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* 2007; 109: 1114–24.

Administration in children. UK licensed product information for conventional formulations of cytarabine indicates that children appear to tolerate proportionally higher doses by weight or surface area than adults, and that where a range of doses is given, children should be treated at the higher dose (see Uses and Administration, above).

UK and US licensed product information for liposomal formulations of cytarabine state that safety and efficacy in children have not been established. A dose of intrathecal liposomal cytarabine 35 mg (given with oral or intravenous dexamethasone 150 micrograms/kg twice daily for 5 days) has been recommended in patients between the ages of 3 and 21 years.[1] A pilot study to determine the feasibility, safety, and pharmacokinetics of this formulation in 6 patients aged less than 3 years found that it was safe and well tolerated when given with dexamethasone; drug exposure after a dose of 25 mg intrathecally was comparable to that after 50 mg in adults and 35 mg in older children.[2]

1. Bomgaars L, *et al.* Phase I trial of intrathecal liposomal cytarabine in children with neoplastic meningitis. *J Clin Oncol* 2004; 22: 3916–21.
2. Peyrl A, *et al.* Pharmacokinetics and safety of intrathecal liposomal cytarabine in children aged <3 years. *Clin Pharmacokinet* 2009; 48: 265–71.

Administration in hepatic or renal impairment. For conventional formulations, UK licensed product information states that cytarabine should be used with caution in hepatic impairment, and suggests a reduced dose in patients whose liver function is poor; however, no specific

dose recommendations are given and no definition of the degree of hepatic impairment. Dosage reduction is not considered necessary in patients with renal impairment.

US licensed product information states that patients with renal or hepatic impairment may be more likely to have CNS toxicity after high-dose cytarabine, which should be used with caution and possibly at a reduced dose in these patients; no specific dose recommendations are given.

Leukoencephalopathy. There are anecdotal reports[1-3] of marked improvement in patients with progressive multifocal leukoencephalopathy secondary to AIDS or chemotherapy-induced immunosuppression who were given intravenous or intrathecal cytarabine. However, a randomised multicentre study[4] indicated that cytarabine was ineffective and had no role in this condition (see also Infections in Immunocompromised Patients, p. 960.2). Others[5] have suggested that even intrathecal dosage may not provide adequate delivery of cytarabine to target cells, and that delivering the drug directly into the brain under pressure might be an alternative. Cytarabine has also been used with cidofovir.[6]

1. O'Riordan T, *et al.* Progressive multifocal leukoencephalopathy-remission with cytarabine. *J Infect* 1990; **20:** 51–4.
2. Portegies P, *et al.* Response to cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1991; **337:** 680–1.
3. Nicoli F, *et al.* Efficacy of cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* 1992; **339:** 306.
4. Hall CD, *et al.* Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. *N Engl J Med* 1998; **338:** 1345–51.
5. Levy RM, *et al.* Convection-enhanced intraparenchymal delivery (CEID) of cytosine arabinoside (AraC) for the treatment of HIV-related progressive multifocal leukoencephalopathy (PML). *J Neurovirol* 2001; **7:** 382–5.
6. Terrier B, *et al.* Leucoencéphalite multifocale progressive en dehors du sida: efficacité de l'association cytarabine-cidofovir. *Rev Med Interne* 2007; **28:** 488–91.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The major dose-limiting adverse effect of cytarabine is bone-marrow depression, manifest as leucopenia (particularly granulocytopenia), thrombocytopenia, and anaemia, sometimes with striking megaloblastic changes. Myelosuppression appears to be more evident after continuous infusions. Leucopenia is biphasic, with a nadir at 7 to 9 days after a dose and another, more severe, at 15 to 24 days. The nadir of the platelet count occurs at about 12 to 15 days. Recovery generally occurs in a further 10 days.

Gastrointestinal disturbances may occur: nausea and vomiting may be more severe when doses are given rapidly (but other adverse effects are reported to be worse when the drug is given by infusion). Other adverse effects reported include hepatic dysfunction, renal dysfunction, neurotoxicity, bleeding complications, rashes, oral and anal ulceration, gastrointestinal haemorrhage, oesophagitis, and conjunctivitis. A syndrome of bone and muscle pain, fever, malaise, conjunctivitis, and rash, sometimes described as flu-like, has been reported 6 to 12 hours after cytarabine doses, and may be treated or prevented with corticosteroids. Anaphylactoid reactions and pancreatitis have occurred rarely. There may be local pain, cellulitis, and thrombophlebitis at the site of injection.

Intrathecal use of the liposomal cytarabine formulation commonly causes chemical arachnoiditis manifesting as neck stiffness or pain, nausea, vomiting, headache, and fever. Dexamethasone should be used prophylactically to reduce the incidence and severity of this complication. Other rare adverse effects include encephalopathy, and focal seizures. Intrathecal use of conventional cytarabine formulations has rarely been associated with severe spinal cord toxicity, necrotising encephalopathy, blindness, and other neurotoxicities. If given intrathecally, preservative-free diluents must be used.

High-dose therapy has been associated with particularly severe gastrointestinal and CNS effects, including severe ulceration of the gastrointestinal tract, pneumatosis cystoides leading to peritonitis, necrotising colitis and bowel necrosis, peripheral neuropathy, and cerebral and cerebellar dysfunction, with personality changes, somnolence, and coma. There may also be corneal toxicity leading to punctate keratitis and haemorrhagic conjunctivitis, sepsis, liver abscess, severe skin rash leading to desquamation, alopecia, and cardiac disorders including pericarditis and fatal cardiomyopathy. Pulmonary toxicity sometimes fatal, has occurred.

Cytarabine is teratogenic in *animals* (but see Pregnancy, below).

In addition to frequent white blood cell and platelet counts, blood-uric acid should be monitored because of the risk of hyperuricaemia secondary to lysis of neoplastic cells, and renal and hepatic function should be periodically assessed. Cytarabine should be given with care to patients with impaired liver function; dosage reduction may be necessary.

The toxicity of cytarabine has been reviewed.[1] The principal toxicity of standard dosage regimens is myelosuppression but bleeding complications and gastrointestinal toxicity are also major problems at standard doses. With the high-dose regimens neurological toxicity may be dose-limiting: severe and sometimes irreversible symptoms have been seen in some 6 to 10% of patients receiving a cumulative dose of 36 g/m^2. Ocular toxicity may occur in up to 80% of patients at the highest doses. Since cytarabine toxicity is largely dose-related, low-dose cytarabine is generally well tolerated, even in elderly patients (who are more susceptible): its only significant toxicity is myelosuppression.

1. Stentoft J. The toxicity of cytarabine. *Drug Safety* 1990; **5:** 7–27.

Effects on the nervous system. Although paraplegia has been reported with intrathecal cytarabine[1] (see also under Benzyl Alcohol, p. 1740.3) and peripheral neuropathy has occurred in a patient who had received only conventional intravenous doses,[2] the majority of cases of neurotoxicity associated with cytarabine appear to be in patients given high-dose regimens.[3-7] Although some cases have manifested as demyelinating peripheral neuropathy,[3,4] including a syndrome of painful legs and involuntary movements in the toes which showed some response to carbamazepine,[3] most studies have reported in particular a syndrome of cerebellar toxicity,[5-8] with symptoms such as dysarthria, nystagmus, and ataxia. Toxicity appears to be dose-related: in one series[5] CNS toxicity occurred in none of 12 patients given total doses of up to 24 g/m^2 of cytarabine, 3 of 19 patients receiving 36 g/m^2, and 1 of 12 patients given 48 g/m^2, none of which were life-threatening or irreversible, whereas 4 of 6 patients given 54 g/m^2 (as 4.5 g/m^2 every 12 hours for 12 doses) developed neurotoxicity, which was fatal in one and irreversible in another. However, persistent, severe cerebellar toxicity has also been reported in a patient who had received a total dose of only 36 g/m^2 (as 3 g/m^2 every 12 hours).[8] There is some evidence[6] that patients aged over 50, and those who have recently received conventional-dose cytarabine[7] may be at increased risk. Intracranial hypertension (pseudotumor cerebri) has occurred rarely.[9] Neurological effects possibly related to cytarabine were seen in 2 out of 5 heavily pre-treated children given intrathecal liposomal cytarabine;[10] in 1 case, acute encephalopathy was probably caused by high-dose methotrexate but aggravated by cytarabine, and in the other case, persistent generalised seizures developed after the sixth intrathecal injection of cytarabine.

1. Saleh MN, *et al.* Intrathecal cytosine arabinoside-induced acute, rapidly reversible paralysis. *Am J Med* 1989; **86:** 729–30.
2. Russell JA, Powles RL. Neuropathy due to cytosine arabinoside. *BMJ* 1974; **4:** 652–3.
3. Malapert D, Degos JD, Jambes douloureuses et orteils instables: neuropathie induite par la cytarabine. *Rev Neurol (Paris)* 1989; **145:** 869–71.
4. Openshaw H, *et al.* Acute polyneuropathy after high dose cytosine arabinoside in patients with leukemia. *Cancer* 1996; **78:** 1899–1905.
5. Lazarus HM, *et al.* Central nervous system toxicity of high-dose systemic cytosine arabinoside. *Cancer* 1981; **48:** 2577–82.
6. Graves T, Hooks MA. Drug-induced toxicities associated with high-dose cytosine arabinoside infusions. *Pharmacotherapy* 1989; **9:** 23–8.
7. Barnett MJ, *et al.* Neurotoxicity of high-dose cytosine arabinoside. *Prog Exp Tumor Res* 1985; **29:** 177–82.
8. Dworkin LA, *et al.* Cerebellar toxicity following high-dose cytosine arabinoside. *J Clin Oncol* 1985; **3:** 613–16.
9. Fort JA, Smith LD. Pseudotumor cerebri secondary to intermediate-dose cytarabine HCl. *Ann Pharmacother* 1999; **33:** 576–8.
10. Benesch M, *et al.* Feasibility and toxicity of intrathecal liposomal cytarabine in 5 children and young adults with refractory neoplastic meningitis. *J Pediatr Hematol Oncol* 2007; **29:** 222–6.

Effects on the skin. A syndrome of pain and erythema of the palms and soles, progressing to bullae and desquamation, has been seen in patients receiving intermediate- or high-dose cytarabine.[1-3] The syndrome is similar to the palmar-plantar erythrodysesthesia syndrome (p. 730.1) reported in patients receiving chemotherapy not including cytarabine,[4] although some considered the two forms of toxicity distinct.[5] Cutaneous small vessel necrotising vasculitis[6] and Henoch-Schönlein purpura[7] have been reported after therapy with cytarabine.

1. Baer MR, *et al.* Palmar-plantar erythrodysesthesia and cytarabine. *Ann Intern Med* 1985; **102:** 556.
2. Peters WG, Willemze R. Palmar-plantar skin changes and cytarabine. *Ann Intern Med* 1985; **103:** 805.
3. Calista D, Landi C. Cytarabine-induced actal erythema: a localized form of toxic epidermal necrolysis? *J Eur Acad Dermatol Venereol* 1998; **10:** 274–5.
4. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; **101:** 798–800.
5. Vogelzang NJ, Ratain MJ. Cancer chemotherapy and skin changes. *Ann Intern Med* 1985; **103:** 303–4.
6. Ahmed I, *et al.* Cytosine arabinoside-induced vasculitis. *Mayo Clin Proc* 1998; **73:** 239–42.
7. Aktas B, *et al.* Severe Henoch-Schönlein purpura induced by cytarabine. *Ann Pharmacother* 2009; **43:** 792–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cytarabine 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 29/09/11)

Pregnancy. Although there has been a report of limb and ear deformities in the infant of a woman given cytarabine at the estimated time of conception and 4 to 8 weeks later,[1] no congenital abnormalities were noted in 17 infants, 5 therapeutic abortions, and one still-birth (after pre-eclamptic toxaemia) resulting from over 20 known cases in which cytarabine was given during pregnancy.[2]

For a report of a fetal sinusoidal heart rate pattern and neonatal pancytopenia after a woman was given combination chemotherapy including cytarabine, see Pregnancy, under Etoposide, p. 791.3.

1. Wagner VM, *et al.* Congenital abnormalities in baby born to cytarabine treated mother. *Lancet* 1980; **ii:** 98–9.
2. Morgenstern G. Cytarabine in pregnancy. *Lancet* 1980; **ii:** 259.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Antifungals. Cytarabine may inhibit the action of *flucytosine*—see p. 581.3.

Antineoplastics. Acute pancreatitis has been reported in patients given cytarabine who had previously received *asparaginase* therapy.[1] Subclinical damage to the pancreas by asparaginase may have rendered it susceptible to cytarabine.

For a report of hepatic dysfunction in patients who had received cytarabine and *daunorubicin* see under Daunorubicin Hydrochloride, p. 779.3.

Giving cytarabine after *fludarabine* is reported to result in a fivefold increase in intracellular cytarabine concentrations in leukaemic cells,[2] producing improved clinical response rates.

1. Altman AJ, *et al.* Acute pancreatitis in association with cytosine arabinoside therapy. *Cancer* 1982; **49:** 1384–6.
2. Avramis VI, *et al.* Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a phase I/II study in pediatric patients with relapsed leukemias. *Clin Cancer Res* 1998; **4:** 45–52.

Pharmacokinetics

Cytarabine is not effective orally due to rapid deamination in the gastrointestinal tract; less than 20% of an oral dose is absorbed. After intravenous injection it disappears rapidly from the plasma with an initial half-life of about 10 minutes; the terminal elimination half-life ranges from 1 to 3 hours. It is converted by phosphorylation to an active form, which is rapidly deaminated, mainly in the liver and the kidneys, to inactive 1-β-D-arabinofuranosyluracil (uracil arabinoside, ara-U). The majority of an intravenous dose is excreted in the urine within 24 hours, mostly as the inactive metabolite with about 10% as unchanged cytarabine.

There is only moderate diffusion of cytarabine across the blood-brain barrier after intravenous injection, but, because of low deaminase activity in the CSF, concentrations achieved after continuous intravenous infusion or intrathecal injection are maintained for longer in the CSF than are those in plasma, with a terminal elimination half-life of 3.5 hours. After intrathecal doses of the liposomal formulation, a terminal elimination half-life of 100 to 263 hours was seen. Cytarabine also crosses the placenta.

References.

1. Slevin ML, *et al.* The pharmacokinetics of subcutaneous cytosine arabinoside in patients with acute myelogenous leukaemia. *Br J Clin Pharmacol* 1981; **12:** 507–10.
2. DeAngelis LM, *et al.* Pharmacokinetics of ara-C and ara-U in plasma and CSF after high-dose administration of cytosine arabinoside. *Cancer Chemother Pharmacol* 1992; **29:** 173–7.
3. Hamada A, *et al.* Clinical pharmacokinetics of cytarabine formulations. *Clin Pharmacokinet* 2002; **41:** 705–18.
4. Peyrl A, *et al.* Pharmacokinetics and safety of intrathecal liposomal cytarabine in children aged <3 years. *Clin Pharmacokinet* 2009; **48:** 265–71.
5. Lamba JK. Genetic factors influencing cytarabine therapy. *Pharmacogenomics* 2009; **10:** 1657–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Citagenin; *Austria*: Alexan; ARA-cell†; DepoCyte; *Belg.*: Cytosar; DepoCyte; *Braz.*: Aracytin; Citarax; Darbin; Faulddita; Tabine; *Canad.*: Cytosar; DepoCyt; *Chile*: Alexan†; Aracytin; Laracit; *China*: Alexan (爱力生); Cytosar (赛德萨); Saidewei (赛德威); *Cz.*: Alexan; Cytosar; DepoCyte; *Denm.*: Arabine; DepoCyte; *Fin.*: Arabine†; DepoCyte; *Fr.*: Aracytine; DepoCyte; *Ger.*: Alexan†; ARA-cell; DepoCyte; *Gr.*: Arace; Aracytin; Citabion; DepoCyte; *Hong Kong*: Alexan; Cytosar; *Hung.*: Alexan; Cytosar; DepoCyte; *India*: Arasid; Biobin; Cancyt; Cybin; Cytabin; Cytaraside; Cytarine; Cytrosar; Oncotar; *Indon.*: Alexan; Cytosar-U†; *Irl.*: DepoCyte; *Israel*: Alexan; Cytosar; *Ital.*: Aracytin; DepoCyte; *Jpn*: Cylocide; Starasid; *Malaysia*: Cytosar-U; *Mex.*: Cytosar; Ifarab†; Lar-

The symbol † denotes a preparation no longer actively marketed

acit; *Medsara*; *Mokcell*; *Novumtrax†*; *Neth.*: Alexan†; DepoCyte; *Norw.*: DepoCyte; *Philipp.*: Cancyt; Cytosar-U; Cytox; Leucyt; Tabine; *Pol.*: Alexan; Cytosar; DepoCyte; *Port.*: ARAcell; Citaloxan; Cytosar; DepoCyte; *Rus.*: Alexan (Алексан); Cytosar (Цитозар); *S.Afr.*: Alexan†; Cytosar; Laracit; *Spain*: DepoCyte; *Swed.*: Arabine; DepoCyte; *Switz.*: Cytosar; DepoCyte; *Thai.*: Alexan; Cytarine; Cytosar; *Turk.*: Alexan; ARAcell; Cytonal; *UK*: DepoCyte; *Ukr.*: Cytosar (Цитозар); *USA*: DepoCyt; *Venez.*: Cytosar.

Pharmacopoeial Preparations
BP 2014: Cytarabine Injection;
USP 36: Cytarabine for Injection.

Dabrafenib *(USAN, pINN)*

Dabrafénib; Dabrafenibum; GSK-2118436A; Йофопастат.
N-{3-[5-(2-Aminopyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide.
$C_{23}H_{20}F_3N_5O_2S_2$=519.6
CAS — 1195765-45-7.
UNII — QGP4HA4G1B.

Dabrafenib Mesilate *(pINNM)*

Dabrafénib, Mésilate de; Dabrafenib Mesylate (USAN); Dabrafenibi Mesilas; GSK-2118436B; Mesilato de dabrafenib; Йофопастата Мезилат.
$C_{23}H_{20}F_3N_5O_2S_2.CH_4O_3S$=615.7
CAS — 1195768-06-9.
UNII — B6DC89I63E.

Profile

Dabrafenib is an inhibitor of BRAF kinases that is used in the treatment of unresectable or metastatic melanoma (p. 714.3) with BRAF V600E mutations; it should not be used in patients with wild-type BRAF melanoma. It is given as the mesilate salt but doses are expressed as the base; 50 mg of dabrafenib is equivalent to about 59.25 mg dabrafenib mesilate. The usual oral dose is equivalent to 150 mg twice daily, taken 12 hours apart; capsules should be swallowed whole and taken on an empty stomach. A missed dose should not be taken within 6 hours of the next dose. Doses may need to be withheld or reduced if toxicity occurs. Where dose adjustment is required, the first dose reduction is to 100 mg twice daily, the second reduction to 75 mg twice daily, and the third reduction to 50 mg twice daily; dabrafenib should be stopped if the patient is unable to tolerate 50 mg twice daily. Treatment is continued until disease progression or unacceptable toxicity occurs. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Commonly reported adverse effects with dabrafenib include skin reactions, headache, fever, arthralgia, cough, and nasopharyngitis. New primary cutaneous malignancies such as squamous cell carcinoma, keratoacanthoma, and melanoma have occurred during treatment. Other effects include hyperglycaemia, uveitis, and iritis. Dabrafenib should be avoided during pregnancy and women of childbearing potential should use contraception during and for 4 weeks after treatment.

References.
1. Ballantyne AD, Garnock-Jones KP. Dabrafenib: first global approval. *Drugs* 2013; 73: 1367–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Tafinlar; *USA*: Tafinlar.

Dacarbazine *(BAN, USAN, rINN)*

Dacarbazin; Dacarbazina; Dacarbazinum; Dakarbatsiini; Dakarbazin; DIC; DTIC; Imidazole Carboxamide; NSC-45388; WR-139007; Дакарбазин.
5-(3,3-Dimethyltriazeno)imidazole-4-carboxamide.
$C_6H_{10}N_6O$=182.2
CAS — 4342-03-4 (dacarbazine); 64038-56-8 (dacarbazine citrate).
ATC — L01AX04.
ATC Vet — QL01AX04.
UNII — 7GR28W0FJI.

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

Ph. Eur. 8: (Dacarbazine). A white or slightly yellowish, crystalline powder. Slightly soluble in water and in anhydrous alcohol; practically insoluble in dichloromethane. Store at 2 degrees to 8 degrees. Protect from light.

USP 36: (Dacarbazine). Store in airtight containers at 2 degrees to 8 degrees. Protect from light.

Incompatibility. Dacarbazine has been reported to be incompatible with hydrocortisone sodium succinate but not with the sodium phosphate.[1] It has been reported to be incompatible with heparin,[2] although only with concentrated dacarbazine solutions (25 mg/mL).

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; 6: 42–52.
2. Nelson RW, *et al.* Visual incompatibility of dacarbazine and heparin. *Am J Hosp Pharm* 1987; 44: 2028.

Stability. References to the photodegradation of dacarbazine solution.[1-4] Dacarbazine is more sensitive to direct sunlight than to artificial lighting or diffuse daylight.

1. Stevens MFG, Peatey L. Photodegradation of solutions of the antitumour drug DTIC. *J Pharm Pharmacol* 1978; 30 (suppl): 47P.
2. Horton JK, Stevens MFG. Search for drug interactions between the antitumour agent DTIC and other cytotoxic agents. *J Pharm Pharmacol* 1979; 31 (suppl): 64P.
3. Kirk B. The evaluation of a light-protecting giving set. *Intensive Therapy Clin Monit* 1987; 8: 78–86.
4. El Aatmani M, *et al.* Stability of dacarbazine in amber glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2002; 59: 1351–6.

Uses and Administration

Dacarbazine is a cell-cycle non-specific antineoplastic that is thought to function as an alkylating agent after it has been activated in the liver. Dacarbazine is used mainly in the treatment of metastatic malignant melanoma (p. 714.3). It is also given to patients with Hodgkin's disease (p. 696.1), notably with doxorubicin, bleomycin, and vinblastine (ABVD). Dacarbazine is used with other drugs in the treatment of soft-tissue sarcoma (p. 718.2), except mesothelioma and Kaposi's sarcoma, and may be given in neuroblastoma (p. 716.2), and other tumours.

Dacarbazine is given by the intravenous route. Injections may be given over 1 minute. The reconstituted solution can be further diluted with up to 300 mL of glucose 5% or sodium chloride 0.9% and given by infusion over 15 to 30 minutes; doses of 200 mg/m² and over are usually infused.

Dacarbazine is licensed for use as a single agent for **metastatic melanoma** in doses of 2 to 4.5 mg/kg daily for 10 days, repeated at intervals of 4 weeks, or 200 to 250 mg/m² daily for 5 days, repeated at intervals of 3 weeks. It can also be given in a dose of 850 mg/m² by intravenous infusion at 3-week intervals. In the treatment of **Hodgkin's disease** doses of 150 mg/m² daily for 5 days repeated every 4 weeks, or 375 mg/m² every 15 days have been given with other agents. In the treatment of **soft-tissue sarcoma**, dacarbazine 250 mg/m² is given daily for 5 days repeated every 3 weeks; it is usually given with doxorubicin.

References.
1. D'Incan M, Souteyrand P. Dacarbazine (Déticène). *Ann Dermatol Venereol* 2001; 128: 517–25.
2. Eggermont AMM, Kirkwood JM. Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years? *Eur J Cancer* 2004; 40: 1825–36.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Leucopenia and thrombocytopenia with dacarbazine, although usually moderate, may be severe. The nadir of the white cell count usually occurs 21 to 25 days after a dose. Anorexia, nausea, and vomiting occur in more than 90% of patients initially but tolerance may develop after repeated doses. Less frequent adverse effects include diarrhoea, skin reactions, alopecia, a flu-like syndrome, facial flushing and paraesthesia, headache, blurred vision, seizures, and rare but potentially fatal hepatotoxicity. There may be local pain at the injection site; extravasation produces pain and tissue damage. Anaphylaxis has occurred occasionally.

Dacarbazine should be used with caution in hepatic and renal impairment, and consideration given to reducing the dose. Haematological monitoring is required during therapy. Dacarbazine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. A report[1] of haemorrhagic cystitis associated with dacarbazine treatment for melanoma. The patient developed gross haematuria with inflammation and oedema of the bladder wall 2 weeks after completing 3 cycles of monotherapy with dacarbazine; the condition responded to symptomatic management with saline lavage and oral and intravenous hydration. Two subsequent transient episodes of haematuria resolved spontaneously.

1. Mohammadianpanah M, *et al.* Hemorrhagic cystitis in a patient receiving conventional doses of dacarbazine for metastatic malignant melanoma: case report and review of the literature. *Clin Ther* 2007; 29: 1161–5.

Effects on the liver. Dacarbazine has been associated with fatal hepatic vascular toxicity, caused by thrombosis of the hepatic veins, necrosis, and extensive haemorrhage.[1] As the reaction usually occurs during the second course of dacarbazine it is thought to be immune mediated, and early corticosteroid treatment has been tried with a few reported cases of patient survival.[2] Other adverse hepatic effects have included[3] necrosis without inflammation, granulomatous hepatitis, and acute toxic hepatitis during the first course of dacarbazine. Morphological studies have suggested that dacarbazine may exert a toxic effect on the microfilamentous cytoskeleton of the hepatocytes.[3]

1. Ceci G, *et al.* Fatal hepatic vascular toxicity of DTIC: is it really a rare event? *Cancer* 1988; 61: 1988–91.
2. Herishanu Y, *et al.* The role of glucocorticoids in the treatment of fulminant hepatitis induced by dacarbazine. *Anticancer Drugs* 2002; 13: 177–9.
3. Dancygier H, *et al.* Dacarbazine (DTIC)-induced human liver injury. *Int* 1982; 23: A447.

Handling. Dacarbazine is irritant; avoid contact with skin and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dacarbazine 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 28/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Levodopa. For a report of dacarbazine reducing the effects of levodopa, see Antineoplastics, p. 907.2.

Pharmacokinetics

Dacarbazine is poorly absorbed from the gastrointestinal tract. On intravenous injection it is rapidly distributed with an initial plasma half-life of about 20 minutes; the terminal half-life is reported to be about 5 hours. The volume of distribution is larger than body water content, suggesting localisation in some body tissues, probably mainly the liver. Only about 5% is bound to plasma protein. It crosses the blood-brain barrier to a limited extent; concentrations in CSF are about 14% of those in plasma. Dacarbazine is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2 and CYP2E1 (and possibly in the tissues by CYP1A1) to its active metabolite 5-(3-methyltriazeno-1-yl)-imidazole-4-carboxamide (MTIC), which spontaneously decomposes to the major metabolite 5-amino-imidazole-4-carboxamide (AIC). About half of a dose is excreted unchanged in the urine by tubular secretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Oncocarbil; *Austr.*: DTIC†; *Braz.*: Baxcarbas†; Dacarb; Evodazin; Fauldacar; *Chile*: Deticene; *China*: Ai Li Da (艾立达); *Fin.*: Dacatic; *Fr.*: Detice; *Ger.*: Detimedac; *Gr.*: Dacarbion; Deticene; *Hong Kong*: DTI; *India*: Arzi; Dabaz; Dacarba; Dacarex; Dacarin; Dacarzine; Dicazin; Decarb; Oncodac; *Israel*: Dacin; Deticene†; *Mex.*: Acocarb; Detilem†; Ifadac†; *Neth.*: Deticene; *Philipp.*: Duticin; *Pol.*: Deticene†; Fauldetic; *S.Afr.*: DTIC-Dome; *Singapore*: Dtic; *Switz.*: Dacin; *Turk.*: Deticene; *USA*: DTIC-Dome.

Pharmacopoeial Preparations
BP 2014: Dacarbazine Injection;
USP 36: Dacarbazine for Injection.

Dactinomycin *(BAN, USAN, rINN)*

Actinomicina D; Actinomycin C_1; Actinomycin D; Dactinomicina; Dactinomycine; Dactinomycinum; Daktinomis 1; Daktinomycin; Daktinomysiini; Daktynomycyna; Meractinomycin; NSC-3053; Дактиномицин.
$N^{2,1},N^{2',1'}$-(2-Amino-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-diyldicarbonyl)bis[threonyl-D-valylprolyl(*N*-methylglycyl)(*N*-methylvaline) 1,5→3,1-lactone].
$C_{62}H_{86}N_{12}O_{16}$=1255.4
CAS — 50-76-0.
ATC — L01DA01.
ATC Vet — QL01DA01.
UNII — 1CC1JFE158.

Description. Dactinomycin is an antineoplastic antibiotic produced by *Streptomyces parvulus* and other species of *Streptomyces*.

Cactinomycin (actinomycin C; HBF-386; NSC-18268 is a mixture of dactinomycin (actinomycin D) (10%), actinomycin C_2 (45%), and actinomycin C_3 (45%) produced by *Streptomyces chrysomallus*.

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, *Pol.*, and *US*.

USP 36: (Dactinomycin). A bright red, somewhat hygroscopic, crystalline powder, affected by light and heat. It has a potency of not less than 950 and not more than 1030 micrograms/mg, calculated on the dried basis. Soluble in water at 10 degrees and slightly soluble in water at 37 degrees; freely soluble in alcohol; very slightly soluble in

ether. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Adsorption. Dactinomycin binds to cellulose ester filters,[1] and such filtration should be avoided.[2] Although it has been suggested that significant amounts of drug may be adsorbed to glass or plastic,[3] dactinomycin is reportedly compatible with glass and PVC infusion containers,[4] and giving into the tubing of a fast-running intravenous infusion is recommended—see Uses and Administration, below.

1. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; 40: 1323–8.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; 17: 532–8.
3. Rapp RP, *et al.* Guidelines for the administration of commonly-used intravenous drugs—1984 update. *Drug Intell Clin Pharm* 1984; 18: 218–32.
4. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; 38: 1914–18.

Uses and Administration

Dactinomycin is a highly toxic antibiotic with antineoplastic properties. It inhibits the proliferation of cells in a cell-cycle non-specific way by forming a stable complex with DNA and interfering with DNA-dependent RNA synthesis. It may enhance the cytotoxic effects of radiotherapy (see also Adverse Effects, below). Dactinomycin also has immunosuppressant properties.

It has been used, usually with other drugs or radiotherapy, in the treatment of Wilms' tumour (p. 709.1), gestational trophoblastic tumours (p. 691.2), nonseminomatous testicular cancer (p. 715.1), and sarcomas such as rhabdomyosarcoma (see Soft-tissue Sarcoma, p. 718.2) and Ewing's sarcoma (see Bone Sarcoma, p. 717.3).

In the treatment of Wilms' tumour, childhood rhabdomyosarcoma, or Ewing's sarcoma, an intravenous dose of 15 micrograms/kg daily for 5 days has been used in combination regimens. In adults, gestational trophoblastic tumours have been treated with 12 micrograms/kg daily for 5 days as a single agent, or 500 micrograms on days 1 and 2 of combination regimens. Metastatic nonseminomatous testicular cancer has been treated with 1 mg/m^2 on day 1 of combination regimens. The dose intensity for adults or children should not exceed 15 micrograms/kg or 400 to 600 micrograms/m^2 daily for 5 days per 2-week cycle, and lower doses may need to be used in some chemotherapy combinations or with radiotherapy. Using a regional perfusion technique to localise the drug has permitted the use of higher doses, 50 micrograms/kg being suggested for an isolated lower extremity or pelvis and 35 micrograms/kg for an upper extremity.

Great care must be taken to avoid extravasation and it should be given, for preference, into the tubing of a fast-running intravenous infusion. Platelet and white cell counts should be performed frequently to detect bone-marrow depression; if either count shows a marked decrease the drug should be withheld until recovery occurs, which may take up to 3 weeks (see also Bone-marrow Depression, p. 730.3).

Administration in children. Dactinomycin is used in children in the treatment of malignant diseases as outlined in Uses and Administration, above. For a discussion of dactinomycin pharmacokinetics in children, see under Pharmacokinetics, below.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Apart from nausea and vomiting adverse effects are often delayed, beginning 2 to 4 days after the completion of a course of treatment and reaching a maximum after 1 to 2 weeks. Fatalities have occurred. Haematological and gastrointestinal effects (particularly stomatitis and diarrhoea) may prove dose-limiting. Myelosuppression is apparent 1 to 7 days after therapy and may be manifest first as thrombocytopenia; the nadir of the platelet and white cell counts usually occurs within 14 to 21 days, with recovery in 21 to 25 days. Other adverse effects include oral and gastrointestinal effects such as cheilitis, oesophagitis, gastrointestinal ulceration, and proctitis; fever, malaise, hypocalcaemia, myalgia, alopecia, pneumonitis, and kidney and liver abnormalities. Skin reactions include eruptions, acne, toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Hepatotoxicity, including fatal hepatic failure, has been reported; veno-occlusive disease (mainly hepatic) may be fatal, especially in children younger than 2 years. Anaphylactoid reactions have occurred. Dactinomycin is very irritant and extravasation results in severe tissue damage. Regional perfusion therapy has also resulted in damage to soft tissues and oedema.

The effects of radiotherapy are enhanced by dactinomycin and severe reactions may follow the use of high doses. Erythema and pigmentation of the skin may occur in areas previously irradiated. An increased incidence of second primary tumours has been seen in patients treated with radiation and dactinomycin.

Dactinomycin should not be given to patients with varicella or herpes zoster, as severe and even fatal systemic disease may occur. Its use is best avoided in infants under about 1 year of age as they are reported to be highly susceptible to the toxicity of dactinomycin. Blood counts and renal and hepatic function should be monitored frequently.

Effects on the liver. Although pulsed doses (given every 3 or 6 weeks) less than about 50 micrograms/kg or 1.5 mg/m^2 do not seem to be associated with an unacceptable degree of hepatotoxicity,[1] giving dactinomycin as a single dose of 60 micrograms/kg (about 1.8 mg/m^2) every 3 weeks to children with Wilms' tumour was associated with a high incidence of severe hepatotoxicity;[2] reduction of the dose to 45 micrograms/kg every 3 weeks reduced this incidence to levels comparable with a standard regimen of 15 micrograms/kg daily for 5 successive days.[3] Others have not seen such a high incidence of hepatotoxicity with doses of 60 micrograms/kg (despite some raised liver enzyme values), but in this case the high dose was given only every 6 weeks.[4] In general, dactinomycin should be given with caution to children with a history of antecedent liver damage, including abdominal irradiation or recent halothane anaesthesia.[1]

Reversible veno-occlusive disease has been seen particularly in children with Wilms' tumour given dactinomycin and vincristine. A literature review[5] noted a significant predominance in right-sided Wilms' tumour, possibly because the tumour mass could interfere with blood flow in the hepatic veins, which might make the liver more susceptible to the effects of dactinomycin. One study[6] found age of less than 1 year to be a risk factor and a study in children with rhabdomyosarcoma given dactinomycin, vincristine, and cyclophosphamide also found that young age (under 3 years) was associated with a greater risk of severe hepatotoxicity.[7] US licensed product information states that veno-occlusive disease (primarily hepatic) may be fatal, especially in children younger than 2 years of age.

1. Pritchard J, *et al.* Hepatotoxicity of actinomycin-D. *Lancet* 1989; i: 168.
2. D'Angio GJ. Hepatotoxicity with actinomycin D. *Lancet* 1987; ii: 104.
3. D'Angio GJ. Hepatotoxicity and actinomycin D. *Lancet* 1990; 335: 1290.
4. de Camargo B. Hepatotoxicity and actinomycin D. *Lancet* 1990; 335: 1290.
5. Tornesello A, *et al.* Veno-occlusive disease of the liver in right-sided Wilms' tumours. *Eur J Cancer* 1998; 34: 1220–3.
6. Bisogno G, *et al.* Veno-occlusive disease of the liver in children treated for Wilms tumor. *Med Pediatr Oncol* 1997; 29: 245–51.
7. Arndt C, *et al.* Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. *J Clin Oncol* 2004; 22: 1894–1901. Correction [dosage error]. *ibid.*: 3434.

Handling. Dactinomycin is irritant; avoid contact with skin and mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dactinomycin 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 29/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Pharmacokinetics

Intravenous doses of dactinomycin are rapidly distributed with high concentrations in bone marrow and nucleated cells. It undergoes only minimal metabolism and is slowly excreted in urine and bile. The terminal plasma half-life is reported to be about 36 hours. It does not cross the blood-brain barrier but is thought to cross the placenta.

In children. A study[1] involving 31 patients aged between 1 and 20 years given dactinomycin in intravenous doses of 0.7 to 1.5 mg/m^2 found that the pharmacokinetics of the drug were variable, but could be described by a 3-compartment model. Peak plasma concentrations varied from 3.2 to 99.2 nanograms/mL, and both peak plasma concentration and exposure were inversely related to bodyweight. Since there was evidence that exposure was also related to more severe toxicity, younger patients might be at greater risk with a regimen based on surface area; conversely the practice of capping the dose at 2 mg in older patients might result in underdosage.

For evidence that younger patients do have more liver toxicity with dactinomycin, see Effects on the Liver, above.

1. Veal GJ, *et al.* Pharmacokinetics of dactinomycin in a pediatric patient population: a United Kingdom Children's Cancer Study Group Study. *Clin Cancer Res* 2005; 11: 5893–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cosmegen; *Austral.*: Cosmegen; *Austria*: Cosmegen; *Belg.*: Lyovac Cosmegen; *Braz.*: Cosmegen; *Canad.*: Cosmegen; *Fin.*: Cosmegen†; *Gr.*: Cosmegen; *Hong Kong*: Cosmegen; *India*: Cosmegen; Dacmozen; Dactino; *Irl.*: Cosmegen; *Ital.*: Cosmegen; *Mex.*: Ac-De†; Cosmegen; *Neth.*: Lyovac Cosmegen†; *Norw.*: Cosmegen†; *NZ*: Cosmegen; *Philipp.*: Cosmegen†; Trepar; *Rus.*: Cosmegen (Космеген); *S.Afr.*: Cosmegen; *Singapore*: Cosmegen†; *Swed.*: Cosmegen†; *Switz.*: Cosmegen; *Thai.*: Lyovac Cosmegen; *Turk.*: Cosmegen; *UK*: Cosmegen†; *USA*: Cosmegen.

Pharmacopoeial Preparations
USP 36: Dactinomycin for Injection.

Dasatinib *(BAN, USAN, rINN)*

BMS-354825; Dasatinibum; Дазатиниб.

N-(2-Chloro-6-methylphenyl)-2-{[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino}-5-thiazolecarboxamide.

$C_{22}H_{26}ClN_7O_2S$=488.0

CAS — 302962-49-8.

ATC — L01XE06.

ATC Vet — QL01XE06.

UNII — RBZ1571X5H (dasatinib); X78UG0A0RN (anhydrous dasatinib).

Uses and Administration

Dasatinib is an oral inhibitor of several tyrosine kinases including BCR-ABL (Philadelphia chromosome) and SRC family tyrosine kinases. It is used for the treatment of adults with all phases of chronic myeloid leukaemia (CML; p. 694.2) who have resistance or intolerance to previous therapy, including imatinib, and as first-line treatment in those with Philadelphia chromosome-positive chronic phase CML. It is also used for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL; p. 692.3) who are resistant to or intolerant of prior therapy.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

The recommended oral starting dose of dasatinib in chronic phase CML is 100 mg once daily; tablets, which should be swallowed whole, not crushed or chewed, should be taken consistently either in the morning or the evening. The recommended starting dose for accelerated, myeloid, or lymphoid blast phase CML or Philadelphia chromosome-positive ALL is 140 mg once daily. Dosage may be adjusted according to response and tolerability; doses of up to 140 mg once daily have been used in patients with chronic phase CML, and up to 180 mg once daily in those with advanced phase, or with ALL. Treatment is continued until disease progression or unacceptable toxicity occurs. For dose adjustments in toxicity, see Administration in Subsequent Cycles, p. 778.1.

If concurrent use of potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments are considered necessary.

- An *increased* dose of dasatinib should be considered in those patients given strong CYP3A4 inducers, and the patient should be monitored for toxicity.
- For those given a strong CYP3A4 inhibitor, the dose of dasatinib should be *reduced* to 20 mg daily in those patients taking 100 mg daily, and to 40 mg daily in those taking 140 mg daily. If this is not tolerated, then either drug should be stopped; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of dasatinib is increased.

References.

1. Talpaz M, *et al.* Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006; 354: 2531–41.
2. Hochhaus A, *et al.* Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007; 109: 2303–9. Correction. *ibid.*; 110: 1438.
3. Cortes J, *et al.* Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood* 2007; 109: 3207–13.
4. Guilhot F, *et al.* Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood* 2007; 109: 4143–50.
5. Ottmann O, *et al.* Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. *Blood* 2007; 110: 2309–15.
6. Anonymous. Dasatinib (Sprycel) for CML and Ph+ALL. *Med Lett Drugs Ther* 2007; 49: 6–7.

7. Olivieri A, Manzione L. Dasatinib: a new step in molecular target therapy. *Ann Oncol* 2007; 18 (suppl): vi42–vi46.
8. Keam SJ. Dasatinib: in chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. *BioDrugs* 2008; 22: 59–69.
9. Tyler T. Once-daily dasatinib for treatment of patients with chronic myeloid leukemia. *Ann Pharmacother* 2009; 43: 920–7.
10. Cortes JE, *et al.* Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol* 2010; 28: 398–404.
11. Lindauer M, Hochhaus A. Dasatinib. *Recent Results Cancer Res* 2010; 184: 83–102.
12. Kim LC, *et al.* Dasatinib in solid tumors. *Expert Opin Invest Drugs* 2010; 19: 415–25.

Administration in subsequent cycles. Licensed product information for dasatinib recommends adjustment of the oral dose in patients who develop marked haematological or other toxicity.

For patients with chronic phase chronic myeloid leukaemia (CML) started on a dose of 100 mg daily in whom neutrophil counts are below 500 cells/mm^3, the drug should be stopped until neutrophil counts recover to at least 1000 cells/mm^3; similarly if platelet counts are less than 50 000 cells/mm^3 the drug should be stopped until they exceed this value. If this recovery in blood counts occurs in 7 days or less, treatment should be resumed at the previous dose. If the fall in neutrophil counts recurs for more than 7 days, or the fall in platelet counts is extreme (below 25 000 cells/mm^3) treatment should again be stopped and only be resumed at a lower dose of 80 mg daily. If a second recurrence is seen, treatment should be resumed at a dose of 50 mg daily in those given dasatinib as first-line treatment; treatment should be stopped in those that are resistant to or intolerant of prior therapy.

Similarly, in patients with accelerated phase CML, blast phase CML, or Philadelphia chromosome-positive acute lymphoblastic leukaemia started on 140 mg daily, in whom neutrophil counts are below 500 cells/mm^3 or platelets below 10 000 cells/mm^3 (and in whom the cytopenia is not related to the disease), treatment should be stopped, and only restarted once cell counts are at least twice these values. Treatment is resumed at the original dose on the first occasion, but if cytopenia recurs, it should be resumed at 100 mg daily on the second occasion, and 80 mg daily on the third.

If severe non-haematological toxicity occurs, treatment should again be stopped, and only resumed, at a lower dose if appropriate, once toxicity has resolved.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of dasatinib include fluid retention, gastrointestinal disturbances, and bleeding. Fluid retention may be severe, and can result in pleural and pericardial effusion, pulmonary oedema, and ascites. Myelosuppression, manifest as neutropenia, thrombocytopenia, or anaemia, occurs more frequently in patients with advanced chronic myeloid leukaemia (CML) or acute lymphoblastic leukaemia than in patients in chronic phase CML. Recovery generally occurs after dose interruption and/or reduction, although treatment may need to be stopped. Febrile neutropenia and, rarely, red cell aplasia have been reported. Full blood counts should be measured weekly for the first 2 months and then monthly thereafter. Severe bleeding events, including fatal CNS and gastrointestinal haemorrhages, have been reported, mostly in conjunction with thrombocytopenia although dasatinib also causes reversible platelet dysfunction *in vivo*. Treatment interruption and blood transfusion may be required for gastrointestinal haemorrhages. Caution is required when giving dasatinib with other drugs that affect platelet function or with anticoagulants (see Interactions, below). Embolic events including pulmonary embolism and deep-vein thrombosis have also been reported.

Cardiac failure, arrhythmias, and hypertension are common; hypotension, angina, myocardial infarction (including fatalities), pericarditis, myocarditis, acute coronary syndrome, and cor pulmonale occur more rarely. Dasatinib has the potential to prolong the QT interval, and should be given with caution to patients at risk of this, such as those with hypokalaemia or hypomagnesaemia, those on antiarrhythmic therapy or other drugs that prolong the QT interval, or those receiving cumulative high doses of anthracyclines.

Other common adverse effects include headache, pyrexia, chills, musculoskeletal pain, arthralgia, myalgia, asthenia, fatigue, chest pain, electrolyte disturbances, appetite and weight disturbances, mucositis, colitis, flushing, and skin disorders such as rash, alopecia, dermatitis, pruritus, acne, dry skin, and hyperhidrosis.

Respiratory adverse effects include dyspnoea, cough, pulmonary hypertension, pneumonitis, bronchospasm, respiratory distress syndrome, and interstitial lung disease. Infections, including pneumonia, are common; sepsis, although uncommon, may be fatal. Renal failure, urinary frequency, proteinuria, and liver disorders such as hepatitis, cholecystitis, and cholestasis have been reported. CNS adverse effects include depression, insomnia, dizziness, dysgeusia, somnolence, and neuropathy, and less commonly, anxiety, confusion, decreased libido, syncope, tremor, and amnesia. Stroke, transient ischaemic attacks, convulsions, and optic neuritis have been reported rarely. Visual disturbances, dry eye, tinnitus, conjunctivitis, and vertigo have occurred.

Uncommon adverse effects include tumour lysis syndrome, hyperuricaemia, hypoalbuminaemia, pancreatitis, gynaecomastia, irregular menstruation, rhabdomyolysis, hypersensitivity including erythema nodosum, and other skin disorders such as acute febrile neutrophilic dermatosis, photosensitivity, pigmentation disorders, panniculitis, skin ulcers, bullous conditions, nail disorders, and palmar-plantar erythrodysesthesia syndrome. Rare adverse effects include livedo reticularis (a mottled blue discoloration of the skin associated with poor venous return) and protein-losing gastroenteropathy.

Caution is advised when using dasatinib in patients with hepatic impairment.

Effects on the skin. Panniculitis has been reported with the use of dasatinib, which resolved upon stopping therapy. In one case, dasatinib was restarted with prednisone, and no recurrence of panniculitis was noted. In another patient, however, a rash recurred on restarting therapy that was not sensitive to corticosteroid treatment.[1]

1. Assouline S, *et al.* Panniculitis during dasatinib therapy for imatinib-resistant chronic myelogenous leukemia. *N Engl J Med* 2006; 354: 2623–4.

Lupus. A patient developed arthralgia and fatigue 3 months after starting dasatinib for chronic myeloid leukaemia. Symptoms worsened, drug-induced lupus was suspected, and dasatinib was stopped 9 months after starting therapy. Fever, arthralgia, fatigue, hepatosplenomegaly and pleuro-pericardial effusions all resolved fully within 1 month. It was suggested that the risk of developing dasatinib-associated autoimmunity be assessed prospectively by screening for autoantibodies before starting treatment *with dasatinib*.[1]

1. Rea D, *et al.* Dasatinib-induced lupus. *Lancet* 2008; 372: 713–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dasatinib 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 27/09/11)

Interactions

Dasatinib is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals, macrolide antibacterials, HIV-protease inhibitors, and nefazodone may increase blood concentrations of dasatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of dasatinib. When use with such drugs cannot be avoided, dose adjustment of dasatinib may be necessary (see Uses and Administration, p. 777.3). Since St John's wort may decrease dasatinib concentrations unpredictably, these drugs should not be given together.

Dasatinib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and may alter blood concentrations of other drugs that are substrates of this enzyme.

Since the solubility of dasatinib is dependent on pH, use with antacids should be avoided. If antacid therapy is needed, it should be given at least 2 hours before or 2 hours after the dose of dasatinib. Similarly, histamine H_2-receptor antagonists or proton pump inhibitors such as famotidine or omeprazole should not be given with dasatinib as long-term suppression of gastric acid secretion is likely to reduce dasatinib exposure.

Dasatinib prolongs the QT interval and the effect may be additive when given with other drugs with similar effects. Dasatinib also causes thrombocytopenia and bleeding, which may be additive with antiplatelet drugs, anticoagulants, and NSAIDs.

References.

1. Eley T, *et al.* Phase 1 study of the effect of gastric acid pH modulators on the bioavailability of oral dasatinib in healthy subjects. *J Clin Pharmacol* 2009; 49: 700–9.

Pharmacokinetics

Peak plasma concentrations of dasatinib occur between 0.5 and 6 hours after an oral dose. The mean terminal half-life is about 5 hours. Consumption of a high-fat meal may increase exposure to dasatinib, but this effect is not considered to be of clinical significance. Dasatinib is extensively distributed and metabolised. Metabolism occurs mainly via the cytochrome P450 isoenzyme CYP3A4, forming an active metabolite. Plasma protein binding of dasatinib and its active metabolite is about 96% and 93%, respectively. Elimination is mainly via the faeces; about 4% is recovered in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sprycel; *Austral.*: Sprycel; *Austria*: Sprycel; *Belg.*: Sprycel; *Braz.*: Sprycel; *Canad.*: Sprycel; *Chile*: Sprycel; *Cz.*: Sprycel; *Denm.*: Sprycel; *Fr.*: Sprycel; *Ger.*: Sprycel; *Gr.*: Sprycel; *Hong Kong*: Sprycel; *Hung.*: Sprycel; *Indon.*: Sprycel†; *Irl.*: Sprycel; *Israel*: Sprycel; *Ital.*: Sprycel; *Malaysia*: Sprycel; *Neth.*: Sprycel; *Norw.*: Sprycel; *NZ*: Sprycel; *Pol.*: Sprycel; *Port.*: Sprycel; *Rus.*: Sprycel (Спрайсел); *S.Afr.*: Sprycel; *Singapore*: Sprycel; *Spain*: Sprycel; *Swed.*: Sprycel; *Switz.*: Sprycel; *Thai.*: Sprycel; *Turk.*: Sprycel; *UK*: Sprycel; *USA*: Sprycel.

Daunorubicin *(BAN, rINN)*

Daunomycin; Daunorubicina; Daunorubicine; Daunorubicinum; Daunorubisiini; FI-6339; RP-13057; Rubidomicin; Rubidomycin; Даунорубицин.

(1*S*,3*S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxonaphthacen-1-yl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside.

$C_{27}H_{29}NO_{10}$=527.5

CAS — 20830-81-3.

ATC — L01DB02.

ATC Vet — QL01DB02.

UNII — ZS7284E0ZP.

Daunorubicin Citrate *(BANM, rINNM)*

Citrato de daunorubicina; Daunorubicine, Citrate de; Daunorubicini Citras; Даунорубицина Цитрат.

ATC — L01DB02.

UNII — 5L84T2Z6NP.

Daunorubicin Hydrochloride

(BANM, USAN, rINNM)

Cloridrato de Daunorrubicina; Daunomycin Hydrochloride; Daunoribisin Hidroklorür; Daunorubicin hydrochlorid; Daunorubicina, hidrocloruro de; Daunorubicine, Chlorhydrate de; Daunorubicin-hidroklorid; Daunorubicinhydrochlorid; Daunorubicinhydroklorid; Daunorubicini Hydrochloridum; Daunorubicino hidrochloridas; Daunorubisiinihydrokloride; FI-6339 (daunorubicin); Hidrocloruro de daunorubicina; NDC-0082-4155; NSC-82151; RP-13057 (daunorubicin); Rubidomycin Hydrochloride; Даунорубицина Гидрохлорид.

(1*S*,3*S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxonaphthacen-1-yl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-pyranoside hydrochloride; (8*S*-*cis*)-8-Acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride.

$C_{27}H_{29}NO_{10}$.HCl=564.0

CAS — 23541-50-6.

ATC — L01DB02.

ATC Vet — QL01DB02.

UNII — UD984I04LZ.

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

Ph. Eur. 8: (Daunorubicin Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces coeruleorubidus* or *S. peucetius* or obtained by any other means. It is manufactured by methods designed to minimise or eliminate the presence of histamine. An orange-red, hygroscopic, crystalline powder. It contains between 95 and 102% of the hydrochloride (anhydrous and solvent-free basis). Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Daunorubicin Hydrochloride). An orange-red, hygroscopic, crystalline powder. It has a potency equivalent to not less than 842 and not more than 1030 micrograms of the base per mg. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone; very slightly soluble in chloroform. A 0.5% solution in water has a pH of 4.5 to 6.5. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Incompatibility. Daunorubicin is incompatible with heparin sodium,[1] and has also been reported to be incompatible with a solution of dexamethasone sodium phosphate.

1. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; 17: 532–8.

Stability. In a study[1] of the stability of anthracycline antineoplastic agents in 4 infusion fluids (glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid) daunorubicin hydrochloride was stable in all 4, the percentage remaining after 24 hours being 98.5%, 97.4%, 94.7%, and 95.4% respectively. Stability appeared to be partly related to pH; daunorubicin was more stable as the pH of the mixture became more acidic, with the best stability in glucose 5% with a pH of 4.5. Although daunorubicin solutions are degraded by light, the effect is reported not to be significant at concentrations of 500 micrograms/mL or above; however, below this concentration precautions should be taken to protect solutions from light, and storage should be in polyethylene or polypropylene containers to minimise adsorptive losses.[2] It has been suggested that formulation with the food colouring Scarlet GN, which absorbs light over the same spectral region as daunorubicin, would stabilise daunorubicin solutions to light.[3]

Liposomal daunorubicin citrate should be diluted with glucose 5% solution as aggregation of the liposomes may result with sodium chloride. In addition, licensed product information advises that liposomal daunorubicin should not be mixed with substances containing benzyl alcohol or other detergent-like molecules, which can lead to premature rupture of the liposomes.

1. Poochikian GK, *et al.* Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; 38: 483–6.
2. Wood MJ, *et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; 15: 291–300.
3. 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

Daunorubicin is an antineoplastic anthracycline antibiotic with actions similar to those of doxorubicin (p. 783.2), to which it is closely related. It is used with other antineoplastics to induce remissions in acute leukaemias. Daunorubicin is given in combination regimens for acute lymphoblastic leukaemia (see p. 692.3) and acute myeloid leukaemias (see p. 693.1). It has also been tried in some other malignancies. A liposomal formulation of daunorubicin has been developed for use in the management of advanced Kaposi's sarcoma in patients with AIDS (see also p. 718.1).

In the conventional formulation, daunorubicin is usually given as the hydrochloride, but doses are expressed in terms of the base. Daunorubicin hydrochloride 21.4 mg is equivalent to about 20 mg daunorubicin. The liposomal formulation contains daunorubicin citrate, equivalent to about 2 mg/mL of daunorubicin base.

In US treatment regimens for adult acute lymphoblastic or myeloid leukaemia, the usual dose of *conventional* daunorubicin hydrochloride is the equivalent of daunorubicin 45 mg/m² daily on days 1 to 3 of the first course; in acute myeloid leukaemia, this dose is also given on days 1 and 2 of subsequent courses. Courses may be repeated if needed, after bone-marrow evaluation. In the UK, for remission induction in acute leukaemias, a dose of 40 to 60 mg/m² can be given on alternate days for a course of up to 3 injections. Daunorubicin hydrochloride is given as a solution in sodium chloride 0.9% into a fast-running intravenous infusion of sodium chloride 0.9% or glucose 5%.

For doses in children and the elderly, see below. Dosage should be reduced in patients with impaired hepatic or renal function (see below).

In the treatment of Kaposi's sarcoma, *liposomal* daunorubicin citrate is given intravenously every 2 weeks starting with a dose of 40 mg/m², and continued for as long as disease control can be maintained. It is diluted with glucose 5% (sodium chloride 0.9% should not be used) to a daunorubicin concentration between 0.2 and 1 mg/mL, and given over 30 to 60 minutes.

Blood counts should be determined frequently during treatment as daunorubicin has a potent effect on bone-marrow function (see also Bone-marrow Depression, p. 730.3). Cardiac function should be monitored at regular intervals to detect signs of cardiotoxicity. The total cumulative dose of daunorubicin in adults should not exceed 550 to 600 mg/m²; in patients who have received radiotherapy to the chest it may be advisable to limit the total cumulative dose to about 400 mg/m². Product information for liposomal daunorubicin recommends determining left ventricular ejection fraction (LVEF) at baseline and after cumulative doses of 320 mg/m², and every 160 mg/m² thereafter. In patients who have received prior radiotherapy to the chest, or who have pre-existing cardiac disease, or who have had previous anthracycline therapy (equivalent to more than *doxorubicin* 300 mg/m²) LVEF should be assessed at baseline and after every 160 mg/m² of liposomal daunorubicin.

Administration. *HIGH-DOSE THERAPY.* Two multicentre studies in patients with acute myeloid leukaemia compared the use of a standard induction dose of a conventional daunorubicin formulation (45 mg/m²), with an escalated dose of 90 mg/m², given for 3 days in a regimen with cytarabine.[1,2] In patients aged 60 and under, the high-dose regimen was associated with an increased rate of complete remission (70.6 versus 57.3% in the conventional dose group), and improved overall survival (median values of 23.7 versus 15.7 months) on follow-up for a median of 25 months.[2] Although this study suggested little benefit in the subgroup of patients older than 50, in the other, which was restricted to those 60 and over, comparable improvements in remission and overall survival were seen with high-dose therapy in those between 60 and 65 years of age,[1] but patients older than this did not show any benefit. The higher doses of anthracycline were not associated with an increase in mortality or moderate to severe adverse events, even in older patients.

1. Löwenberg B, *et al.* Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON), German AML Study Group (AMLSG), and Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med* 2009; 361: 1235–48. Correction. *ibid.* 2010; 362: 1155. [dose]
2. Fernandez HF, *et al.* Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med* 2009; 361: 1249–59.

Administration in children. Daunorubicin hydrochloride is licensed for the induction of remission in children with acute leukaemia. Doses may vary according to country, and the combination regimen used.

In the USA, a dose of daunorubicin 25 mg/m² is given intravenously once a week, in combination regimens, to children with acute lymphoblastic leukaemia. Complete remission is generally obtained within 4 courses; however, if only partial remission is obtained after 4 courses, up to 2 further courses may be given. For children less than 2 years of age, or with a body-surface of less than 0.5 m², a dose of 1 mg/kg is used instead.

In the UK, children with acute myeloid or lymphoblastic leukaemia who are 2 years and older may be given the same dose as adults (see Uses and Administration, above). Children under 2 years of age, or with a body-surface of less than 0.5 m² may be given an intravenous dose of 1 mg/kg daily.

Precautions and monitoring are as for adults; cardiotoxicity may occur more frequently in children. A total cumulative dose of 300 mg/m² should not be exceeded; in children under 2 years, the total cumulative dose should not exceed 10 mg/kg.

The safety and efficacy of *liposomal* daunorubicin citrate in paediatric patients has not been established. However, a study in 24 patients aged between 2 and 23 years, who were given doses of 30 or 60 mg/m², indicated that the pharmacokinetics showed less variability than has been reported for conventional formulations, and no substantial differences related to age.[1]

1. Hempel G, *et al.* Population pharmacokinetics of liposomal daunorubicin in children. *Br J Clin Pharmacol* 2003; 56: 370–7.

Administration in the elderly. Daunorubicin hydrochloride should be used with care in elderly patients with inadequate bone marrow reserves. In the UK, a dosage reduction of up to 50% is recommended. In the USA, for patients with acute myeloid leukaemia and aged 60 years and over, an intravenous dose of daunorubicin 30 mg/m² daily on days 1 to 3 of the first course, and days 1 and 2 of subsequent courses, is recommended for combination treatment regimens. Precautions and monitoring are as for younger adults (see Uses and Administration, above); cardiotoxicity may occur more frequently in the elderly. However, see also High-dose Therapy, above.

The safety and efficacy of *liposomal* daunorubicin citrate in elderly patients has not been established.

Administration in hepatic impairment. Doses of daunorubicin should be reduced in hepatic impairment. Some licensed product information for daunorubicin hydrochloride recommends that patients with serum-bilirubin concentrations of 12 to 30 micrograms/mL (or 20 to 50 micromoles/litre) should receive 75% of the usual daily dose, and those with concentrations greater than 30 micrograms/mL (or above 50 micromoles/litre) should be given 50% of the usual daily dose.

Limited data exist for liposomal daunorubicin citrate; in the USA, similar dosage reductions to those given for the hydrochloride are recommended.

Administration in renal impairment. Doses of daunorubicin should be reduced in renal impairment. Some licensed product information for daunorubicin hydrochloride recommends that patients with serum-creatinine concentrations of 12 to 30 micrograms/mL (or 105 to 265 micromoles/litre) should receive 75% of the usual daily dose, and those with concentrations greater than 30 micrograms/mL (or 265 micromoles/litre) should be given 50% of the usual daily dose.

Limited data exist for liposomal daunorubicin citrate; in the USA, similar dosage reductions to those given for the hydrochloride are recommended in patients with a serum-creatinine concentration greater than 30 micrograms/mL.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p. 784.1 and p. 785.1.

Cardiotoxicity is more likely when the total cumulative dose of daunorubicin exceeds 550 to 600 mg/m² in adults, 300 mg/m² in children, or in children aged under 2 years, 10 mg/kg. The total cumulative dose should be limited to 400 mg/m² in patients who have had previous radiation therapy to the chest. US licensed product information for the standard formulation of daunorubicin recommends an ECG and/or determination of left ventricular ejection fraction (LVEF) before each course. Product information for liposomal daunorubicin recommends evaluating cardiac function before each course of daunorubicin and determining LVEF at baseline and after cumulative doses of 320 mg/m², and every 160 mg/m² thereafter. In patients who have pre-existing cardiac disease, or who have had previous radiotherapy to the chest or anthracycline therapy (more than 300 mg/m² *doxorubicin* or equivalent) LVEF should be assessed at baseline and after every 160 mg/m² of liposomal daunorubicin. Daunorubicin should be used in reduced doses in hepatic and renal impairment.

Liposomal formulations of daunorubicin may be associated with a reduced potential for local tissue necrosis although current clinical experience is limited and such toxicity remains a possibility. An acute syndrome of back pain, flushing, and chest tightness may occur during infusion of such products, but generally resolves on slowing or temporarily stopping the infusion.

Effects on the heart. For a discussion of the cardiotoxicity of anthracyclines, and its management, see Effects on the Heart, under Doxorubicin, p. 784.1.

Effects on the skin and nails. For reports of hyperpigmentation in patients given daunorubicin, see under Doxorubicin, p. 784.3.

Handling and disposal. Daunorubicin hydrochloride is irritant; avoid contact with skin and mucous membranes.

For a method for the destruction of daunorubicin in wastes see under Doxorubicin, p. 785.1.

Pregnancy. For a report of a fetal sinusoidal heart rate pattern and neonatal pancytopenia after a woman was given combination chemotherapy including daunorubicin, see Pregnancy, under Etoposide, p. 791.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies daunorubicin 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 29/09/11)

Interactions

As for Doxorubicin, p. 785.2.

Antineoplastics. Hepatic dysfunction was reported[1] in 13 patients given cumulative doses of daunorubicin 180 to 450 mg/m². Ten of them had also received *tioguanine* or *cytarabine*, or a combination of these. The authors also noted that other studies had suggested that the related drug doxorubicin might enhance the hepatotoxicity of *mercaptopurine*, and thought that a similar interaction could occur between daunorubicin and tioguanine.

1. Penta JS, *et al.* Hepatotoxicity of combination chemotherapy for acute myelocytic leukemia. *Ann Intern Med* 1977; 87: 247–8.

Pharmacokinetics

After intravenous injection, daunorubicin is rapidly distributed into body tissues, particularly the liver, lungs, kidneys, spleen, and heart with an initial distribution half-life of about 45 minutes. It is rapidly metabolised in the liver, and is excreted in bile and urine as unchanged drug and metabolites. The major metabolite, daunorubicinol, has antineoplastic activity. Up to 25% of a dose is excreted in urine in an active form over several days (the terminal plasma elimination half-lives of daunorubicin and its major metabolite are reported to be 18.5 and 26.7 hours respectively); an estimated 40% is excreted in bile.

Daunorubicin does not appear to cross the blood-brain barrier, but crosses the placenta.

The pharmacokinetics of liposomal doxorubicin are significantly different from those of the conventional drug formulation, with a decreased uptake by normal tissues (although tumour neovasculature is reported to have increased permeability to the liposomes), and a terminal half-life of 4 to 5 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Daunoblastina†; Daunogobbi; Maxidauno; *Austral.*: DaunoXome†; *Austria*: Daunoblastin; DaunoXome†; *Belg.*: Cerubidine; *Braz.*: Daunoblastina; Daunocin; DaunoXome†; *Canad.*: Cerubidine; *Chile*: Cerubidine†; Daurocina†; Oncodaunotec†; *China*: Daunoblastina (柔红霉素); *Denm.*: Cerubidin; DaunoXome; *Fin.*: DaunoXome; *Fr.*: Cerubidine; DaunoXome; *Ger.*: Daunoblastin; DaunoXome†; *Gr.*: Cerubidine; Daunoblastina; DaunoXome; *Hong Kong*: Daunoblastina; *Hung.*: Daunoblastina; *India*: Daunobin; Daunocin; Daunoplus; Daunorubitec; Daunoside; Daunotec; Norubin; *Irl.*: Cerubidin; DaunoXome; *Israel*: Cerubidine; *Ital.*: Daunoblastina; DaunoXome; *Mex.*: Rubilem; *Neth.*: Cerubidine; DaunoXome; *Norw.*: Cerubidin; DaunoXome; *Port.*: DaunoXome; *Rus.*: DaunoXome (Даунозом)†; *S.Afr.*: Daunoblastin; *Singapore*: Daunoblastina; Daunocin; *Spain*: Daunoblastina; *Swed.*: Cerubidin; DaunoXome†; *Switz.*: Cerubidine†; *UK*: DaunoXome; *USA*: Cerubidine; DaunoXome; *Venez.*: Daunoblastina.

Pharmacopoeial Preparations

USP 36: Daunorubicin Hydrochloride for Injection.

Decitabine *(BAN, USAN, rINN)*

5-Aza-2′-deoxycytidine; DAC; Decitabina; Décitabine; Decitabinum; NSC-127716; Децитабин.

4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one.

$C_8H_{12}N_4O_4$=228.2

CAS — 2353-33-5.

ATC — L01BC08.

ATC Vet — QL01BC08.

UNII — 776B62CQ27.

Uses and Administration

Decitabine is an antineoplastic antimetabolite structurally related to cytarabine (p. 774.1). It is reported to cause DNA hypomethylation by the inhibition of DNA methyltransferase, which has the potential to alter gene expression (reactivate silent genes) and limit disease progression and resistance. Decitabine is used in the treatment of myelodysplastic syndromes (p. 694.3); it is also used in the management of newly diagnosed or secondary acute myeloid leukaemia (p. 693.1) in patients 65 years of age or older who are not candidates for standard induction chemotherapy.

Decitabine is given by intravenous infusion, diluted to a final concentration of 0.1 to 1 mg/mL in sodium chloride 0.9%, glucose 5%, or lactated Ringer's injection.

For the treatment of **myelodysplastic syndromes** the recommended dose is 15 mg/m² infused over 3 hours and given every 8 hours for 3 days; this 3-day cycle is repeated every 6 weeks, for a minimum of 4 cycles. If haematological recovery from a cycle is incomplete, cycle length may be increased to as much as every 10 weeks and the dose reduced to 11 mg/m² every 8 hours upon restarting therapy; this dose may be maintained or increased in subsequent cycles as clinically indicated. An alternative regimen is decitabine 20 mg/m² infused over 1 hour and given once daily for 5 days; this 5-day cycle is repeated every 4 weeks, for at least 4 cycles. If myelosuppression occurs, subsequent cycles should be delayed until haematological recovery.

Decitabine treatment should be delayed if serum creatinine is 2 mg per 100 mL or greater, or if total bilirubin is 2 or more times the upper limit of normal, or if the patient has an active or uncontrolled infection.

For the treatment of **acute myeloid leukaemia** the recommended dose of decitabine is 20 mg/m² infused over 1 hour and given once daily for 5 days; this 5-day cycle is repeated every 4 weeks, for at least 4 cycles. If myelosuppression occurs, subsequent cycles should be delayed until haematological recovery.

Decitabine is also under investigation for the treatment of chronic myeloid leukaemia (p. 694.2). It is also reported to increase fetal haemoglobin in patients with sickle-cell disease (p. 1123.2).

References.

1. DeSimone J, *et al.* Maintenance of elevated fetal hemoglobin levels by decitabine during dose interval treatment of sickle cell anemia. *Blood* 2002; **99**: 3905–8.
2. Momparler RL. Pharmacology of 5-aza-2′-deoxycytidine (decitabine). *Semin Hematol* 2005; **42** (suppl 2): S9–S16.
3. Kantarjian HM, Issa JP. Decitabine dosing schedules. *Semin Hematol* 2005; **42** (suppl 2): S17–S22. Correction. *ibid.*; 274.
4. Lubbert M, Minden M. Decitabine in acute myeloid leukemia. *Semin Hematol* 2005; **42** (suppl 2): S38–S42.
5. Issa JP, Byrd JC. Decitabine in chronic leukemias. *Semin Hematol* 2005; **42** (suppl 2): S43–S49.
6. Kuykendall JR. 5-Azacytidine and decitabine monotherapies of myelodysplastic disorders. *Ann Pharmacother* 2005; **39**: 1700–9.
7. Momparler RL. Epigenetic therapy of cancer with 5-aza-2′-deoxycytidine (decitabine). *Semin Oncol* 2005; **32**: 443–51.
8. Kantarjian H, *et al.* Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer* 2006; **106**: 1794–1803.
9. McKeage K, Croom KF. Decitabine in myelodysplastic syndromes. *Drugs* 2006; **66**: 951–8.
10. Jabbour E, *et al.* Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. *Cancer* 2008; **112**: 2341–51.
11. Steensma DP, *et al.* Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. *J Clin Oncol* 2009; **27**: 3842–8.
12. Santos FP, *et al.* Decitabine in the treatment of myelodysplastic syndromes. *Expert Rev Anticancer Ther* 2010; **10**: 9–22.
13. Daskalakis M, *et al.* Decitabine. *Recent Results Cancer Res* 2010; **184**: 131–57.
14. Ganetsky A. The role of decitabine for the treatment of acute myeloid leukemia. *Ann Pharmacother* 2012; **46**: 1511–17.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. The most common adverse effect of decitabine is myelosuppression, which may be severe and dose-limiting. Fatalities have been reported. Other common adverse effects include fatigue, pyrexia, gastrointestinal disturbances, petechiae, and hyperglycaemia. Cardiorespiratory arrest, increased blood bilirubin, intracranial haemorrhage, abnormal liver function tests, pulmonary oedema, atrial fibrillation, central line infection, or febrile neutropenia may force treatment to be stopped or delayed. Other adverse effects which may be dose-limiting include lethargy, oedema, tachycardia, depression, or pharyngitis.

Pharmacokinetics

On intravenous dosage decitabine shows biphasic disposition. Plasma protein binding is negligible. The exact route of metabolism and excretion is not known; one pathway appears to be deamination by cytidine deaminase, which is found principally in the liver, but also in granulocytes, the intestinal epithelium, and whole blood. A terminal elimination half-life of about 0.5 hours has been reported after a 72-hour infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dacogen; Detavi; *Braz.*: Dacogen; *Chile*: Dacogen; *China*: Dacogen (达珂); *Israel*: Dacogen; *Malaysia*: Dacogen; *Neth.*: Dacogen; *Philipp.*: Dacogen; *Rus.*: Dacogen (Дакоген); *Switz.*: Dacogen; *Thai.*: Dacogen; *Turk.*: Dacogen; *UK*: Dacogen; *USA*: Dacogen.

Denileukin Diftitox *(USAN, rINN)*

$DAB_{389}IL2$; Denileucina diftitox; Denileukin Difitox (BAN); Dénileukine Diftitox; Denileukinum Diftitoxum; LY-335348; Денилейкин Дифтитокс.

CAS — 173146-27-5.

ATC — L01XX29.

ATC Vet — QL01XX29.

UNII — 25E79B5CTM.

Uses and Administration

Denileukin diftitox is a recombinant interleukin fusion toxin comprised of interleukin-2 linked to the A and B fragments of diphtheria toxin. It is given by intravenous infusion for the management of persistent or recurrent cutaneous T-cell lymphoma (see Mycosis Fungoides, p. 698.3), in patients whose malignant cells express the CD25 interleukin-2 receptor. The concentration of denileukin diftitox must be at least 15 micrograms/mL during all steps in the preparation of the solution for infusion. The recommended dose is 9 or 18 micrograms/kg daily, given over 15 minutes or more, for 5 consecutive days every 3 weeks.

References.

1. Olsen E, *et al.* Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001; **19**: 376–88.
2. Martin A, *et al.* A multicenter dose-escalation trial with denileukin diftitox (ONTAK, DAB(389)IL-2) in patients with severe psoriasis. *J Am Acad Dermatol* 2001; **45**: 871–81.
3. Talpur R, *et al.* Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK). *Leuk Lymphoma* 2002; **43**: 121–6.
4. Frankel AE, *et al.* A phase II study of DT fusion protein denileukin diftitox in patients with fludarabine-refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2003; **9**: 3555–61.
5. Eklund JW, Kuzel TM. Denileukin diftitox: a concise clinical review. *Expert Rev Anticancer Ther* 2005; **5**: 33–8.
6. Foss F. Clinical experience with denileukin diftitox (ONTAK). *Semin Oncol* 2006; **33** (suppl 3): 11–16.
7. Duvic M, Talpur R. Optimizing denileukin diftitox (Ontak) therapy. *Future Oncol* 2008; **4**: 457–69.
8. Manoukian G, Hagemeister F. Denileukin diftitox: a novel immunotoxin. *Expert Opin Biol Ther* 2009; **9**: 1445–51.
9. Prince HM, *et al.* Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2010; **28**: 1870–7.

Adverse Effects and Precautions

Denileukin diftitox can cause an acute hypersensitivity reaction within 24 hours of infusion with symptoms reminiscent of a cytokine release syndrome. Anaphylaxis and death have also been reported. A more delayed flu-like syndrome may also occur up to several days after infusion. Vascular leak syndrome, characterised by hypotension, oedema, or hypoalbuminaemia, may also be delayed. Gastrointestinal disturbances, chills, fever, and asthenia are common. Other adverse effects include rash, predisposition to cutaneous infections, and thrombotic events. Visual loss has been reported; although recovery was reported in some patients, in most cases impairment persisted.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Ontak; *USA*: Ontak.

Diaziquone *(USAN, rINN)*

Aziridinylbenzoquinone; AZQ; CI-904; Diazicuona; Diaziquonum; NSC-182986; Диазихон.

Diethyl 2,5-bis-(1-aziridinyl)-3,6-dioxo-1,4-cyclohexadiene-1,4-dicarbamate.

$C_{16}H_{20}N_4O_6$=364.4

CAS — 57998-68-2.

UNII — FQL5EUP13W.

Profile

Diaziquone has been investigated as an antineoplastic in the treatment of malignant brain tumours and acute myeloid leukaemia. It is thought to act as an alkylating agent. Adverse effects include bone-marrow suppression, manifesting chiefly as leucopenia and thrombocytopenia, gastrointestinal disturbances, and alopecia. Anaphylactoid reactions have occurred.

Docetaxel *(BAN, USAN, rINN)*

Docetaksel; Docétaxel; Docetaxelum; Docetaxol; Docetaxolum; Dosetaksel; Dosetaksoli; NSC-628503; RP-56976; Доцетаксел.

(2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate; *tert*-Butyl {(1*S*,2*S*)-2-[(2*S*,5*R*,7*S*,10*R*,13*S*)-4-acetoxy-2-benzoyloxy-1,7,10-trihydroxy-9-oxo-5,20-epoxytax-11-en-13-yloxycarbonyl]-2-hydroxy-1-phenylethyl}carbamate.

$C_{43}H_{53}NO_{14}$=807.9

CAS — 114977-28-5 (anhydrous docetaxel); 148408-66-6 (docetaxel trihydrate).

ATC — L01CD02.

ATC Vet — QL01CD02.

UNII — 15H5577CQD (docetaxel); o99121PHCA (anhydrous docetaxel).

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

Ph. Eur. 8: (Docetaxel, Anhydrous). A white or almost white, crystalline, hygroscopic powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light.

Ph. Eur. 8: (Docetaxel Trihydrate). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in dichloromethane. Protect from light.

USP 36: (Docetaxel). A white or almost white, crystalline powder. Practically insoluble in water; soluble in methyl alcohol; freely soluble in acetone. Protect from light.

Incompatibility and stability. Various formulations of docetaxel are available; some require an initial reconstitution of a concentrate with a solvent (resulting in a premix solution) before further dilution for infusion, whereas others are available in vials as a solution ready for further dilution for infusion. Both the premix solutions and the vials should be used as soon as possible after reconstitution and opening, respectively. However, licensed product information (*Actavis, UK*) states that the premix solution is chemically and physically stable for 8 hours when stored between 2 degrees and 8 degrees or at room temperature (below 25 degrees). The same company states for its solution formulation that physical, chemical, and microbiological stability has been shown for 28 days at 2 degrees to 8

degrees and at 25 degrees under normal lighting conditions (after the first vial opening).

Docetaxel is further diluted with sodium chloride 0.9% or glucose 5% to a concentration not exceeding 740 micrograms/mL; chemical and physical stability, and maximum storage time varies between products:

- *Actavis, UK* (premix solution formulation): 4 hours at about 25 degrees under normal lighting; 4 hours at 5 degrees ± 3 degrees, protected from light; storage not longer than 24 hours at 2 degrees to 8 degrees
- *Actavis, UK* (concentrate solution): 8 hours at about 25 degrees under normal lighting; 3 days at 2 degrees to 8 degrees, protected from light
- *Hospira, UK*: 4 hours when stored below 25 degrees; storage not longer than 24 hours at 2 degrees to 8 degrees
- *Taxotere, Sanofi-Aventis, UK*: 6 hours when stored below 25 degrees; 48 hours at 2 degrees to 8 degrees (in non-PVC bags; see below for further information)

Product literature should therefore be consulted.

The chemical and physical stability of various docetaxel infusion solutions has been studied.[1-3] The *Taxotere* formulation was diluted to 300 or 900 micrograms/mL with sodium chloride 0.9% in polyolefin containers or glass bottles, and stored at 19 degrees to 21 degrees and protected from light.[1] There was no evidence of precipitation in the first 24 hours of storage. However, after this time, HPLC assay revealed concentrations with large standard deviations for some containers, suggesting the existence of microprecipitates. Precipitation was a generalised phenomenon at day 7, especially in glass containers. The results of this study supported the use of docetaxel within 4 hours of preparation, and the authors cautioned that docetaxel (*Taxotere* formulation) was very labile and physical stability could be strongly affected by small variations in handling conditions.[1]

Many docetaxel formulations contain polysorbate 80, which has the potential to leach the plasticiser diethylhexyl phthalate (DEHP) from PVC bags, and use in such containers is to be avoided.[3] In order to minimise patient exposure to DEHP, some manufacturers (*Hospira, UK*) recommend that docetaxel be stored in glass bottles or polypropylene or polyolefin containers, and given through polyethylene-lined giving sets. Similar recommendations are made for paclitaxel, see under Incompatibility, p. 839.3.

1. Eroles AA, *et al.* Stability of docetaxel diluted to 0.3 or 0.9 mg/mL with 0.9% sodium chloride injection and stored in polyolefin or glass containers. *Am J Health-Syst Pharm* 2009; 66: 1565–8.
2. Thiesen J, Krämer I. Physico-chemical stability of docetaxel premix solution and docetaxel infusion solutions in PVC bags and polyolefine containers. *Pharm World Sci* 1999; 21: 137–41.
3. Dalle M, *et al.* Peut-on conditionner les solutions de docétaxel dans des poches en PVC? Can solutions of docetaxel be conditioned in PVC bags? *J Pharm Clin* 2006; 25: 147–52.

Uses and Administration

Docetaxel is a semisynthetic taxane similar to paclitaxel (see p. 839.3). It is manufactured from a taxane precursor derived from the needles of the European yew tree *Taxus baccata*. Docetaxel is used for locally advanced or metastatic breast cancer (p. 702.1). It may be used as first-line treatment with doxorubicin; in the treatment of refractory disease, it is used alone or with capecitabine. In the treatment of metastatic breast cancer that overexpresses HER2 (human epidermal growth receptor 2), docetaxel may be used with trastuzumab as initial therapy. For adjuvant treatment of operable, node-positive breast cancer, docetaxel is given with doxorubicin and cyclophosphamide. Docetaxel is also indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (p. 710.2), either with cisplatin for initial treatment of unresectable disease, or after failure of previous platinum-based chemotherapy. It is used with prednisone or prednisolone in hormone-refractory metastatic prostate cancer (p. 712.3). Docetaxel is given with cisplatin and fluorouracil in the first-line treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction (see Malignant Neoplasms of the Stomach, p. 706.1); it is also used in this combination for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (p. 708.1).

Docetaxel is given by intravenous infusion in glucose 5% or sodium chloride 0.9% at a concentration not exceeding 740 micrograms/mL. Infusion is normally over 1 hour. Premedication with an oral corticosteroid, such as dexamethasone 16 mg daily, for 3 days starting 1 day before docetaxel is recommended with many regimens.

The licensed dose for docetaxel as a single agent in the treatment of **breast cancer** after failure of previous chemotherapy is 60 to 100 mg/m^2 once every 3 weeks. A dose of 75 mg/m^2 once every 3 weeks is given in combination therapy with doxorubicin, or capecitabine, or when used as adjuvant therapy with doxorubicin and cyclophosphamide. When used with trastuzumab, docetaxel is given at a dose of 100 mg/m^2 once every 3 weeks.

The dose for **non-small cell lung cancer** is 75 mg/m^2 once every 3 weeks, for both first-line combination therapy and monotherapy after failure of previous chemotherapy.

For **gastric adenocarcinoma** docetaxel 75 mg/m^2 is given before cisplatin and fluorouracil; treatment is repeated every 3 weeks.

In the induction treatment of **head and neck cancer**, the recommended dose of docetaxel is 75 mg/m^2, given before cisplatin and fluorouracil; treatment is given every 3 weeks for 3 cycles, followed by chemoradiotherapy, or for 4 cycles when followed by radiotherapy alone.

For **prostate cancer**, the dose of docetaxel is 75 mg/m^2 once every 3 weeks, with prednisone or prednisolone 5 mg orally twice daily given continuously. The use of prednisone or prednisolone reduces the need for a premedication corticosteroid; dexamethasone 8 mg may be given at 12 hours, 3 hours, and 1 hour before docetaxel.

Regular blood counts are required, and dosage in subsequent courses should be reduced in patients who develop severe or febrile neutropenia (see also Bone-marrow Depression, p. 730.3), or severe cutaneous reactions or peripheral neuropathy. The dose of docetaxel should be reduced in hepatic impairment, see below. A dose reduction is also suggested when docetaxel is used with strong cytochrome P450 isoenzyme CYP3A4 inhibitors, see Administration with Other Drugs, below.

Novel formulations of docetaxel are under investigation, including a pegylated conjugate, a lyophilised emulsion, and a docetaxel prodrug nanoparticle formulation.

References. For references to taxanes as a class, see Paclitaxel, p. 840.2.

1. Montero A, *et al.* Docetaxel for treatment of solid tumours: a systematic review of clinical data. *Lancet Oncol* 2005; 6: 229–39.
2. Engels FK, *et al.* Potential for improvement of docetaxel-based chemotherapy: a pharmacological review. *Br J Cancer* 2005; 93: 173–7.
3. McKeage K, Keam SJ. Docetaxel: in hormone-refractory metastatic prostate cancer. *Drugs* 2005; 65: 2287–94.
4. Lyseng-Williamson KA, Fenton C. Docetaxel: a review of its use in metastatic breast cancer. *Drugs* 2005; 65: 2513–31.
5. Deeks ED, Scott LJ. Docetaxel: in gastric cancer. *Drugs* 2007; 67: 1893–1901.
6. Bernier J, Vrieling C. Docetaxel in the management of patients with head and neck squamous cell carcinoma. *Expert Rev Anticancer Ther* 2008; 8: 1023–32.
7. Saloustros E, Georgoulias V. Docetaxel in the treatment of advanced non-small-cell lung cancer. *Expert Rev Anticancer Ther* 2008; 8: 1207–22.
8. De Dosso S, Berthold DR. Docetaxel in the management of prostate cancer: current standard of care and future directions. *Expert Opin Pharmacother* 2008; 9: 1969–79.
9. Saloustros E, *et al.* Paclitaxel and docetaxel in the treatment of breast cancer. *Expert Opin Pharmacother* 2008; 9: 2603–16.
10. Caponigro F, *et al.* Docetaxel in the management of head and neck cancer. *Anticancer Drugs* 2009; 20: 639–45.
11. Nishiyama M, Wada S. Docetaxel: its role in current and future treatments for advanced gastric cancer. *Gastric Cancer* 2009; 12: 132–41.
12. Galsky MD, Vogelzang NJ. Docetaxel-based combination therapy for castration-resistant prostate cancer. *Ann Oncol* 2010; 21: 2135–44.

Administration. Docetaxel has been investigated as a low-dose weekly infusion, in patient groups such as the elderly, those with poor performance status, or refractory disease.[1-6] Weekly doses of 30 to 40 mg/m^2 are considered to be of similar efficacy to the standard three-weekly dosage regimen[7] (see also under Paclitaxel, p. 840.2). A pharmacokinetic study in 20 elderly patients suggested that a suitable starting dose might be 26 mg/m^2, increased provided there was no toxicity, but see also below.[8]

1. Hainsworth JD, *et al.* Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *J Clin Oncol* 2001; 19: 3500–5.
2. Mekhail T, *et al.* Phase I trial of weekly docetaxel and gemcitabine in patients with refractory malignancies. *Cancer* 2003; 97: 170–8.
3. Petrioli R, *et al.* Weekly low-dose docetaxel in advanced non-small cell lung cancer previously treated with two chemotherapy regimens. *Lung Cancer* 2003; 39: 85–9.
4. Di Maio M, *et al.* Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2007; 25: 1377–82.
5. Abbrederis K, *et al.* Weekly docetaxel monotherapy for advanced gastric or esophagogastric junction cancer: results of a phase II study in elderly patients or patients with impaired performance status. *Crit Rev Oncol Hematol* 2008; 66: 84–90.
6. Rivera E, *et al.* Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer* 2008; 112: 1455–61.
7. Hainsworth JD. Practical aspects of weekly docetaxel administration schedules. *Oncologist* 2004; 9: 538–45.
8. Hurria A, *et al.* Pharmacokinetics and toxicity of weekly docetaxel in older patients. *Clin Cancer Res* 2006; 12: 6100–5.

Administration in the elderly. A review[1] found no significant data to support dose modifications of docetaxel based on age alone. While elderly patients may be more vulnerable to adverse effects, interpatient variability appears to be more important than age-related variability.

See also Administration, above.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in hepatic impairment. UK licensed product information recommends that doses of docetaxel monotherapy should be reduced from 100 mg/m^2 to 75 mg/m^2 in mild to moderate hepatic impairment, defined as alanine aminotransferase (ALT/SGPT) and/or aspartate aminotransferase (AST/SGOT) more than 1.5 times the upper limit of normal (ULN), and alkaline phosphatase more than 2.5 times the ULN. Hepatic function should be monitored; use should be avoided if possible in severe hepatic impairment. US licensed information advises against the use of docetaxel in patients with bilirubin above ULN, or in those with mild to moderate hepatic impairment (defined as for the UK, above).

Administration with other drugs. Use of docetaxel with strong cytochrome P450 isoenzyme CYP3A4 inhibitors may affect exposure to docetaxel (see Interactions, p. 782.1). Clinical data on appropriate dose adjustment of docetaxel are limited. US licensed product information recommends a 50% dose reduction of docetaxel when use with strong CYP3A4 inhibitors cannot be avoided; this is based on extrapolation from a small pharmacokinetic study of the use of docetaxel with ketoconazole (but see Antifungals, p. 782.2).

For doses of docetaxel when given as part of licensed chemotherapy combination regimens, see Uses and Administration, above.

It has been suggested that administration with inhibitors of CYP3A4 or P-glycoprotein or both might allow *oral* administration of docetaxel to produce viable exposure to the drug; see Antiretrovirals and Immunosuppressants, p. 782.2.

Adverse Effects, Treatment, and Precautions

As for Paclitaxel, p. 841.1. Neutropenia, anaemia and skin reactions are common with docetaxel and may be severe. Fluid retention, resulting in oedema, ascites, pleural and pericardial effusion, and weight gain, is also common, and may be cumulative; premedication with a corticosteroid can reduce fluid retention as well as the severity of hypersensitivity reactions. Asthenia and fatigue have also been reported. Rare cases of ototoxicity, hearing impairment or loss have occurred. Very rare cases of acute myeloid leukaemia and myelodysplastic syndrome have been reported with combination chemotherapy regimens containing docetaxel; haematological follow-up may be required.

Docetaxel should not be used in patients hypersensitive to polysorbate 80, which is contained in the formulation. Patients with hepatic impairment show increased sensitivity to toxic effects of docetaxel, and should be given the drug with great care and in reduced doses, if at all.

A review of 6 adverse effects that have been seen with most docetaxel-based regimens (febrile neutropenia, hypersensitivity reactions, fluid retention, nail toxicity, asthenia, and neuropathy) and their management.[1]

1. Baker J, *et al.* Docetaxel-related side effects and their management. *Eur J Oncol Nurs* 2009; 13: 49–59.

Effects on the eyes. Excessive tear formation (epiphora) severe enough to interfere with reading and driving has been reported in patients given docetaxel. Canalicular stenosis has been described as the mechanism for this effect, and docetaxel has been measured in tear fluid suggesting that irritation of the ocular surface and fibrosis of the tear drainage ducts may be caused by direct contact with docetaxel.[1] Epiphora and canalicular stenosis are more severe and occur more frequently in patients given weekly docetaxel than in those who receive the drug every 3 weeks.[2,3] The mean cumulative dose of docetaxel was found to be higher in those patients who developed stenosis.[2] Management of this adverse effect includes probing and irrigation of the lachrymal ducts and canalicular silicone tubing placement, alone or after surgery. The condition is generally reversible and tubing can be removed 4 to 6 weeks after stopping docetaxel therapy.[4] The use of topical tobramycin and dexamethasone on a tapering regimen can sometimes eliminate the need for silicone intubation or surgery.[3]

Very rare cases of transient visual disturbances such as flashing lights and scotomata have occurred during docetaxel infusion, and in association with hypersensitivity reactions. These were reversible upon stopping the infusion. For reference to a report of glaucoma possibly related to docetaxel, see Paclitaxel, p. 841.2.

1. Esmaeli B, *et al.* Docetaxel secretion in tears: association with lacrimal drainage obstruction. *Arch Ophthalmol* 2002; 120: 1180–2.
2. Esmaeli B, *et al.* Canalicular stenosis secondary to weekly versus every-3-weeks docetaxel in patients with metastatic breast cancer. *Ophthalmology* 2002; 109: 1188–91.
3. Esmaeli B, *et al.* Prospective study of incidence and severity of epiphora and canalicular stenosis in patients with metastatic breast cancer receiving docetaxel. *J Clin Oncol* 2006; 24: 3619–22.
4. Ahmadi MA, Esmaeli B. Surgical treatment of canalicular stenosis in patients receiving docetaxel weekly. *Arch Ophthalmol* 2001; 119: 1802–4.

Effects on the gastrointestinal tract. Ischaemic colitis has occurred in patients treated with docetaxel.[1-3] Some

patients also received vinorelbine, which may have exacerbated this complication.[1,2]

1. Ibrahim NK, *et al.* Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. *Lancet* 2000; 355: 281–3.
2. de Matteis A, *et al.* Intestinal side-effects of docetaxel/vinorelbine combination. *Lancet* 2000; 355: 1098–9.
3. Hussein MAR, *et al.* Docetaxel-related ischemic colitis. *J Clin Oncol* 2005; 23: 9424–5.

Effects on the heart. For comment on the increased risk of heart failure when docetaxel is given with trastuzumab and after anthracyclines, see under Interactions, below.

Effects on the lungs. Reviews[1,2] of interstitial lung disease associated with docetaxel.

1. Grande C, *et al.* Docetaxel-induced interstitial pneumonitis following non-small-cell lung cancer treatment. *Clin Transl Oncol* 2007; 9: 578–81.
2. Alsamarai S, *et al.* Pneumonitis related to docetaxel: case report and review of the literature. *In Vivo* 2009; 23: 635–7.

Effects on the musculoskeletal system. For reference to cases of taxane-induced arthralgia and myalgia successfully treated with gabapentin, see Paclitaxel, p. 841.3.

Effects on the skin, hair, and nails. Palmar-plantar erythrodysesthesia syndrome (p. 730.1) has been reported with the use of docetaxel.[1,2] For reference to the use of vitamin E to alleviate palmar-plantar erythrodysesthesia syndrome caused by docetaxel and capecitabine, see Chemotherapy-induced Toxicity, under Uses of Vitamin E, p. 2120.1. Cases of radiation recall dermatitis associated with docetaxel have also been reported.[3-5] There is a further report of recall dermatitis at sites previously treated with a laser.[6] A hyperpigmented eruption developed in a patient at the site of docetaxel injection after insufficient venous flushing; no eruption occurred after a second infusion with abundant venous flushing.[7] Licensed product information states that very rare cases of bullous eruption such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with docetaxel, but that other factors may have contributed to the development of these reactions.

In a multicentre study, patients given docetaxel wore a frozen glove on the right hand, leaving the left hand unprotected to serve as a control. The use of the glove significantly reduced skin and nail toxicity.[8]

For reference to reports of scleroderma, alopecia, and further adverse effects on the nails after the use of docetaxel, see Paclitaxel, p. 841.3.

1. Eich D, *et al.* Acral erythrodysesthesia syndrome caused by intravenous infusion of docetaxel in breast cancer. *Am J Clin Oncol* 2002; 25: 599–602.
2. Benghiat H, Al-Naimi A. Palmar-plantar erythrodysesthesia secondary to docetaxel chemotherapy: a case report. *J Med Case Reports* 2011; 5: 80.
3. Piroth MD, *et al.* Radiation recall dermatitis from docetaxel. *Onkologie* 2002; 25: 438–40.
4. Kandemir EG, *et al.* Docetaxel-induced radiation recall dermatitis. *Swiss Med Wkly* 2005; 135: 34–5.
5. Borgia P, *et al.* Radiation recall dermatitis after docetaxel administration: absolute indication to replace the drug? *Br J Dermatol* 2005; 153: 674–5.
6. Chu C-Y, Yang C-H. Docetaxel-induced recall dermatitis on previous laser treatment sites. *Br J Dermatol* 2005; 153: 441–3.
7. Aydogan I, *et al.* Persistent serpentine supravenous hyperpigmented eruption associated with docetaxel. *J Eur Acad Dermatol Venereol* 2005; 19: 345–7.
8. Scotté F, *et al.* Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. *J Clin Oncol* 2005; 23: 4424–9.

Hypersensitivity. For a discussion of taxane-induced hypersensitivity, including references to desensitisation protocols, see under Paclitaxel, p. 842.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies docetaxel 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 05/09/11)

Pregnancy. For discussion of the use of taxanes during pregnancy, see Paclitaxel, p. 842.1.

Tumour lysis syndrome. Fatal cases of tumour lysis syndrome (p. 730.2) have been reported after the second-line use of docetaxel.[1,2]

1. Sorscher SM. Tumor lysis syndrome following docetaxel therapy for extensive metastatic prostate cancer. *Cancer Chemother Pharmacol* 2004; 54: 191–2.
2. Ajzensztejn D, *et al.* Tumor lysis syndrome after treatment with docetaxel for non-small-cell lung cancer. *J Clin Oncol* 2006; 24: 2389–91.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Docetaxel is metabolised by the cytochrome P450 isoenzyme CYP3A4 and use with inducers or inhibitors or other substrates of this enzyme may affect exposure to docetaxel. It should be given with caution to patients taking strong CYP3A4 inhibitors including HIV-protease inhibitors such as ritonavir, and azole antifungals like ketoconazole or itraconazole. Ketoconazole has been reported to reduce the clearance of docetaxel (but see below); based on this, US licensed product information recommends a dose reduction of docetaxel when it is given with strong CYP3A4 inhibitors if use together cannot be avoided (see Administration with Other Drugs, p. 781.3).

References.

1. Royer I, *et al.* Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs. *Cancer Res* 1996; 56: 58–65.

Antifungals. In a pharmacokinetic study, no consistent effects on docetaxel concentrations were seen with the addition of *ketoconazole*. Significant inter- and intrapatient variability was noted and a potential interaction could not be excluded.[1] In another study in 7 patients, however, the clearance of docetaxel was significantly reduced by 49% when given with ketoconazole.[2]

1. Van Veldhuizen PJ, *et al.* Docetaxel and ketoconazole in advanced hormone-refractory prostate carcinoma: a phase 1 and pharmacokinetic study. *Cancer* 2003; 98: 1855–62.
2. Engels FK, *et al.* Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel. *Clin Pharmacol Ther* 2004; 75: 448–54.

Antineoplastics. The clearance of a dose of docetaxel was markedly reduced[1] when it was given after 4 days of treatment with *topotecan*, rather than on day 1; this resulted in worsened neutropenia.

Sorafenib may increase systemic exposure to docetaxel.

An increased incidence of febrile neutropenia and gastrointestinal disorders, including 2 fatalities, was reported in patients given docetaxel with *doxorubicin*,[2] although others[3] considered this high incidence unrepresentative of usual toxicity rates with this combination.

Heart failure has been reported in patients given docetaxel with other cytotoxic drugs, especially *trastuzumab*, and particularly after anthracycline-containing therapy. UK licensed product information therefore recommends that patients given docetaxel with trastuzumab should undergo baseline cardiac assessment and cardiac function should be monitored during treatment.

1. Zamboni WC, *et al.* Pharmacokinetic and pharmacodynamic study of the combination of docetaxel and topotecan in patients with solid tumors. *J Clin Oncol* 2000; 18: 3288–94.
2. Brain EGC, *et al.* Life-threatening sepsis associated with adjuvant doxorubicin plus docetaxel for intermediate-risk breast cancer. *JAMA* 2005; 293: 2367–71.
3. Martin M, *et al.* Life-threatening complications from doxorubicin-docetaxel chemotherapy for breast cancer. *JAMA* 2005; 294: 2166.

Antiretrovirals. *HIV-PROTEASE INHIBITORS.* Severe toxicity has been reported after the use of intravenous docetaxel with *ritonavir*, probably due to ritonavir-induced inhibition of cytochrome P450 isoenzyme CYP3A4, causing a significant increase in exposure to docetaxel.[1]

Subsequently, the use of ritonavir to boost systemic exposure to oral docetaxel (which has a low bioavailability) has been investigated.[2,3] Use of these two drugs together was well tolerated,[2] and resulted in enhanced oral absorption and reduced elimination of docetaxel.[3] A pharmacokinetic model has been developed[3] to establish optimal combination regimens.

1. Mir O, *et al.* Severe toxicity related to a pharmacokinetic interaction between docetaxel and ritonavir in HIV-infected patients. *Br J Clin Pharmacol* 2010; 69: 99–101.
2. Oostendorp RL, *et al.* Coadministration of ritonavir strongly enhances the apparent oral bioavailability of docetaxel in patients with solid tumors. *Clin Cancer Res* 2009; 15: 4228–33.
3. Koolen SLW, *et al.* Population pharmacokinetics of intravenously and orally administered docetaxel with or without co-administration of ritonavir in patients with advanced cancer. *Br J Clin Pharmacol* 2010; 69: 465–74.

Immunosuppressants. Oral bioavailability of the taxanes docetaxel and paclitaxel is low, partly due to their affinity for P-glycoprotein;[1,2] metabolism by cytochrome P450 isoenzyme CYP3A4 and poor solubility may also contribute. Studies have found that exposure to oral docetaxel[1,2] and paclitaxel[2] can be increased by use with *ciclosporin*, a P-glycoprotein inhibitor. P-glycoprotein inhibitors might be used to boost the bioavailability of an oral formulation, although ciclosporin is not an ideal candidate because of its immunosuppressive effects.[2]

1. Malingré MM, *et al.* Coadministration of cyclosporine strongly enhances the oral bioavailability of docetaxel. *J Clin Oncol* 2001; 19: 1160–6.
2. Koolen SLW, *et al.* Intravenous-to-oral switch in anticancer chemotherapy: a focus on docetaxel and paclitaxel. *Clin Pharmacol Ther* 2010; 87: 126–9.

Pharmacokinetics

On intravenous dosage docetaxel is rapidly distributed to body tissues. Docetaxel is more than 95% bound to plasma proteins. It is extensively metabolised via hepatic cytochrome P450 isoenzyme CYP3A4 and excreted chiefly in the faeces as metabolites. Only about 6% of a dose is excreted in urine. The terminal elimination half-life is about 11 hours. Clearance is reduced in hepatic impairment.

References.

1. Rudek MA, *et al.* Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. *Eur J Cancer* 2004; 40: 1170–8.
2. Baker SD, *et al.* Clinical pharmacokinetics of docetaxel: recent developments. *Clin Pharmacokinet* 2006; 45: 235–52.
3. Tran A, *et al.* Pharmacokinetics and toxicity of docetaxel: role of CYP 3A, MDR1, and GST polymorphisms. *Clin Pharmacol Ther* 2006; 79: 570–80.
4. Charles KA, *et al.* Predicting the toxicity of weekly docetaxel in advanced cancer. *Clin Pharmacokinet* 2006; 45: 611–22.
5. Baker SD, *et al.* Pharmacogenetic pathway analysis of docetaxel elimination. *Clin Pharmacol Ther* 2009; 85: 155–63.
6. Minami H, *et al.* Population pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice. *Cancer Sci* 2009; 100: 144–9.
7. Franke RM, *et al.* Castration-dependent pharmacokinetics of docetaxel in patients with prostate cancer. *J Clin Oncol* 2010; 28: 4562–7.
8. Gerritsen-van Schieveen P, Royer B. Suivi Thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique du docétaxel. *Therapie* 2010; 65: 201–6.
9. Engels FK, *et al.* Therapeutic drug monitoring for the individualization of docetaxel dosing: a randomized pharmacokinetic study. *Clin Cancer Res* 2011; 17: 353–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Asodocel; Docekehir; Dolectran; Donataxel; Doxetal; Eriox; Plustaxano; Taxotere; Texot; Trazoteva; *Austral.*: Oncotaxel; Taxotere; *Austria*: Ebedoce; Taxotere; *Belg.*: Taxotere; *Braz.*: Docelibbs; Docetere; Oncodocel; Taxotere; Trixotene; *Canad.*: Taxotere; *Chile*: Taxotere; *China*: Ai Su (艾素); Ao Ming Run (奥名润); Duo Pa Tei (多帕菲); Ruilibo (瑞立博); Si Qu Di (斯曲帝); Taxotere (泰索帝); Xi Cun (希存); Yi You Rui Kang (易优瑞康); *Cz.*: Cetaxocure; Docefrez; Taxotere; *Denm.*: Cetadocure; Taxotere; *Fin.*: Taxotere; *Fr.*: Taxotere; *Ger.*: Bendadocel; Docetaxin; Riboxocel; Taxceus; Taxotere; *Gr.*: Taxotere; *Hong Kong*: Taxotere; *Hung.*: Taxotere; *India*: Celtere; Daxotel; Detaxl; Docecad; Docefrez; Docet; Docetax; Docetec; Docetere; Doxel; Ferdotaxx; *Indon.*: Brexel; Docetere; Taxotere; *Irl.*: Docefim; Docefrez; Docirena; Taxotere; *Israel*: Taxotere; *Ital.*: Cetadocure; Taxceus; Taxotere; *Jpn*: Taxotere; *Malaysia*: Taxotere; *Mex.*: Taxotere; *Neth.*: Cetadocure†; Dincilezan; Docefim; Docefrez†; Docirena; Dostradixinol; Taxceus; Taxotere; Tevadocel; Tolnexa; *Norw.*: Taxotere; *NZ*: Taxotere; *Philipp.*: Daxotel; Doci; Hentaxel; Taxotere; *Pol.*: Docefrez; Taxotere; *Port.*: Docefrez; Taxotere; *Rus.*: Tautax (Таутакс); Taxotere (Таксотер); *S.Afr.*: Docetere; Taxotere; *Singapore*: Taxotere; *Spain*: Taxotere; *Swed.*: Taxotere; *Switz.*: Taxotere; *Thai.*: Daxotel; Taxotere; *Turk.*: Doxel; Docitax; Taxotere; *UK*: Taxotere; *Ukr.*: Taxotere (Таксотер); *USA*: Taxotere; *Venez.*: Daxotel; Taxotere.

Pharmacopoeial Preparations
USP 36: Docetaxel Injection.

Doxifluridine *(rINN)*

5-DFUR; Doxifluridina; Doxifluridinum; FUDR; Ro-21-9733; Доксифлуридин; 5′-Deoxy-5-fluorouridine.

$C_9H_{11}FN_2O_5$=246.2

CAS — 3094-09-5.

UNII — V1JK16Y2JP.

Pharmacopoeias. In *Jpn*.

Profile

Doxifluridine is an antineoplastic that probably acts through its conversion in the body to fluorouracil (p. 795.2). It is given orally in the management of malignant neoplasms of the breast (p. 702.1) and gastrointestinal tract (p. 705.2), and of other solid tumours, in doses of 0.8 to 1.2 g daily in divided doses. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Doxifluridine has also been given by the intravenous route.

Pharmacokinetics. Doxifluridine is metabolised to fluorouracil and 5,6-dihydrofluorouracil. It is orally active with a bioavailability of 34 to 47%.

References.

1. Sommadossi J-P, *et al.* Kinetics and metabolism of a new fluoropyrimidine, 5′-deoxy-5-fluorouridine, in humans. *Cancer Res* 1983; 43: 930–3.
2. Van Der Heyden SAM, *et al.* Pharmacokinetics and bioavailability of oral 5′-deoxy-5-fluorouridine in cancer patients. *Br J Clin Pharmacol* 1997; 47: 351–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ai Feng (艾丰); Furtulon (氟铁龙); Ke Fu (可弗); Ke Tuo (克托); Qi Nuo Bi Tong (奇诺必通); Shu Qi (枢绮); Tan Nuo (坦诺); Yi Di An (谊迪安); Zhi Ai (知爱); *Jpn*: Furtulon.

Doxorubicin *(BAN, USAN, rINN)*

Adriamycin; Doksorubisiini; Doxorubicina; Doxorubicine; Doxorubicinum; FI-106; 3-Hydroxyacetyldaunorubicin; 14-Hydroxydaunomycin; Доксорубицин.

8-Hydroxyacetyl (8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione.
$C_{27}H_{29}NO_{11}$=543.5
CAS — 23214-92-8.
ATC — L01DB01.
ATC Vet — QL01DB01.
UNII — 80168379AG.

NOTE. In many countries the name Adriamycin is a trademark.

Doxorubicin Citrate *(BANM, rINNM)*

Citrato de doxorubicina; Doxorubicin Citrate Liposome; Doxorubicine, Citrate de; Doxorubicini Citras; Liposomal Doxorubicin Citrate; Доксорубицина Цитрат.
$C_{27}H_{29}NO_{11}.xC_6H_8O_7$
CAS — 111266-55-8.
ATC — L01DB01.
ATC Vet — QL01DB01.

NOTE. Doxorubicin citrate complex is a constituent of some liposomal products. It is prepared from doxorubicin hydrochloride (below).

Doxorubicin Hydrochloride *(BANM, rINNM)*

Cloridrato de Doxorrubicina; Doksorubicino hidrochloridas; Doksorubicyny chlorowodorek; Doksorubisilinihydrokloridi; Doksorubisin Hidroklorür; Doxorubicin Hydrochloride Liposome; Doxorubicina, hidrocloruro de; Doxorubicine, Chlorhydrate de; Doxorubicin-hidroklorid; Doxorubicin-hydrochlorid; Doxorubicinhydrochlorid; Doxorubicinhydroklorid; Doxorubicini hydrochloridum; Hidrocloruro de doxorubicina; Liposomal Doxorubicin Hydrochloride; NSC-123127; Доксорубицина Гидрохлорид.
$C_{27}H_{29}NO_{11}.HCl$=580.0
CAS — 25316-40-9.
ATC — L01DB01.
ATC Vet — QL01DB01.
UNII — 82F2G78L4E.

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

Ph. Eur. 8: (Doxorubicin Hydrochloride). The hydrochloride of a substance isolated from certain strains of *Streptomyces coeruleorubidus* or *S. peucetius* or obtained by any other means. It contains between 98 and 102% of the hydrochloride, calculated on the anhydrous substance. An orange-red, hygroscopic, crystalline powder. Soluble in water; slightly soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Store in airtight containers.

USP 36: (Doxorubicin Hydrochloride). A red-orange, hygroscopic, crystalline or amorphous powder. It contains not less than 98% and not more than 102% of $C_{27}H_{29}NO_{11}$.HCl, calculated on the anhydrous, solvent-free basis. Soluble in water, in sodium chloride 0.9%, and in methyl alcohol; practically insoluble in chloroform, in ether, and in other organic solvents. A 0.5% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. It may exist in an amorphous form, which should be stored at -25 degrees to -10 degrees.

Incompatibility. Admixture of doxorubicin hydrochloride with cefalotin sodium, dexamethasone, diazepam, or hydrocortisone sodium succinate is reported to result in immediate precipitation;[1] similarly precipitation has occurred when doxorubicin hydrochloride was mixed with furosemide or heparin sodium.[2] A mixture of fluorouracil or aminophylline with doxorubicin hydrochloride is reported to darken in colour from red to purple, indicating degradation of doxorubicin.[1] For mention of the compatibility of doxorubicin with paclitaxel, see p. 839.3.

Liposomal doxorubicin differs in its incompatibilities from conventional formulations: whereas the latter are reportedly incompatible with allopurinol, cefepime, and ganciclovir, there was no visual evidence of this with the liposomal formulation. However, it was incompatible with several solutions including amphotericin B, docetaxel, gallium nitrate, hydroxyzine hydrochloride, metoclopramide hydrochloride, miconazole, mitoxantrone hydrochloride, morphine sulfate and some other opioids, paclitaxel, sodium bicarbonate, and some antibacterials.[3]

1. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; 6: 42–52.
2. Cohen MH, *et al.* Drug precipitation within IV tubing: a potential hazard of chemotherapy administration. *Cancer Treat Rep* 1985; 69: 1325–6.
3. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 2708–13.

Stability. Although sensitive to light at low concentrations, doxorubicin is not subject to significant photodegradation at clinical concentrations and special precautions to protect solutions from light during use do not appear to be necessary.[1,2]

UK licensed product information for conventional formulations of doxorubicin hydrochloride state that, from a microbiological perspective, reconstituted solutions should be used immediately, and that storage time should not be longer than 24 hours at 2 degrees to 8 degrees, unless dilution has taken place under controlled and validated aseptic conditions. Chemical and physical stability varies between products:

- *Hameln, UK*: 48 hours at 2 degrees to 8 degrees and 24 hours at 25 degrees, in either sodium chloride 0.9% or glucose 5%, when prepared in glass containers and protected from light
- *Hospira, UK*: 21 days at 2 degrees to 8 degrees after reconstitution in either sodium chloride 0.9% or water for injection, in glass or polypropylene containers
- Doxorubicin 0.2% solution, *Medac, UK*: undiluted, 7 days at 15 degrees to 25 degrees, in glass containers and protected from light
- Doxorubicin powder for solution for injection, *Medac, UK*: 2 mg/mL in sodium chloride 0.9%—7 days at 15 degrees to 25 degrees and 14 days at 2 degrees to 8 degrees; 500 micrograms/mL in water for injection—24 hours below 25 degrees; 50 micrograms/mL to 5 mg/mL in sodium chloride 0.9%—7 days at 15 degrees to 25 degrees

Solutions of doxorubicin in sodium chloride solution 0.9% were reported[3] to be stable for 24 days when stored in PVC minibags at 25 degrees and for even longer if stored in minibags or polypropylene syringes at 4 degrees. Stability in solution seems to be partly related to pH, with doxorubicin becoming more stable[3-5] at acid pH. A fall in pH of the solution also significantly decreases the loss of doxorubicin by adsorption and precipitation onto the surface of a positively-charged in-line filter.[6]

Pegylated liposomal doxorubicin formulations (*Caelyx, UK* and *Doxil, USA*) should be diluted only with glucose 5%. If not used immediately, they may be stored for 24 hours at 2 degrees to 8 degrees.

1. Tavoloni N, *et al.* Photolytic degradation of adriamycin. *J Pharm Pharmacol* 1980; 32: 860–2.
2. Wood MJ, *et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; 15: 291–300.
3. Wood MJ, *et al.* Stability of doxorubicin, daunorubicin and epirubicin in plastic syringes and minibags. *J Clin Pharm Ther* 1990; 15: 279–89.
4. Poochikian GK, *et al.* Stability of anthracycline antitumor agents in four infusion fluids. *Am J Hosp Pharm* 1981; 38: 483–6.
5. Beijnen JH, *et al.* Stability of anthracycline antitumour agents in infusion fluids. *J Parenter Sci Technol* 1985; 39: 220–2.
6. Francomb MM, *et al.* Effect of pH on the adsorption of cytotoxic drugs to a 96 hour intravenous filter. *Pharm J* 1991; 247: R26.

Uses and Administration

Doxorubicin is an anthracycline antineoplastic antibiotic. It is thought to have multiple modes of action including intercalation of DNA leading to an inhibition of DNA and RNA synthesis, inhibition of topoisomerase II, free radical formation, and alterations in cell membranes. Doxorubicin is a cell-cycle non-specific agent. It also has antibacterial and immunosuppressant properties.

Doxorubicin is effective against many tumours as indicated by the cross-references given below. It is used, often with other antineoplastics, in the treatment of Hodgkin's disease, non-Hodgkin's lymphomas, acute leukaemias, bone and soft-tissue sarcomas, neuroblastoma, Wilms' tumour, and malignant neoplasms of the bladder, breast, lung, ovary, and stomach. It has also been used in other tumours. Liposomal doxorubicin is used in the management of Kaposi's sarcoma in patients with AIDS, for the treatment of metastatic breast and ovarian cancers, and with bortezomib for the treatment of multiple myeloma.

Doxorubicin hydrochloride is given by intravenous injection into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 3 minutes or more. When used as a single agent, the dose of the *conventional* formulation is 60 to 75 mg/m² once every 3 or 4 weeks, or 1.2 to 2.4 mg/kg, once every 3 weeks. Alternatively, doses of 20 to 25 mg/m² have been given daily for 3 days every 3 or 4 weeks, although dividing the dose in this way may increase the incidence of mucositis. A regimen of 20 mg/m² as a single weekly dose may be used, and is reported to be associated with a lower incidence of cardiotoxicity.

Doses may need to be reduced if doxorubicin is given with other antineoplastics: a dose of 30 to 60 mg/m² every 3 weeks has been suggested. Obese patients may need a reduced dose, as may children, elderly patients, and patients with hepatic impairment (see below).

The total cumulative dose should not exceed 450 to 550 mg/m²; in patients who have received radiotherapy to the chest, or other cardiotoxic drugs, it may be advisable to further limit the total cumulative dose.

In the management of AIDS-related Kaposi's sarcoma *pegylated liposomal* doxorubicin hydrochloride is given in an intravenous dose of 20 mg/m² infused over 30 minutes once every 2 to 3 weeks. For the treatment of breast and ovarian cancers, the suggested dose of this liposomal formulation is 50 mg/m² infused over 1 hour once every 4 weeks. In the treatment of multiple myeloma, liposomal doxorubicin hydrochloride is given at a dose of 30 mg/m² on day 4 of the bortezomib regimen (see p. 752.1); it is given as an infusion over 1 hour immediately after the bortezomib infusion. In all these conditions, treatment should be continued for as long as the patient responds satisfactorily and tolerates treatment. The pegylated liposomal formulation should be diluted only with glucose 5%; generally, doses below 90 mg are diluted in 250 mL, and doses over 90 mg are diluted in 500 mL.

A *non-pegylated liposomal* formulation is also available and contains a doxorubicin citrate complex prepared with the aid of doxorubicin hydrochloride. It is given in the treatment of metastatic breast cancer in doses equivalent to doxorubicin hydrochloride 60 to 75 mg/m² every 3 weeks, with cyclophosphamide 600 mg/m². Doses are given by intravenous infusion over 1 hour, diluted in sodium chloride 0.9% or glucose 5% to a final concentration of 0.4 to 1.2 mg/mL doxorubicin hydrochloride.

Blood counts should be made routinely during treatment with doxorubicin (see also Bone-marrow Depression, p. 730.3) and cardiac function should be monitored at regular intervals for early signs of cardiotoxicity.

Doxorubicin hydrochloride has also been instilled into the bladder in the local treatment of malignant neoplasms. For this purpose 50 mL of a 1 mg/mL solution may be instilled into the bladder for about one hour; treatment may be given at weekly to monthly intervals. Doxorubicin has also been given intra-arterially.

Various novel formulations of doxorubicin have been investigated. Doxorubicin with carbon/iron carrier particles (MTC-DOX) is a magnetically targeted treatment, using an external magnet to keep the drug at the tumour site, that has been investigated for hepatocellular carcinoma. A polymer of doxorubicin and polyisohexylcyanoacrylate in nanoparticle form is under investigation for the treatment of hepatocellular carcinoma. Doxorubicin-eluting beads, for injection directly into the brain, and glutathione-pegylated liposomal doxorubicin are under investigation for the treatment of glioma. Hydrophilic microspheres reconstituted with a solution of doxorubicin hydrochloride have been used for chemoembolisation of hepatic tumours. Doxorubicin linked to a gonadotrophin-releasing hormone agonist is being investigated for the treatment of ovarian cancer.

Reviews of liposomal formulations.

1. Sharpe M, *et al.* Polyethylene glycol-liposomal doxorubicin: a review of its use in the management of solid and haematological malignancies and AIDS-related Kaposi's sarcoma. *Drugs* 2002; 62: 2089–2126.
2. Forbes C, *et al.* A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer. *Health Technol Assess* 2002; 6: 1–119.
3. O'Shaughnessy JA. Pegylated liposomal doxorubicin in the treatment of breast cancer. *Clin Breast Cancer* 2003; 4: 318–28.
4. Orditura M, *et al.* Pegylated liposomal doxorubicin: pharmacologic and clinical evidence of potent antitumor activity with reduced anthracycline-induced cardiotoxicity. *Oncol Rep* 2004; 12: 549–56.
5. Thigpen JT, *et al.* Role of pegylated liposomal doxorubicin in ovarian cancer. *Gynecol Oncol* 2005; 96: 10–18.
6. Soloman R, Gabizon AA. Clinical pharmacology of liposomal anthracyclines: focus on pegylated liposomal doxorubicin. *Clin Lymphoma Myeloma* 2008; 8: 21–32.
7. Patil RR, *et al.* Engineered nanocarriers of doxorubicin: a current update. *Crit Rev Ther Drug Carrier Syst* 2008; 25: 1–61.
8. Plosker GL. Pegylated liposomal doxorubicin: a review of its use in the treatment of relapsed or refractory multiple myeloma. *Drugs* 2008; 68: 2535–51.
9. Leonard RCF, *et al.* Improving the therapeutic index of anthracycline chemotherapy: focus on liposomal doxorubicin (Myocet®). *Breast* 2009; 18: 218–24.
10. Gaitanis A, Staal S. Liposomal doxorubicin and nab-paclitaxel: nanoparticle cancer chemotherapy in current clinical use. *Methods Mol Biol* 2010; 624: 385–92.

Administration in children. Doxorubicin is used for paediatric malignancies; UK licensed product information for conventional formulations advises that adult dosage regimens (see above) may be suitable for children, but dose reductions may be needed, particularly in young children.

References.

1. Creutzig U, *et al.* Favourable outcome of patients with childhood acute promyelocytic leukaemia after treatment with reduced cumulative anthracycline doses. *Br J Haematol* 2010; 149: 399–409.

Administration in the elderly. UK licensed product information for doxorubicin in conventional formulations advises that the dose may need to be reduced in the elderly; in patients over 70 years of age, a total cumulative dose of 450 mg/m² has been recommended.

Administration in hepatic impairment. Doses of doxorubicin should be adjusted as follows in patients with liver dysfunction:

- serum-bilirubin concentrations of 12 to 30 micrograms/mL: half the normal dose
- serum-bilirubin greater than 30 micrograms/mL: quarter of the usual dose.

Slightly different schedules may apply to liposomal products but may vary between preparations.

Amyloidosis. For mention of the use of doxorubicin in patients with amyloidosis (and of the increased risk this may carry in cardiac amyloidosis) see p. 819.3.

Malignant neoplasms. Doxorubicin plays a major role in combination regimens for chemotherapy of solid malignancies; it is often employed for tumours of the breast and lung (see p. 702.1 and p. 710.2) and for Wilms' tumour and neuroblastoma or retinoblastoma in children (see p. 709.1, p. 716.2, and p. 717.2) and has been used for malignancies of the bladder (p. 700.2); for various gynaecological cancers including those of the endometrium, and ovary (see p. 704.3, and p. 711.2); for cancer of the liver, stomach, and pancreas (p. 709.3, p. 706.1, p. 712.1); and for neoplasms of prostate, and thymus (p. 712.3 and p. 715.3). It is also used in the treatment of sarcomas of bone and soft-tissue (see p. 717.3 and p. 718.2) and liposomal doxorubicin is used in patients with Kaposi's sarcoma (see p. 718.1).

In addition, doxorubicin is a component of the ABVD regimen used to treat Hodgkin's disease (see p. 696.1) and is part of the CHOP regimen used for non-Hodgkin's lymphoma (p. 696.3). Doxorubicin is also used in Burkitt's lymphoma (p. 697.3), mycosis fungoides (p. 698.3), and the lymphomas associated with AIDS (see p. 697.2). It has been employed in acute lymphoblastic leukaemia (p. 692.3), in chronic lymphocytic leukaemia as part of the CHOP regimen (though with uncertain benefit—see p. 693.3), and in multiple myeloma (p. 699.2).

Adverse Effects and Treatment

For general discussions see Antineoplastics, p. 726.1 and p. 730.2.

Doxorubicin and other anthracyclines cause pronounced bone-marrow depression, which may be dose-limiting. White cell count reaches a nadir 10 to 15 days after a dose and usually recovers by about 21 days.

The anthracyclines may produce cardiotoxicity, both as an acute, usually transient disturbance of cardiac function marked by ECG abnormalities and, sometimes, arrhythmias; and as a delayed, sometimes fatal, irreversible congestive heart failure, which may occur suddenly. Severe cardiotoxicity is more likely in adults given total cumulative doses of doxorubicin greater than 450 to 550 mg/m^2, and may occur months or even years after use. However, congestive heart failure has been reported even with doses of 240 to 300 mg/m^2. Cardiotoxicity may occur at lower cumulative doses in those previously treated with other anthracyclines or antineoplastics, or with radiotherapy to the chest.

Gastrointestinal disturbances include moderate or sometimes severe nausea and vomiting; mucositis (stomatitis and oesophagitis) may progress to ulceration. Alopecia, usually reversible, occurs in the majority of patients. The urine may be coloured red. Occasional hypersensitivity reactions may occur. Hyperuricaemia may occur due to tumour lysis syndrome. Other adverse effects include conjunctivitis, lachrymation, urticarial rashes, hyperpigmentation of the oral mucosa and/or nails, onycholysis, drowsiness, renal or hepatic damage, and transient increases in liver enzymes.

Doxorubicin and other anthracyclines are very irritant and thrombophlebitis can occur; extravasation is serious and may produce extensive local necrosis and ulceration. If extravasation occurs, the injection should be immediately stopped and restarted in another vein; the appropriate management of such events is contentious (see p. 731.3) but may include ice packs, tissue irrigation, corticosteroids, and if necessary, surgery. Local erythematous streaking along the vein and facial flushing may be indicative of too rapid an injection. Intravesical instillation can cause bladder and urethral irritation, haematuria, and haemorrhagic cystitis.

Combination therapy including doxorubicin has rarely been associated with secondary acute myeloid leukaemia (see also Carcinogenicity, p. 726.2). *Animal* data have shown doxorubicin to be embryotoxic, teratogenic, and mutagenic. Doxorubicin may cause infertility.

Formulations of liposomal doxorubicin appear to be associated with a reduced potential for local tissue necrosis, and possibly a reduced incidence of cardiotoxicity. Conversely, palmar-plantar erythrodysesthesia (p. 730.1) appears to be more common, and may be dose-limiting. In addition, an acute anaphylactoid-like reaction may be seen on initial infusion, but this generally resolves on slowing or temporarily stopping the infusion.

Effects on the heart. Cardiotoxicity has been a major factor in limiting the use of the anthracyclines, doxorubicin and daunorubicin. Anthracycline derivatives have been developed with the aim of reducing the inherent cardiotoxicity of this class of compounds, including aclarubicin (p. 735.2), epirubicin (p. 787.1), idarubicin (p. 805.2), mitoxantrone (p. 833.1), and pixantrone (p. 847.2). However, although this strategy has met with some success, all these compounds exhibit some degree of cardiotoxicity.

Toxicity is essentially of 2 kinds: acute, usually reversible ECG changes, including a wide range of arrhythmias, and a delayed, usually irreversible dose-related cardiomyopathy, resulting in congestive heart failure.[1-3] The latter may be further subdivided into early-onset, occurring up to about a year afterwards, and late-onset toxicity occurring years after treatment,[2,4,5] which may be fatal. Late cardiac failure may occur up to 18 years after anthracycline therapy.[2,6,7] The 1-year mortality rate for patients with doxorubicin-induced New York Heart Association (NYHA) class III to IV heart failure is 40%, and the 2-year mortality rate is 60%.[8]

- The single most important determinant of cardiotoxicity appears to be the *total cumulative dose*, with the risk of toxicity becoming ever greater at total cumulative doxorubicin doses of 550 mg/m^2 or more.[8-14] However, patients vary widely in sensitivity,[2,10,13] and these values represent relatively arbitrary choices on a continuum of risk: there is no single safe dose.[1,5,13] Even at doses that produce no symptoms, subclinical myocardial damage may occur, and in children this may result in diminished cardiac reserve and heart disease in later life.[1,15,16]
- The *dosage schedule* also appears to be important; relatively high single doses on an infrequent schedule appear to be more cardiotoxic than lower, more closely spaced doses, suggesting that cardiotoxicity is related to peak blood concentrations of doxorubicin.[10]
- Cardiotoxicity is also reported to be more likely in *children and elderly* patients, and in those who have received prior *radiotherapy* to the chest.[3,4,9,10,12] Previous *cardiovascular disease* also increases the risk.[1,2,9] *Females* appear to be at greater risk than males.[8,17] *Other risk factors* include hypertension, liver disease, whole body hyperthermia, African American ancestry, and trisomy-21.[3,5,9]
- Use with cyclophosphamide, trastuzumab, or *other antineoplastics* with cardiotoxic potential may increase the likelihood of cardiomyopathy.[9,10]

Prevention. Much effort has gone into ways of predicting and preventing anthracycline-induced cardiotoxicity. Although ECG changes are commonly monitored, most of the changes are not predictive of cardiomyopathy and severe cardiotoxicity can occur without ECG changes. However, a persistent reduction in the voltage of the QRS wave is generally indicative of the need to perform further tests. Non-invasive cardiac *monitoring*, by means of echocardiography or radionuclide angiography, is useful in predicting the development of cardiomyopathy, but may give normal results until damage is quite advanced; sensitivity may be improved with exercise stress tests.[1-3] Measurement of left ventricular ejection fraction (LVEF) is frequently used for baseline evaluation, and at regular intervals thereafter.[9,18] Indium-111 antimyosin imaging detects abnormal cardiac uptake of indium-111 antimyosin, which can be seen even in the absence of any change in LVEF, and can be predictive of an impending fall in LVEF; this technique is highly sensitive but is time-consuming and not widely available.[10] Endomyocardial biopsy is the most sensitive indicator of cardiomyopathy, but it is invasive and again not widely available.[9,10,18] The Childrens Cancer Study Group[19] has issued guidelines for monitoring using ECG, echocardiography, and radionuclide angiocardiography in patients receiving anthracyclines. The role of such techniques in predicting late-onset cardiotoxicity remains to be clarified,[2] and there is disagreement on the best manner of monitoring anthracycline-induced cardiotoxicity. This reflects conflicting data and the scarcity of well-designed studies, but the Childrens Cancer Study Group guideline, or one that incorporates a baseline cardiac evaluation with follow-up as the anthracycline dose increases, has been advocated as a reasonable approach to monitoring anthracycline-induced cardiotoxicity.[13]

There is some preliminary evidence to suggest that concentrations of cardiac troponins and natriuretic peptides could be used as predictive markers of myocardial damage.[9,10,18,20,21]

Dexrazoxane (p. 1548.1) has shown some protective effect against the cardiotoxicity of doxorubicin and other anthracyclines, and is used to reduce cardiomyopathy in women receiving doxorubicin for metastatic breast cancer.

Alteration of the dosage schedule to weekly rather than three-weekly dosage, or the use of continuous infusion, have been advocated as ways of reducing doxorubicin cardiotoxicity; an anthracycline infusion time of six hours or longer has been shown to reduce the risk of heart failure and seemed to reduce the risk of subclinical cardiac damage.[22] Anthracyclines formulated in *liposomes* have also been used to reduce the risk.[2,5,8-11,13,18] The cardiac safety of liposomal daunorubicin has not been established, but non-pegylated liposomal doxorubicin has better cardiac safety than conventional doxorubicin,[11,21,23] while pegylated liposomal doxorubicin has a significanly reduced risk of cardiotoxicity.[11,21] (However, haematological and mucocutaneous toxicity, and palmar-plantar erythrodysesthesia are greater with liposomal formulations and may limit their use.[24])

Treatment. Management is essentially that of standard cardiac failure (p. 1262.3), with diuretics, beta blockers, ACE inhibitors, and ultimately, cardiac transplantation (p. 1938.2).[3,8,9,21]

1. Hale JP, Lewis IJ. Anthracyclines: cardiotoxicity and its prevention. *Arch Dis Child* 1994; 71: 457–62.
2. Shan K, *et al.* Anthracycline-induced cardiotoxicity. *Ann Intern Med* 1996; 125: 47–58.
3. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1998; 339: 900–905.
4. Adams MJ, Lipshultz SE. Pathophysiology of anthracycline- and radiation-associated cardiomyopathies: implications for screening and prevention. *Pediatr Blood Cancer* 2005; 44: 600–6.
5. Lipshultz SE, *et al.* Anthracycline associated cardiotoxicity in survivors of childhood cancer. *Heart* 2008; 94: 525–33.
6. Goorin AM, *et al.* Initial congestive heart failure, six to ten years after doxorubicin chemotherapy for childhood cancer. *J Pediatr* 1990; 116: 144–7.
7. Steinherz LJ, *et al.* Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA* 1991; 266: 1672–7.
8. Wouters KA, *et al.* Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. *Br J Haematol* 2005; 131: 561–78.
9. Birtle AJ. Anthracyclines and cardiotoxicity. *Clin Oncol (R Coll Radiol)* 2000; 12: 146–52.
10. Jain D. Cardiotoxicity of doxorubicin and other anthracycline derivatives. *J Nucl Cardiol* 2000; 7: 53–62.
11. Theodoulou M, Hudis C. Cardiac profiles of liposomal anthracyclines: greater cardiac safety versus conventional doxorubicin? *Cancer* 2004; 100: 2052–63.
12. Petit T. Toxicité cardiaque des anthracyclines: anthracycline-induced cardiotoxicity. *Bull Cancer* 2004; 91 (suppl): S159–S165.
13. Jannazzo A, *et al.* Monitoring of anthracycline-induced cardiotoxicity. *Ann Pharmacother* 2008; 42: 99–104.
14. Iarussi D, *et al.* Recent advances in the prevention of anthracycline cardiotoxicity in childhood. *Curr Med Chem* 2001; 8: 1649–60.
15. Yeung ST, *et al.* Functional myocardial impairment in children treated with anthracyclines for cancer. *Lancet* 1991; 337: 816–18.
16. Lipschultz SE, *et al.* Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991; 324: 808–15.
17. Lipshultz SE, *et al.* Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 1995; 332: 1738–43.
18. Ewer MS, *et al.* Cardiac safety of liposomal anthracyclines. *Semin Oncol* 2004; 31 (6 suppl (3)): 161–81.
19. Steinherz LJ, *et al.* Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Committee of the Childrens Cancer Study Group. *Pediatrics* 1992; 89: 942–9.
20. Sparano JA, *et al.* Predicting cancer therapy-induced cardiotoxicity: the role of troponins and other markers. *Drug Safety* 2002; 25: 301–11.
21. Gianni L, *et al.* Anthracycline cardiotoxicity: from bench to bedside. *J Clin Oncol* 2008; 26: 3777–84.
22. van Dalen EC, *et al.* Different dosage schedules for reducing cardiotoxicity in cancer patients receiving anthracycline chemotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/05/10).
23. van Dalen EC, *et al.* Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 18/05/10).
24. Orditura M, *et al.* Pegylated liposomal doxorubicin: pharmacologic and clinical evidence of potent antitumor activity with reduced anthracycline-induced cardiotoxicity (review). *Oncol Rep* 2004; 12: 549–56.

Effects on the liver. Hepatitis and non-specific hepatocellular damage has been reported in patients receiving doxorubicin as part of combination therapy.[1] A characteristic hepatotoxicity can also be produced by the combination of radiotherapy with doxorubicin.[2]

1. Avilés A, *et al.* Hepatic injury during doxorubicin therapy. *Arch Pathol Lab Med* 1984; 108: 912–13.
2. Price LA. Surviving malignant disease: medical and oncological aspects. *Br J Hosp Med* 1983; 30: 8–12.

Effects on the skin and nails. Hyperpigmentation has occurred in patients given daunorubicin, doxorubicin, or idarubicin.[1-6] Reports described pigmentation of the skin and transverse hyperpigmented bands of the nails. Effects on the skin resolved over several weeks, and bands on the nails moved with normal nail growth. Dark-skinned patients appear to be more susceptible to this adverse effect. Biopsy has found an increase in melanin granules in the affected tissues. An unusual blue-grey pigmentation of the face was reported in a patient given doxorubicin.[7]

There have been reports of subacute cutaneous lupus erythematosus after treatment with doxorubicin plus cyclophosphamide for breast cancer.[8,9] A change of chemotherapy regimen and corticosteroids successfully treated some patients, but lesions continued to flare after each cycle in one patient with Sjögren's syndrome despite a change to paclitaxel and trastuzumab; symptoms eventually resolved when chemotherapy was complete.[9] In another case[8] skin lesions kept developing even after the chemotherapy regimen was complete, and although oral corticosteroids improved the lesions, they reappeared when the corticosteroids were withdrawn; complete resolution was seen with thalidomide.

For specific reference to treatment of alopecia caused by doxorubicin, and for extravasation, see p. 730.3 and p. 731.3.

1. Kelly TM, *et al.* Hyperpigmentation with daunorubicin therapy. *Arch Dermatol* 1984; 120: 262–3.
2. Kumar L, Kochupillai V. Doxorubicin induced hyperpigmentation. *N Z Med J* 1990; 103: 165.

3. Curran CF. Doxorubicin-associated hyperpigmentation. *N Z Med J* 1990; **103**: 517.
4. Anderson LL, *et al.* Cutaneous pigmentation after daunorubicin chemotherapy. *J Am Acad Dermatol* 1992; **26**: 255–6.
5. Borecky DJ, *et al.* Idarubicin-induced pigmentary changes of the nails. *Cutis* 1997; **59**: 203–4.
6. Kroumpouzos G, *et al.* Generalized hyperpigmentation with daunorubicin chemotherapy. *J Am Acad Dermatol* 2002; **46** (suppl): S1–S3.
7. Konohana A. Blue-gray pigmentation in a patient receiving doxorubicin. *J Dermatol* 1992; **19**: 250–2.
8. Guhl G, *et al.* Chemotherapy-induced subacute lupus erythematosus. *Lupus* 2009; **18**: 859–60.
9. Funke AA, *et al.* Subacute cutaneous lupus erythematosus exacerbated or induced by chemotherapy. *Arch Dermatol* 2010; **146**: 1113–16.

Palmar-plantar erythrodysesthesia syndrome. Palmar-plantar erythrodysesthesia syndrome (p. 730.1) is associated with the use of liposomal doxorubicin, and recommendations have been made for its management.[1] The most effective way of preventing the syndrome was to maintain doses at not more than 10 mg/m² weekly (typically as a single infusion of 40 mg/m² every 4 weeks). At such doses, the syndrome, if it occurred was typically mild and easily managed. Dose-intensity modification was also thought likely to be beneficial in managing the syndrome if it developed, although evidence to support this was lacking.

UK licensed product information states that pyridoxine (in daily doses of 50 to 150 mg) and corticosteroids have been used for the prophylaxis and treatment of this condition although clinical data for their efficacy are lacking; other strategies include keeping the hands and feet cool with cold water soaks or baths, avoiding heat or hot water, and not wearing socks, gloves, or tight-fitting shoes.

1. von Moos R, *et al.* Pegylated liposomal doxorubicin-associated hand-foot syndrome: recommendations of an international panel of experts. *Eur J Cancer* 2008; **44**: 781–90.

Precautions

For a general discussion see Antineoplastics, p. 732.2.

Doxorubicin and other anthracyclines are generally contra-indicated in patients with heart disease. The total cumulative dose should be limited, and cardiac function, including left ventricular ejection fraction, should be assessed before and monitored during treatment (see Effects on the Heart, p. 784.1). Blood counts should be monitored and doses should not be repeated while there is bone-marrow depression or ulceration of the mouth. Doxorubicin should be given with great care in reduced doses to patients with hepatic impairment; dosage reduction may also be necessary in children and the elderly. Extravasation results in severe tissue damage and doxorubicin and other anthracyclines should not be given by intramuscular or subcutaneous injection. The adverse effects of irradiation may be enhanced by doxorubicin and skin reactions previously induced by radiotherapy may recur; the total cumulative dose should be reduced to no more than 400 mg/m² in patients who have received radiotherapy to the chest or heart. Different liposomal formulations may not be interchangeable with conventional formulations, or with each other.

Breast feeding. Doxorubicin and its metabolites have been detected in breast milk.[1] The American Academy of Pediatrics considers[2] that doxorubicin is concentrated in breast milk, that it may possibly cause immune suppression in the infant, has unknown effects on growth, and an association with carcinogenesis.

1. Egan PC, *et al.* Doxorubicin and cisplatin excretion into human milk. *Cancer Treat Rep* 1985; **69**: 1387–9.
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 29/06/04)

Handling and disposal. Doxorubicin hydrochloride is irritant; avoid contact with skin and mucous membranes.

A method for the destruction of doxorubicin or daunorubicin *wastes* using sulfuric acid and potassium permanganate.[1] Residues produced by degradation of daunorubicin by this method showed no mutagenicity *in vitro*; some mutagenicity was seen with high concentrations of residues from doxorubicin.

Urine and faeces produced for up to 7 days after a dose of doxorubicin should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes; some antineoplastic agents. *IARC Scientific Publications* 73. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235**: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies doxorubicin 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 29/09/11)

Pregnancy. Although doxorubicin has been reported to be undetectable in amniotic fluid[1,2] it has been found in fetal tissue (liver, kidney, and lungs) at concentrations several times those in maternal plasma,[2] indicating that it does cross the placenta. The effect of anthracyclines on the outcome of 160 pregnancies has been analysed.[3] Most women had received combination chemotherapy that included doxorubicin or daunorubicin, for haematological malignancies or breast cancer. Most outcomes (73%) were normal. There were 5 malformations, most often associated with regimens that also included antimetabolites or alkylating agents; the malformations were highly variable. Fetal toxicity was associated with chemotherapy use for solid tumours during the first trimester, and the risk of severe fetal toxicity was significantly increased with doxorubicin doses above 70 mg/m² per cycle. Fetal cardiotoxicity occurred in 2 cases and was associated with anthracycline use during the second and third trimesters. It has been suggested that the use of epirubicin may reduce the risk of fetal myocardiopathy, but a brief review of the literature[4] suggested that its toxicity profile in pregnancy was very similar to that of doxorubicin. Fetal death was more frequent in women with acute leukaemia; it was associated with disease progression and the authors recommended that chemotherapy should not be postponed.

For a report of a healthy infant born to a woman treated with a doxorubicin-containing chemotherapy regimen, see Pregnancy, under Teniposide, p. 867.2.

UK licensed product information for doxorubicin cautions against use in pregnancy. Recommendations vary, but some advise that men and women both take effective contraceptive measures during treatment and for 3 to 6 months after therapy.

1. Roboz J, *et al.* Does doxorubicin cross the placenta? *Lancet* 1979; **ii**: 1382–3.
2. D'Incalci M, *et al.* Transplacental passage of doxorubicin. *Lancet* 1983; **i**: 75.
3. Germann N, *et al.* Anthracyclines during pregnancy: embryo–fetal outcome in 160 patients. *Ann Oncol* 2004; **15**: 146–50.
4. Mir O, *et al.* Chemotherapy for breast cancer during pregnancy: is epirubicin safe? *Ann Oncol* 2008; **19**: 1814–15.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. The total cumulative dose of doxorubicin should be reduced in patients who have received other cardiotoxic drugs such as daunorubicin or cyclophosphamide. Doxorubicin is reported to inhibit the intracellular activation of stavudine and hence its antiviral effect.

Antibacterials. Hypersensitivity reactions to doxorubicin or daunorubicin have been reported in 2 patients with recent exposure to *clindamycin*, one of whom had exhibited hypersensitivity to that antibiotic.[1] The possibility of cross-sensitivity between anthracyclines and clindamycin should be considered.

1. Arena FP, Sherlock S. Doxorubicin hypersensitivity and clindamycin. *Ann Intern Med* 1990; **112**: 150.

Antineoplastics. Giving doxorubicin with or after drugs, such as *streptozocin*[1] or *methotrexate*,[2] that can impair hepatic function, has resulted in increased doxorubicin toxicity, possibly due to reduced hepatic clearance. A high incidence of cardiotoxicity (manifest as congestive heart failure) has been reported in patients given doxorubicin with *paclitaxel* (which also has cardiotoxic effects).[3] Any interaction may be schedule dependent.[4] Similarly an increased incidence of cardiotoxicity has been seen when *trastuzumab* was given with or after anthracyclines (see Effects on the Heart under Trastuzumab, p. 876.3).

Valspodar inhibits P-glycoprotein, and a pharmacokinetic study[5] found that it decreased clearance of doxorubicin and prolonged the terminal half-life, increasing exposure to doxorubicin and myelosuppressive effects. The authors suggested that the dose of doxorubicin might need to be reduced by about 60%.

Sorafenib may increase systemic exposure to doxorubicin.

For a suggestion that doxorubicin might enhance the hepatotoxicity of *mercaptopurine*, see under Daunorubicin Hydrochloride, p. 779.3.

For a report of an increased incidence of febrile neutropenia and gastrointestinal complications when doxorubicin is used with *docetaxel*, see Antineoplastics, under Docetaxel, p. 782.2.

In a pharmacokinetic study, both paclitaxel and docetaxel increased exposure to liposomal doxorubicin, although the effect was less pronounced with docetaxel.[6]

For mention of changes in exposure to pegylated or liposomal doxorubicin and *vinflunine* when these drugs were used together, see Interactions, under Vinflunine, p. 885.2.

1. Anonymous. Two drugs may not be better than one. *JAMA* 1976; **236**: 913.
2. Robertson JH, *et al.* Toxicity of doxorubicin and methotrexate in osteogenic sarcoma. *BMJ* 1976; **1**: 23.
3. Gianni L, *et al.* Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995; **13**: 2688–99.
4. Danesi R, *et al.* Pharmacokinetic optimisation of treatment schedules for anthracyclines and paclitaxel in patients with cancer. *Clin Pharmacokinet* 1999; **37**: 195–211.
5. Advani R, *et al.* A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance. *Clin Cancer Res* 2001; **7**: 1221–9.
6. Briasoulis E, *et al.* Interaction pharmacokinetics of pegylated liposomal doxorubicin (Caelyx) on coadministration with paclitaxel or docetaxel. *Cancer Chemother Pharmacol* 2004; **53**: 452–7.

General anaesthetics. For reference to QT-interval prolongation during anaesthesia with *isoflurane* in women who had received anthracycline-based chemotherapy for breast cancer, see p. 1907.3.

Immunosuppressants. Increased plasma-doxorubicin concentrations and myelotoxicity have occurred when *ciclosporin* was used to modulate tumour resistance.[1] Severe neurological toxicity occurred in another patient given doxorubicin after long-term ciclosporin therapy.[2] It has been suggested that the use of ciclosporin or its analogues (see Antineoplastics, above for the effect of valspodar) to modulate doxorubicin resistance should be undertaken with caution.[3]

1. Rushing DA, *et al.* The effects of cyclosporine on the pharmacokinetics of doxorubicin in patients with small cell lung cancer. *Cancer* 1994; **74**: 834–41.
2. Barbui T, *et al.* Neurological symptoms and coma associated with doxorubicin administration during chronic cyclosporin therapy. *Lancet* 1992; **339**: 1421.
3. Beck WT, Kuttesch JF. Neurological symptoms associated with cyclosporin plus doxorubicin. *Lancet* 1992; **340**: 496.

Thalidomide. In a comparison of two treatment regimens for multiple myeloma (thalidomide, dexamethasone, cisplatin, cyclophosphamide, and etoposide, with or without doxorubicin), there was an increased risk of deep-vein thrombosis in those patients who received the combination that included doxorubicin.[1] The authors cited a previous study[2] in which the addition of thalidomide to an antineoplastic regimen increased the risk of deep-vein thrombosis, and concluded that patients with multiple myeloma treated with the combination of doxorubicin and thalidomide are at increased risk.

1. Zangari M, *et al.* Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood* 2002; **100**: 1168–71.
2. Zangari M, *et al.* Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. *Blood* 2001; **98**: 1614–15.

Pharmacokinetics

After intravenous injection, doxorubicin is rapidly cleared from the blood, and distributed into tissues including lungs, liver, heart, spleen, and kidneys. It undergoes rapid metabolism in the liver to metabolites including the active metabolite doxorubicinol (adriamycinol). About 40 to 50% of a dose is stated to be excreted in bile within 7 days, of which about half is as unchanged drug. Only about 5% of a dose is excreted in urine within 5 days. It does not cross the blood-brain barrier but may cross the placenta and is distributed into breast milk. The disappearance of doxorubicin from the blood is triphasic: mean half-lives are 12 minutes, 3.3 hours and about 30 hours.

The pharmacokinetics of *liposomal* formulations are somewhat different from the conventional drug. The use of macrogols in the surface layer of the liposomes (pegylation) reduces removal of liposomes by macrophages. This results in prolonged circulation in the plasma, with relatively little tissue distribution, but tumour neovasculature is reported to permit penetration of liposomes into tumour tissue. Pharmacokinetics are reported to be biphasic with mean half-lives of 5 hours and 55 to 75 hours respectively. A non-pegylated liposomal formulation also exists and is reported to produce higher peak plasma concentrations of total doxorubicin than conventional formulations, but lower free (not liposome-encapsulated) concentrations. Clearance is reduced, and peak plasma concentrations of doxorubicinol delayed.

References.

1. Speth PAJ, *et al.* Clinical pharmacokinetics of doxorubicin. *Clin Pharmacokinet* 1988; **15**: 15–31.
2. Rushing DA, *et al.* The disposition of doxorubicin on repeated dosing. *J Clin Pharmacol* 1993; **33**: 698–702.
3. Pisciotti SC, *et al.* Pharmacokinetics and pharmacodynamics of doxorubicin in patients with small cell lung cancer. *Clin Pharmacol Ther* 1993; **53**: 555–61.
4. Amantea MA, *et al.* Population pharmacokinetics and pharmacodynamics of pegylated-liposomal doxorubicin in patients with AIDS-related Kaposi's sarcoma. *Clin Pharmacol Ther* 1997; **61**: 301–11.
5. Danesi R, *et al.* Pharmacokinetic-pharmacodynamic relationships of the anthracycline anticancer drugs. *Clin Pharmacokinet* 2002; **41**: 431–44.

6. Swenson CE, *et al.* Pharmacokinetics of doxorubicin administered i.v. as Myocet (TLC D-99; liposome-encapsulated doxorubicin citrate) compared with conventional doxorubicin when given in combination with cyclophosphamide in patients with metastatic breast cancer. *Anticancer Drugs* 2003; 14: 239–46.
7. Gabizon A, *et al.* Pharmacokinetics of pegylated liposomal doxorubicin: review of animal and human studies. *Clin Pharmacokinet* 2003;42: 419–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Adriblastina; Caelyx; Colhidrol; Dicladox; Doxocris; Doxokebir; Doxopeg; Doxtie; Nagun; Onkostatil; Roxorin; Varidoxo; ***Austral.***: Caelyx; ***Austria***: Adriblastin; Caelyx; DOXO-Cell†; Myocet; ***Belg.***: Adriblastina; Caelyx; Doxorubin†; Myocet; ***Braz.***: Adriblastina; Biorrub; Caelyx; Doxolem; Doxopeg; Evorubicin; Fauldoxo; Oncodox; Rubex; Rubidox; ***Canad.***: Caelyx; Myocet; ***Chile***: Adriblastina†; Caelyx; Daxotel; Doxopeg; ***China***: Caelyx (楷莱); ***Cz.***: Adriblastina; Caelyx; Doxolem†; Myocet; Xorucin; ***Denm.***: Caelyx; Myocet; ***Fin.***: Caelyx; ***Fr.***: Adriblastine; Caelyx; Myocet; ***Ger.***: Adriblastin†; Adrimedac; Axidoxo; Caelyx; DOXO-Cell; Myocet; Ribodoxo; ***Gr.***: Adriblastina; Caelyx; Doxiprol; Doxorubin; Doxosan; Doxotil; Myocet; Rubidox; ***Hong Kong***: Caelyx; Sindroxocin; ***Hung.***: Adriblastina; Caelyx; Myocet; ***India***: Adrim; Adrosal; Cadria; Caelyx; Cardia; Dobicin; Dobixin; Doxobin; Doxolem; Doxomed; Doxorex; Doxorubin; Doxulip; Doxutec; Duxocin; Lyphidox; Naprodox; Oncodox; Oncodria; ***Indon.***: Adricin; Caelyx; Pallagicin†; Rubidox†; ***Irl.***: Caelyx; Myocet; ***Israel***: Adriblastina; Doxil; Myocet; ***Ital.***: Adriblastina; Caelyx; Myocet; ***Jpn***: Adriacin; ***Malaysia***: Caelyx; Doxorubin; ***Mex.***: Adriblastina; Caelyx; Doxolem; Doxopeg; Doxotec; Doxtie†; Ifadox†; ***Neth.***: Caelyx; Debdox; Doxorubin; Myocet; ***Norw.***: Caelyx; Myocet; ***NZ***: Caelyx; Doxorubin; ***Philipp.***: AD Mycin; Adriblastina; Adrim; Adrosal; Axibin; Caelyx; Doxorubin; Rubidox†; ***Pol.***: Adriblastina; Adrimedac; Biorubina; Caelyx; Myocet; Rastocin†; ***Port.***: Caelyx; DOXO-cell; Fauldoxo; Myocet; ***Rus.***: Caelyx (Келикс); Rastocin (Растошин); Sindroxocin (Синдроксошин); ***S.Afr.***: Adriblastina; Caelyx; ***Singapore***: Adriblastina; Caelyx; Diox; Ebedoxo; ***Spain***: Caelyx; Farmiblastina; Myocet; ***Swed.***: Caelyx; Myocet; ***Switz.***: Adriblastin; Caelyx; ***Thai.***: AD Mycin; Adriblastina; Adrim; Caelyx; Doxolem; Doxorubin; Lipo-Dox; ***Turk.***: Adriblastina; Caelyx; Doxo-Teva; ***UK***: Caelyx; Myocet; ***Ukr.***: Adriblastina (Адриластин)†; Caelyx (Келикс)†; Lipodox (Липодокс); ***USA***: Doxil; Lipodox; ***Venez.***: Adriblastina; Adrim; Caelyx; Doxonolver.

Pharmacopoeial Preparations
BP 2014: Doxorubicin Injection;
USP 36: Doxorubicin Hydrochloride for Injection; Doxorubicin Hydrochloride Injection.

Edrecolomab *(USAN, rINN)*

17-1A Antibody; C1; Édrécolomab; Edrecolomabum; Monoclonal Antibody 17-1A; Эдреколомаб.
Immunoglobulin G2a (mouse monoclonal 17-1A γ-chain anti-human colon cancer tumor-associated antigen), disulfide with mouse monoclonal 17-1A light chain, dimer.
CAS — 156586-89-9.
ATC — L01XC01.
ATC Vet — QL01XC01.
UNII — 0KYI9U9FSJ.

Profile

Edrecolomab is a monoclonal antibody of murine origin directed at epithelial cell surface glycoproteins that has been used as adjuvant therapy after surgery in patients with colorectal cancer (p. 706.3), although reports of improved survival do not seem to have been borne out.

References.
1. Riethmüller G, *et al.* Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. *Lancet* 1994; 343: 1177–83.
2. Riethmüller G, *et al.* Monoclonal antibody therapy for resected Dukes' C colorectal cancer: seven-year outcome of a multicenter randomized trial. *J Clin Oncol* 1998; 16: 1788–94.
3. Adkins JC, Spencer CM. Edrecolomab (monoclonal antibody 17-1A). *Drugs* 1998; 56: 619–26.
4. Punt CJA, *et al.* Edrecolomab alone or in combination with fluorouracil and folinic acid in the adjuvant treatment of stage III colon cancer: a randomised study. *Lancet* 2002; 360: 671–7.
5. Hartung G, *et al.* Adjuvant therapy with edrecolomab versus observation in stage II colon cancer: a multicenter randomized phase III study. *Onkologie* 2005; 28: 347–50.
6. Fields ALA, *et al.* Adjuvant therapy with the monoclonal antibody edrecolomab plus fluorouracil-based therapy does not improve overall survival of patients with stage III colon cancer. *J Clin Oncol* 2009; 27: 1941–7.
7. Schmoll H-J, Arnold D. When wishful thinking leads to a misty-eyed appraisal: the story of the adjuvant colon cancer trials with edrecolomab. *J Clin Oncol* 2009; 27: 1926–9.

Efaproxiral *(USAN, rINN)* ⊗

Efaproxiral; Efaproxiralum; RSR-13; Эфапроксирал.
2-(4-[2-[(3,5-Dimethylphenyl)amino]-2-oxoethyl]phenoxy)-2-methyl propanoic acid.
$C_{20}H_{23}NO_4$=341.4
CAS — 131179-95-8.
ATC — L01XD06.
ATC Vet — QL01XD06.
UNII — J81E81G364.

NOTE. The names Efaproxyn and Revaproxyn have been used as trade marks for efaproxiral.

Efaproxiral Sodium *(USAN, rINNM)* ⊗

Efaproxiral sódico; Efaproxiral Sodique; Natrii Efaproxiralum; Натрий Эфапроксирал.
$C_{20}H_{22}NNaO_4$=363.4
CAS — 170787-99-2.
ATC — L01XD06.
ATC Vet — QL01XD06.
UNII — 3L83QP52XI.

Profile

Efaproxiral is an allosteric modifier of haemoglobin that enhances the diffusion of oxygen to hypoxic tumour tissue, making it more sensitive to radiotherapy. It has been investigated in the treatment of brain metastases from solid tumours.

Elacytarabine *(USAN, rINN)*

CP-4055; Elacitarabina; Élacytarabine; Elacytarabinum; Элацитарабин.
4-Amino-1-{5-*O*-[(9*E*)-octadec-9-enoyl]-β-D-arabinofuranosyl}pyrimidin-2(1*H*)-one.
$C_{27}H_{45}N_3O_6$=507.7
CAS — 188181-42-2.
UNII — TA7WJG93AR.

NOTE. The name Elacyt has been used as a trade mark for elacytarabine.

Profile

Elacytarabine is a lipid-conjugated derivative of cytarabine (p. 774.1) that is under investigation for the treatment of acute myeloid leukaemia.

Elesclomol *(USAN, rINN)*

Élesclomol; Elesclomolum; STA-4783; Элескломол.
Propanedioic acid, bis[2-methyl-2-(phenylthioxomethyl) hydrazide]; 1-*N*′-benzenecarbothioyl-3-(2-benzenecarbothioyl-2-methylhydrazinyl)-*N*′-methyloxopropanehydrazide.
$C_{19}H_{20}N_4O_2S_2$=400.5
CAS — 488832-69-5.
UNII — 6UK191M53P.

Profile

Elesclomol is an oxidative stress inducer that is under investigation as a treatment for metastatic melanoma.

References.
1. Berkenblit A, *et al.* Phase I clinical trial of STA-4783 in combination with paclitaxel in patients with refractory solid tumors. *Clin Cancer Res* 2007; 13: 584–90.
2. Kirshner JR, *et al.* Elesclomol induces cancer cell apoptosis through oxidative stress. *Mol Cancer Ther* 2008; 7: 2319–27.
3. O'Day S, *et al.* Phase II, randomized, controlled, double-blinded trial of weekly elesclomol plus paclitaxel versus paclitaxel alone for stage IV metastatic melanoma. *J Clin Oncol* 2009; 27: 5452–8.

Endostatin

rhEndostatin (recombinant human endostatin); YH-16 (recombinant human endostatin).

NOTE. The name Endu has been used as a trade mark for recombinant human endostatin.

Profile

Endostatin is an endogenous human protein fragment of collagen type XVIII that has anti-angiogenic properties. A recombinant human form has been used for non-small cell lung cancer and is under investigation for the treatment of other malignancies such as metastatic melanoma and gastrointestinal tumours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Endostar (恩度).

Enocitabine *(rINN)*

Behenoyl Cytarabine; Behenoylcytosine Arabinoside; BH AC; Enocitabina; Énocitabine; Enocitabinum; NSC-239136; Эноцитабин.
N-(1-β-D-Arabinofuranosyl-1,2-dihydro-2-oxo-4-pyrimidinyl) docosanamide.
$C_{31}H_{55}N_3O_6$=565.8
CAS — 55726-47-1.
UNII — 9YVR68W306.

Profile

Enocitabine is an antineoplastic that is converted in the body to cytarabine (p. 774.1). It has been used similarly in the treatment of acute leukaemias.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Sunrabin.

Entinostat *(USAN, rINN)*

Entinostatum; MS-27-275; MS-275; SNDX-275; Энтиностат.
Pyridin-3-ylmethyl ([4-[[2-aminophenyl)carbamoyl]phenyl} methyl)carbamate.
$C_{21}H_{20}N_4O_3$=376.4
CAS — 209783-80-2.
UNII — 1ZNY4FKK9H.

Profile

Entinostat is an orally active histone deacetylase inhibitor that is under investigation for the treatment of Hodgkin's disease.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.
1. Knipstein J, Gore L. Entinostat for treatment of solid tumors and hematologic malignancies. *Expert Opin Invest Drugs* 2011; 20: 1455–67.

Enzalutamide *(USAN, pINN)*

Enzalutamida; Enzalutamidum; MDV-3100; Энзалутамид.
4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide.
$C_{21}H_{16}F_4N_4O_2S$=464.4
CAS — 915087-33-1.
UNII — 93T0T9GKNU.

Uses and Administration

Enzalutamide is a nonsteroidal anti-androgen that competitively inhibits binding to androgen receptors. It is used in the treatment of metastatic castration-resistant prostate cancer (p. 712.3) in patients who have previously been treated with docetaxel. The usual oral dose is 160 mg once daily. Treatment should be withheld if severe toxicity occurs and then restarted after 1 week, or when symptoms have improved, at either the usual dose or a reduced dose (80 or 120 mg once daily) if warranted.

Use with strong cytochrome P450 isoenzyme CYP2C8 inhibitors should be avoided. If a strong CYP2C8 inhibitor must be used, the dose of enzalutamide should be reduced to 80 mg once daily. The original dose may be resumed after the inhibitor has been stopped.

References.
1. Scher HI, *et al.* AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; 367: 1187–97.
2. Golshayan AR, Antonarakis ES. Enzalutamide: an evidence-based review of its use in the treatment of prostate cancer. *Core Evid* 2013; 8: 27–35.
3. Pal SK, *et al.* Enzalutamide for the treatment of prostate cancer. *Expert Opin Pharmacother* 2013; 14: 679–85.

Adverse Effects and Precautions

The most commonly reported adverse effects with enzalutamide are asthenia or fatigue, muscular weakness, arthralgia, musculoskeletal and back pain, diarrhoea, peripheral oedema, headache, flushing, hypertension, respiratory-tract infections, dizziness, insomnia, anxiety, paraesthesia, and haematuria. Seizures have occurred in patients taking enzalutamide and it should be used with caution in those with predisposing factors.

Interactions

Enzalutamide is metabolised by the cytochrome P450 isoenzymes CYP2C8 and CYP3A4, and use with inhibitors or inducers of these isoenzymes may affect exposure to

enzalutamide. The strong CYP2C8 inhibitor gemfibrozil increased exposure to enzalutamide and its active metabolite by 2.2-fold; consequently, the use of strong CYP2C8 inhibitors with enzalutamide should be avoided, or the dose of enzalutamide reduced if use together is necessary (see Uses and Administration, p. 786.3). The increase in exposure to enzalutamide and its active metabolite was less prominent (1.3-fold) with the strong CYP3A4 inhibitor itraconazole. The effects of strong or moderate inducers of CYP2C8 or CYP3A4 on enzalutamide have not been evaluated and licensed product information recommends that their use together should be avoided.

Enzalutamide itself is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. The exposure of drugs that are substrates of these isoenzymes may be decreased when given with enzalutamide; use with enzalutamide should be avoided for those that also have a narrow therapeutic index.

Pharmacokinetics

Peak plasma concentrations of enzalutamide occur about 1 hour after an oral dose and with daily dosing steady state is reached after 28 days. Enzalutamide is about 97% bound to plasma proteins, mainly albumin; the major active metabolite *N*-desmethyl enzalutamide is about 95% bound to plasma proteins. Enzalutamide is metabolised in the liver by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8, the latter of which is mainly responsible for the formation of the active metabolite. Over 70% of a dose is excreted as metabolites in the urine, and 14% in the faeces. The mean terminal half-life after a single dose is about 6 days for enzalutamide and about 8 days for *N*-desmethyl enzalutamide.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Xtandi; *USA*: Xtandi.

Enzastaurin Hydrochloride *(USAN, rINNM)*

Enzastaurine, Chlorhydrate d'; Enzastaurini Hydrochloridum; Hidrocloruro de enzastaurina; LY-317615; Энзастаурина Гидрохлорид.

3-(1-Methyl-1*H*-indol-3-yl)-4-[1-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione hydrochloride.

$C_{32}H_{29}N_5O_2$,HCl=552.1

CAS — 359017-79-1.

UNII — KX7K68Z2UH.

Profile

Enzastaurin hydrochloride is a protein kinase C inhibitor that has been investigated for the treatment of gliomas and is being tried in other malignancies including non-Hodgkin's lymphoma, and with pemetrexed in non-small cell lung cancer.

References.

1. Sorbera LA, *et al.* Enzastaurin hydrochloride. *Drugs Of The Future* 2007; 32: 297–309. Correction. *ibid.*; 751.
2. Ma S, Rosen ST. Enzastaurin. *Curr Opin Oncol* 2007; 19: 590–5.
3. Chen YB, LaCasce AS. Enzastaurin. *Expert Opin Invest Drugs* 2008; 17: 939–44.
4. Wick W, *et al.* Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol* 2010; 28: 1168–74.
5. Galanis E, Buckner JC. Enzastaurin in the treatment of recurrent glioblastoma: a promise that did not materialize. *J Clin Oncol* 2010; 28: 1097–8.
6. Giovannetti E, *et al.* Pharmacological aspects of the enzastaurin-pemetrexed combination in non-small cell lung cancer (NSCLC). *Curr Drug Targets* 2010; 11: 12–28.

Epirubicin Hydrochloride

(BANM, USAN, rINNM)

Epirubicina, hidrocloruro de; Épirubicine, chlorhydrate d'; Epirubicin-hidroklorid; Epirubicin-hydrochlorid; Epirubicin-hydrochlorid; Epirubicinhydroklorid; Epirubicini Hydrochloridum; Epirubicino hidrochloridas; Epirubisiinihydrokloridi; Epirubisin Hidroklorür; Hidrocloruro de epirubicina; IMI-28; Pidorubicin Hydrochloride; Эпирубицина Гидрохлорид; 4'-Epiadriamycin Hydrochloride; 4'-Epidoxorubicin Hydrochloride.

(8*S*,10*S*)-10-(3-Amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyloxy)-8-glycolloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxynaphthacene-5,12-dione hydrochloride.

$C_{27}H_{29}NO_{11}$,HCl=580.0

CAS — 56420-45-2 (epirubicin); 56390-09-1 (epirubicin hydrochloride).

ATC — L01DB03.

ATC Vet — QL01DB03.

UNII — 22966TX7J5.

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

Ph. Eur. 8: (Epirubicin Hydrochloride). A substance obtained by chemical transformation of a substance produced by certain strains of *Streptomyces peucetius*. An orange-red powder. Soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.0 to 5.5. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Epirubicin Hydrochloride). An orange-red powder. Soluble in water and methyl alcohol; slightly soluble in anhydrous alcohol; practically insoluble in acetone. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Incompatibility. Licensed product information states that epirubicin hydrochloride is incompatible with heparin or fluorouracil, resulting in precipitation, and that it is hydrolysed in alkaline solutions.

Stability. Epirubicin was not subject to significant photodegradation at clinical concentrations,[1,2] and special precautions to protect solutions from light during use do not appear to be necessary. However, photodegradation may be significant at lower concentrations (below 500 micrograms/mL).[1]

1. Wood *MJ, et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; 15: 291–300.
2. Pujol M, *et al.* Stability study of epirubicin in NaCl 0.9% injection. *Ann Pharmacother* 1997; 31: 992–5.

Uses and Administration

Epirubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (p. 783.2). It is used, alone or with other antineoplastics, in acute leukaemias, lymphomas, multiple myeloma, and in solid tumours including Wilms' tumour (p. 709.1), cancer of the bladder (p. 700.2), breast (p. 702.1), and stomach (p. 706.1).

Epirubicin hydrochloride is given by intravenous injection of a solution in sodium chloride 0.9% or Water for Injections into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 3 to 5 minutes, or by infusion over up to 30 minutes. It is given as a single agent in usual doses of 60 to 90 mg/m² as a single dose every 3 weeks; this dose may be divided over 2 or 3 days if desired. A regimen of 20 to 30 mg/m² once a week has been tried in palliative care or in those who do not tolerate the higher dose. High-dose regimens, of 120 mg/m² or more every 3 weeks, or 45 mg/m² for 3 consecutive days every 3 weeks have been used.

Doses may need to be reduced if epirubicin is given with other antineoplastics. Doses should also be reduced in patients with liver impairment (see below) and in those whose bone-marrow function is impaired by age or previous chemotherapy or radiotherapy.

A total cumulative dose of 0.9 to 1 g/m² should not generally be exceeded, because of the risk of cardiotoxicity.

Epirubicin has also been given by intravesical instillation in the local treatment of bladder cancer. Instillation of 50 mg weekly as a 0.1% solution (in sodium chloride 0.9% or sterile water) for 8 weeks has been suggested, reduced to 30 mg in 50 mL weekly if chemical cystitis develops; for carcinoma *in-situ*, the dose may be increased, if tolerated, to 80 mg in 50 mL weekly. For the prophylaxis of recurrence in patients who have undergone transurethral resection, 50 mg weekly for 4 weeks, followed by 50 mg instilled once a month for 11 months is the suggested regimen. The solution should be retained in the bladder for 1 hour.

Blood counts should be made routinely during treatment with epirubicin (see also Bone-marrow Depression, p. 730.3) and cardiac function should be carefully monitored. Liver function should be assessed before and if possible during therapy.

References.

1. Plosker GL, Faulds D. Epirubicin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cancer chemotherapy. *Drugs* 1993; 45: 788–856.
2. Coukell AJ, Faulds D. Epirubicin: an updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of breast cancer. *Drugs* 1997; 53: 453–82.
3. Onrust SV, *et al.* Epirubicin: a review of its intravesical use in superficial bladder cancer. *Drugs Aging* 1999; 15: 307–33.
4. Ormrod D, *et al.* Epirubicin: a review of its efficacy as adjuvant therapy and in the treatment of metastatic disease in breast cancer. *Drugs Aging* 1999; 15: 389–416.
5. Earl H, Iddawela M. Epirubicin as adjuvant therapy in breast cancer. *Expert Rev Anticancer Ther* 2004; 4: 189–95.

Administration in hepatic impairment. Doses of epirubicin should be halved in patients with moderate liver dysfunction (serum bilirubin concentrations of 12 to 30 micrograms/mL), while those with severe liver impairment (serum bilirubin greater than 30 micrograms/mL) should be given a quarter of the usual dose.

Amyloidosis. For reference to a regimen including epirubicin used to control disease in a patient with amyloidosis, see p. 819.3.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p. 784.1. Cardiotoxicity and myelotoxicity may be less than with doxorubicin. Cardiotoxicity is more likely when the total cumulative dose exceeds 0.9 to 1 g/m².

Effects on the heart. For further discussion of the cardiotoxicity of anthracyclines, see under Adverse Effects of Doxorubicin, p. 784.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies epirubicin 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 29/09/11)

Interactions

As for Doxorubicin, p. 785.2.

Antineoplastics. Increased exposure to epirubicin, and a consequent increase in myelotoxicity, has been reported in patients given epirubicin immediately after *paclitaxel*, compared with patients who received epirubicin before paclitaxel.[1] Similar interactions have been seen when paclitaxel was given before other anthracyclines.[2] These and other studies[3,4] have suggested that paclitaxel given in this way is associated with a reduced conversion of epirubicin to the less myelotoxic metabolite, epirubicinol, although the interaction is complex, and may involve both disposition and pharmacodynamics.

1. Venturini M, *et al.* Sequence effect of epirubicin and paclitaxel treatment on pharmacokinetics and toxicity. *J Clin Oncol* 2000; 18: 2116–25.
2. Danesi R, *et al.* Pharmacokinetic optimisation of treatment schedules for anthracyclines and paclitaxel in patients with cancer. *Clin Pharmacokinet* 1999; 37: 195–211.
3. Grasselli G, *et al.* Clinical and pharmacologic study of the epirubicin and paclitaxel combination in women with metastatic breast cancer. *J Clin Oncol* 2001; 19: 2222–31.
4. Danesi R, *et al.* Pharmacokinetics and pharmacodynamics of combination chemotherapy with paclitaxel and epirubicin in breast cancer patients. *Br J Clin Pharmacol* 2002; 53: 508–18.

Cimetidine. Cimetidine increased the formation of the active metabolite of epirubicin in a study in 8 patients; there was also a substantial increase in systemic exposure to unchanged epirubicin.[1] The mechanisms and potential clinical significance of the interaction were unclear.

1. Murray LS, *et al.* The effect of cimetidine on the pharmacokinetics of epirubicin in patients with advanced breast cancer: preliminary evidence of a potentially common drug interaction. *Clin Oncol* 1998; 10: 35–8.

Pharmacokinetics

After intravenous doses epirubicin is rapidly and extensively distributed into body tissues, and undergoes metabolism in the liver, with the formation of epirubicinol (13-hydroxyepirubicin) and appreciable amounts of glucuronide derivatives. Epirubicin is eliminated mainly in bile, with a terminal plasma elimination half-life of about 30 to 40 hours. About 10% of a dose is recovered in urine within 48 hours. Epirubicin does not cross the blood-brain barrier.

References.

1. Morris RG, *et al.* Disposition of epirubicin and metabolites with repeated courses to cancer patients. *Eur J Clin Pharmacol* 1991; 40: 481–7.
2. Robert J. Clinical pharmacokinetics of epirubicin. *Clin Pharmacokinet* 1994; 26: 428–38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Crisabon; Cuatroepi; Epidoxo; Epifil; Epikebir†; Farmorubicin; Robanul; ***Austral.***: Pharmorubicin; ***Austria:*** Epi-Cell†; Farmorubicin; ***Belg.***: Farmorubicine; ***Braz.***: Brecila; Farmorubicina; Nuovodox; Rubina†; Tecnomax; ***Canad.***: Pharmorubicin; ***Chile:*** Farmorrubicina; ***China:*** Ai Da Sheng (艾达生); Pharmorubicin (法玛新); ***Cz.***: Epimedac; Farmorubicin; ***Denm.***: Epi-cell; Farmorubicin; ***Fin.***: Farmorubicin; ***Fr.***: Farmorubicine; ***Ger.***: Axirubicin-e; Bendaepi; Epi Teva; Epi-Cell; Epi-NC†; Epimedac; Eracin; Farmorubicin; Riboepi; ***Gr.***: Cenebir; Ciazil; Epibicin; Epibra; Epimedac; Epirub; Epirud†; Farmorubicin; Megarubicin; Rubiprol; ***Hong Kong:*** Episindan; Pharmorubicin; ***Hung.***: Episindan; Farmorubicin; ***India:*** Alrubicin; Epirubitec; Epithra; Epricin; Farmorubicin; ***Irl.***: Pharmorubicin; ***Israel:*** Farmorubicin†; ***Ital.***: Farmorubicina; ***Jpn:*** Farmorubicin; ***Malaysia:*** Pharmorubicin; ***Mex.***: Anthracord; Binarin; Epilem; Farmorubicin; Favicin; ***Neth.***: Farmorubicine; ***Norw.***: Farmorubicin; ***NZ:*** Epiccord; Pharmorubicin; ***Philipp.***: Anthradn; E.P. Mycin; EP Mycin; Neoquabin; Pharmorubicin; ***Pol.***: Bioepicyna; Episindan; Farm-

orubicin; *Port.*: Epi-cell; Farmorubicina; *Rus.*: Epilem (Эпилем); Episindan (Эписиндан); Farmorubicin (Фарморубицин); *S.Afr.*: Epicord; Farmorubicin; *Singapore*: Eberubi; Episindan; Pharmorubicin; *Spain*: Farmorubicina; Sendras†; *Swed.*: Farmorubicin; *Switz.*: Farmorubicin; *Thai.*: Anthracin†; E.P.Mycin†; EP Mycin; Epilem; Pharmorubicin; *Turk.*: Farmorubicin; Pirucin; Rubens; *UK*: Pharmorubicin; *Ukr.*: Farmorubicin (Фарморубицин); *USA*: Ellence; *Venez.*: Farmorubicin.

Pharmacopoeial Preparations
BP 2014: Epirubicin Injection.

Epratuzumab *(rINN)*

AMG-412; Epratuzumab; Epratuzumabum; Эпратузумаб. Immunoglobulin G (human-mouse monoclonal IMMU-hLL2 γ-chain anti-human antigen CD22), disulfide with human-mouse monoclonal IMMU-hLL2 κ-chain, dimer.
CAS — 205923-57-5.
UNII — 3062P60MH9.

Profile

Epratuzumab is a humanised anti-CD22 monoclonal antibody under investigation, alone or conjugated with yttrium-90 (p. 2230.1), for the treatment of non-Hodgkin's lymphoma. It is also under investigation for the treatment of moderate to severe SLE.

References.

1. Davies SL, Martin L. Epratuzumab. *Drugs Of The Future* 2005; 30: 683–7.
2. Leonard JP, *et al.* Combination antibody therapy with epratuzumab and rituximab in relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* 2005; 23: 5044–51.
3. Lindén O, *et al.* Dose-fractionated radioimmunotherapy in non-Hodgkin's lymphoma using DOTA-conjugated, ^{90}Y-radiolabeled, humanized anti-CD22 monoclonal antibody, epratuzumab. *Clin Cancer Res* 2005; 11: 5215–22.
4. Goldenberg DM. Epratuzumab in the therapy of oncological and immunological diseases. *Expert Rev Anticancer Ther* 2006; 6: 1341–53.
5. Leonard JP, Goldenberg DM. Preclinical and clinical evaluation of epratuzumab (anti-CD22 IgG) in B-cell malignancies. *Oncogene* 2007; 26: 3704–13.
6. Leonard JP, *et al.* Durable complete responses from therapy with combined epratuzumab and rituximab: final results from an international multicenter, phase 2 study in recurrent, indolent, non-Hodgkin lymphoma. *Cancer* 2008; 113: 2714–23.

Eptaplatin *(rINN)*

Eptaplatine; Eptaplatino; Eptaplatinum; Heptaplatin; SKI-2053R; Эптаплатин.
cis-[(4*R*,5*R*)-2-Isopropyl-1,3-dioxolane-4,5-bis(methylamine)-*N*,*N*'][malonato(2−)-*O*,*O*']platinum.
$C_{11}H_{20}N_2O_6Pt$=471.4
CAS — 146665-77-2.
UNII — 1352HON1DH.

Profile

Eptaplatin is a platinum derivative that is used as an intravenous antineoplastic in the treatment of gastric cancer. Nephrotoxicity is the main adverse effect.

References.

1. Ahn JH, *et al.* Nephrotoxicity of heptaplatin: a randomized comparison with cisplatin in advanced gastric cancer. *Cancer Chemother Pharmacol* 2002; 50: 104–10.
2. Min YJ, *et al.* Combination chemotherapy with 5-fluorouracil and heptaplatin as first-line treatment in patients with advanced gastric cancer. *J Korean Med Sci* 2004; 19: 369–73.
3. Lee KH, *et al.* Randomized, multicenter, phase III trial of heptaplatin 1-hour infusion and 5-fluorouracil combination chemotherapy comparing with cisplatin and 5-fluorouracil combination chemotherapy in patients with advanced gastric cancer. *Cancer Res Treat* 2009; 41: 12–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Kor.*: Sunpla.

Eribulin *(rINN)*

B-1939; ER-086526; Eribulina; Éribuline; Eribulinum; Эрибулин.
(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12-*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-2-[(2*S*)-3-Amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one.
$C_{40}H_{59}NO_{11}$=729.9
CAS — 253128-41-5.
ATC — L01XX41.
ATC Vet — QL01XX41.
UNII — LR24G6354G.

Eribulin Mesilate *(rINNM)*

E-7389; Eribulin Mesylate (USAN); Éribuline, Mésilate d'; Eribulini Mesilas; Mesilato de eribulina; Эрибулина Мезилат.
(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12-*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-2-[(2*S*)-3-Amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one methanesulfonate.
$C_{40}H_{59}NO_{11}.CH_4O_3S$=826.0
CAS — 441045-17-6.
ATC — L01XX41.
ATC Vet — QL01XX41.
UNII — AV9U0660CW.

Uses and Administration

Eribulin is a synthetic analogue of halichondrin B, a substance isolated from marine sponges. It inhibits tubulin polymerisation and is used in the treatment of refractory locally advanced or metastatic breast cancer (p. 702.1) in patients previously treated with at least 2 chemotherapy regimens, including an anthracycline and a taxane. Eribulin is given as the mesilate, although in some countries the dose is expressed as the base. The recommended dose is eribulin mesilate 1.4 mg/m² (equivalent to eribulin 1.23 mg/m²) given by intravenous injection over 2 to 5 minutes, on days 1 and 8 of a 21-day cycle. The start of treatment should be delayed in patients with absolute neutrophil counts less than 1000 cells/mm³, or platelet counts less than 75 000 cells/mm³, or grade 3 or 4 non-haematological toxicity, until recovery occurs, and similar precautions apply in subsequent cycles once treatment has started. More severe toxicity may also require dose reduction (see Administration in Subsequent Cycles, below). For doses in hepatic or renal impairment, see below.

Eribulin is also under investigation for the treatment of various other malignancies including non-small cell lung cancer, prostate cancer, and sarcoma.

References.

1. Twelves C, *et al.* Phase III trials of eribulin mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer. *Clin Breast Cancer* 2010; 10: 160–3.
2. Cigler T, Vahdat LT. Eribulin mesylate for the treatment of breast cancer. *Expert Opin Pharmacother* 2010; 11: 1587–93.
3. Cortes J, *et al.* EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011; 377: 914–23.

Administration in hepatic impairment. Exposure to eribulin is increased by hepatic impairment and lower doses are recommended. The intravenous dose of eribulin mesilate for mild impairment (Child-Pugh class A) is 1.1 mg/m² (equivalent to eribulin 970 micrograms/m²), and for moderate impairment (Child-Pugh class B) 700 micrograms/m² (equivalent to eribulin 620 micrograms/m²), given on days 1 and 8 of a 21-day cycle. Eribulin has not been studied in those with severe hepatic impairment (Child-Pugh class C).

Administration in renal impairment. No dose adjustment is considered necessary when eribulin is used in those with mild renal impairment, defined by US licensed product information as creatinine clearance (CC) 50 to 80 mL/min; however, exposure to eribulin is increased by moderate renal impairment (CC 30 to 50 mL/min) and a lower intravenous dose of eribulin mesilate 1.1 mg/m² is recommended in the USA, given on days 1 and 8 of a 21-day cycle. The safety of eribulin has not been studied in those with severe renal impairment (CC < 30 mL/min). UK licensed product information states that patients with severe renal impairment (CC < 40 mL/min) may need a reduction in dose, but gives no specific dose recommendation.

Administration in subsequent cycles. If any of the following occur after an intravenous dose of eribulin mesilate:
- absolute neutrophil count (ANC) < 500 cells/mm³ and lasting more than 7 days
- ANC < 1000 cells/mm³ complicated by fever or infection
- platelet count < 25 000 cells/mm³
- platelet count < 50 000 cells/mm³ complicated by haemorrhage or the need for transfusion
- grade 3 or 4 non-haematological toxicity

then subsequent doses should be reduced from 1.4 mg/m² eribulin mesilate (1.23 mg/m² eribulin) to 1.1 mg/m² eribulin mesilate (970 micrograms/m² eribulin).

If such toxicities recur despite dose reduction, then subsequent doses should be further reduced to 700 micrograms/m² eribulin mesilate (620 micrograms/m² eribulin); if severe toxicity continues at this lower dose, then treatment should be stopped. Doses should not be increased again in subsequent cycles once they have been reduced.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects associated with eribulin are neutropenia, anaemia, leucopenia, fatigue, fever, alopecia, peripheral neuropathy, headache, arthralgia, myalgia, anorexia, and gastrointestinal disturbances. Infections, including urinary-tract or upper respiratory-tract infections, nasopharyngitis, rhinitis, and oral candidiasis, are also common, as are pain, especially in the back, bone, chest, or oropharyngeal area, and electrolyte disturbances including hypokalaemia, hypomagnesaemia, and hypophosphataemia.

Other adverse effects include febrile neutropenia, thrombocytopenia, lymphopenia, tachycardia, hot flushes, cough, dyspnoea, abdominal pain, stomatitis, mouth ulceration, dry mouth, peripheral oedema, muscle spasms or weakness, epistaxis, rhinorrhoea, increased lachrymation, conjunctivitis, dysgeusia, vertigo, dizziness, insomnia, depression, and increased liver enzymes. Skin disorders include rash, pruritus, hyperhidrosis, dry skin, erythema, and palmar-plantar erythrodysesthesia; nail disorders have also been reported. Hyperglycaemia and dehydration have occurred, as have chills and flu-like illness.

Less common adverse effects include deep-vein thrombosis, pulmonary embolism, interstitial lung disease, hyperbilirubinaemia, angioedema, and tinnitus. Renal disorders that have been reported include dysuria, haematuria, proteinuria, and renal failure.

Complete blood counts should be measured before each dose of eribulin, and more frequently in those who develop severe cytopenias. Treatment should be delayed or the dose reduced if febrile neutropenia occurs or if severe neutropenia lasts longer than 7 days, see Uses and Administration, above. Severe neutropenia may be more common in patients with elevated liver enzymes or bilirubin.

Patients should be monitored closely for peripheral motor and sensory neuropathy. Treatment should be withheld for severe peripheral neuropathy, see Uses and Administration, above.

Eribulin may prolong the QT interval and ECG monitoring is recommended in patients at higher risk, including those with heart failure, bradyarrhythmias, electrolyte abnormalities, or patients also taking other drugs that prolong the QT interval such as some antiarrhythmics. Hypokalaemia and hypomagnesaemia should be corrected before starting eribulin, and these electrolytes monitored periodically during treatment. Eribulin should not be used in patients with congenital long QT syndrome.

Pharmacokinetics

Eribulin is a substrate for, and a weak inhibitor of, P-glycoprotein. Eribulin is rapidly distributed, and has a large volume of distribution. Plasma protein binding ranges from 49 to 65%. It is eliminated by biliary excretion, mainly as unchanged drug, with 82% of the dose in the faeces and 9% in the urine. The mean elimination half-life is about 40 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Halaven; *Belg.*: Halaven; *Cz.*: Halaven; *Denm.*: Halaven; *Fin.*: Halaven; *Fr.*: Halaven; *Ger.*: Halaven; *Gr.*: Halaven; *Hung.*: Halaven; *Irl.*: Halaven; *Israel*: Halaven; *Ital.*: Halaven; *Jpn*: Halaven; *Neth.*: Halaven; *Norw.*: Halaven; *Pol.*: Halaven; *Port.*: Halaven; *Singapore*: Halaven; *Spain*: Halaven; *Swed.*: Halaven; *Switz.*: Halaven; *UK*: Halaven; *USA*: Halaven.

Erlotinib Hydrochloride

(BANM, USAN, rINNM)

CP-358774-01; Erlotinib, Chlorhydrate d'; Erlotinibi Hydrochloridum; Hidrocloruro de erlotinib; NSC-718781; OSI-774 Эрлотиниба Гидрохлорид.
N-(3-Ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine hydrochloride.
$C_{22}H_{23}N_3O_4.HCl$=429.9
CAS — 183321-74-6 (erlotinib); 183319-69-9 (erlotinib hydrochloride).
ATC — L01XE03.
UNII — DA87705X9K.

Uses and Administration

Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor. It is used for the management of locally advanced or metastatic non-small cell lung cancer (p. 710.2) either in disease that is unresponsive to other therapy, or, in some

countries, as maintenance monotherapy in those with stable disease after platinum-based first-line chemotherapy. It is also used with gemcitabine in the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer (p. 712.1). It is given orally as the hydrochloride but doses are expressed in terms of the base: erlotinib hydrochloride 109 mg is equivalent to about 100 mg of erlotinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The usual dose for non-small cell lung cancer is 150 mg daily, taken at least 1 hour before or 2 hours after food. In the treatment of pancreatic cancer, the recommended dose is 100 mg daily, taken at least 1 hour before or 2 hours after food. Treatment is continued until disease progression or unacceptable toxicity occurs. Where dosage adjustment is necessary, reductions are made in 50 mg steps. Caution is advised in some patients with hepatic or renal impairment (see below).

If concurrent use of potent inhibitors or inducers of cytochrome-P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments of erlotinib are considered necessary.

- When used with a potent CYP3A4 inhibitor, the dose of erlotinib may need to be *reduced*, especially if severe adverse effects occur.
- When given with a potent CYP3A4 inducer, *increases* in the dose of erlotinib should be considered at 2-week intervals with monitoring. The maximum daily dose of erlotinib when used with rifampicin is 450 mg. If the inducer is then stopped, the erlotinib dose will need to be immediately reduced to the indicated starting dose.

Erlotinib is also under investigation in the treatment of malignant glioma.

References.

1. Perez-Soler R. The role of erlotinib (Tarceva, OSI 774) in the treatment of non-small cell lung cancer. *Clin Cancer Res* 2004; 10 (suppl): 4238s–4240s.
2. Pérez-Soler R, *et al.* Determinants of tumor response and survival with erlotinib in patients with non—small-cell lung cancer. *J Clin Oncol* 2004; 22: 3238–47.
3. Anonymous. Erlotinib. *Med Lett Drugs Ther* 2005; 47: 25–6.
4. Smith J. Erlotinib: small-molecule targeted therapy in the treatment of non-small-cell lung cancer. *Clin Ther* 2005; 27: 1513–34.
5. Brown ER, Shepherd FA. Erlotinib in the treatment of non-small cell lung cancer. *Expert Rev Anticancer Ther* 2005; 5: 767–75.
6. Shepherd FA, *et al.* Erlotinib in previously treated non—small-cell lung cancer. *N Engl J Med* 2005; 353: 123–32.
7. Tang PA, *et al.* A review of erlotinib and its clinical use. *Expert Opin Pharmacother* 2006; 7: 177–93.
8. Gridelli C, *et al.* Erlotinib in non-small-cell lung cancer. *Expert Opin Pharmacother* 2007; 8: 2579–92.
9. Saif MW, *et al.* Erlotinib: the first biologic in the management of pancreatic cancer. *Expert Opin Pharmacother* 2008; 9: 1595–1607.
10. Waller LL, *et al.* Using erlotinib to treat patients with non-small cell lung cancer who continue to smoke. *Lung Cancer* 2010; 67: 12–16.
11. Steins M, *et al.* Erlotinib. *Recent Results Cancer Res* 2010; 184: 21–31.
12. Iyer R, Bharthuar A. A review of erlotinib—an oral, selective epidermal growth factor receptor tyrosine kinase inhibitor. *Expert Opin Pharmacother* 2010; 11: 311–20.
13. Cataldo VD, *et al.* Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med* 2011; 364: 947–55.
14. Mountzios G, Syrigos KN. A benefit-risk assessment of erlotinib in non-small-cell lung cancer and pancreatic cancer. *Drug Safety* 2011; 34: 175–86.

Administration in hepatic or renal impairment. Erlotinib is metabolised by the liver. UK licensed product information states that although erlotinib exposure was similar in patients with moderate hepatic impairment (Child-Pugh score 7 to 9) compared with those with adequate hepatic function, caution is advised when using erlotinib in hepatic impairment. Dose reduction or interruption of therapy should be considered if adverse effects occur. Use in severe hepatic impairment is not recommended due to a lack of data.

UK licensed product information also states that no dose adjustments appear necessary in patients with mild to moderate renal impairment, but that use of erlotinib in patients with severe renal impairment is not recommended. There are no data available for patients with a creatinine clearance less than 15 mL/minute or those with a serum creatinine concentration greater than 1.5 times the upper normal limit.

Malignant neoplasms of the skin. Erlotinib has been reported to initially cause inflammation at the site of actinic keratoses, followed by partial regression.[1] A patient with nonresectable, refractory, locally aggressive keratoacanthoma centrifugum marginatum of the scalp, a squamous neoplasm known to be abundant in epidermal growth factor receptors (EGFR), was treated with erlotinib. No new lesions developed and an almost complete regression of existing lesions was seen after 2 months of treatment. The authors suggested that EGFR inhibitors such as erlotinib should be considered for well-differentiated EGFR-expressing squamous skin neoplasms, especially if lesions are recalcitrant, multiple, or surgically nonresectable.[2]

1. Hermanns J-F, *et al.* Erlotinib-responsive actinic keratoses. *Oncol Rep* 2007; 18: 581–4.
2. Buij TK, *et al.* Refractory aggressive keratoacanthoma centrifugum marginatum of the scalp controlled with the epidermal growth factor receptor inhibitor erlotinib. *Br J Dermatol* 2010; 163: 633–7.

Adverse Effects, Treatment, and Precautions

The most common adverse effects associated with erlotinib hydrochloride are rash and diarrhoea. Generally, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun-exposed areas; protective clothing and/or use of sunscreen is advisable, and dose reduction may be needed. Bullous, blistering, and exfoliative skin conditions have been reported, including rare cases suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis, some of which were fatal; erlotinib therapy should be interrupted or stopped if such bullous symptoms occur. Moderate or severe diarrhoea should be treated with an appropriate antidiarrhoeal such as loperamide; dose reduction may be needed. In more severe or persistent cases leading to dehydration, therapy should be stopped temporarily. Hypokalaemia and renal failure (including fatalities) have been reported; some cases were secondary to dehydration or concurrent chemotherapy. Renal function and electrolytes should be monitored in patients at risk of dehydration.

Other common adverse effects include nausea, vomiting, stomatitis, gastrointestinal bleeding, abdominal pain, anorexia, alopecia, pruritus, dry skin, paronychia, conjunctivitis, epistaxis, and fatigue. Alterations in liver function tests have occurred. Rare cases of hepatic failure and hepatorenal syndrome, including fatalities, have been reported. Liver function should be periodically monitored, and treatment interrupted or stopped if liver function changes are severe. Interstitial lung disease has also been reported; again, deaths have occurred. Erlotinib treatment should be interrupted if unexplained pulmonary symptoms occur, such as dyspnoea, cough, and fever. Cases of gastrointestinal perforation, some fatal, have occurred; patients taking anti-angiogenic drugs, taxanes, corticosteroids, or NSAIDs or with a history of peptic ulcer or diverticular disease are at increased risk. Erlotinib should be permanently stopped if perforation occurs. Ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis can also occur, and are risk factors for corneal perforation or ulceration, which has been reported very rarely; erlotinib should be interrupted or stopped in the event of acute or worsening eye pain.

Effects on the ears. Bilateral eardrum perforation with resultant hearing loss has been reported after 1 year of therapy with oral erlotinib.[1] Dosage was reduced from 150 mg daily to 100 mg daily, and 6 months later the left tympanic membrane had healed.

1. Lee SM, *et al.* Bilateral eardrum perforation after long-term treatment with erlotinib. *J Clin Oncol* 2008; 26: 2582–4.

Effects on the liver. Acute hepatitis developed in an elderly man 12 days after starting erlotinib; he was also taking metformin for type 2 diabetes mellitus. Lactic acidosis, which may have been exacerbated by the metformin, developed rapidly, and the patient died. Liver toxicity may be worse in frail elderly patients with comorbidities and multiple medications. Careful monitoring of liver function tests and renal function was advised.[1]

The manufacturers reported on fatalities that had occurred in patients with advanced solid tumours and moderate hepatic impairment as defined by the Child-Pugh criteria; 6 of 10 patients who died had baseline bilirubin values more than 3 times the upper normal limit (ULN), suggesting severe, rather than moderate, hepatic impairment. All patients had liver involvement such as hepatocellular carcinoma, cholangiosarcoma, or liver metastases, and the manufacturers warned that there may be limitations to using Child-Pugh criteria in an oncology population.[2] US licensed product information states that patients with hepatic impairment should be closely monitored and therapy interrupted or stopped if liver function changes are severe, such as doubling of total bilirubin and/or tripling of transaminases in patients with pretreatment values outside the normal range. Therapy should also be interrupted or stopped if total bilirubin is more than 3 times the ULN and/or transaminases are greater than 5 times the ULN in those with normal pretreatment values.

1. Pellegrinotti M, *et al.* Erlotinib-induced hepatitis complicated by fatal lactic acidosis in an elderly man with lung cancer. *Ann Pharmacother* 2009; 43: 542–5.
2. Genentech, OSI. Important safety information (issued September 2008). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM135238.pdf (accessed 22/09/09)

Effects on the skin, hair, and nails. Reviews[1-3] of erlotinib-induced skin rash and its management, including discussion of its potential value as a surrogate marker of disease response. Isotretinoin plus clindamycin has been reported to be effective in treating erlotinib-induced rash;[4] aprepitant has been reported[5] to be effective in treating and preventing associated pruritus (for further information about aprepitant for pruritus, see p. 1822.3).

For reference to other cutaneous adverse effects of epidermal growth factor receptor inhibitors, including erlotinib, see Effects on the Skin, Hair, and Nails, under Cetuximab, p. 763.2.

1. Saif MW, *et al.* Erlotinib-induced skin rash. Pathogenesis, clinical significance and management in pancreatic cancer patients. *JOP* 2008; 9: 267–74.
2. Tsimboukis S, *et al.* Erlotinib-induced skin rash in patients with non-small-cell lung cancer: pathogenesis, clinical significance, and management. *Clin Lung Cancer* 2009; 10: 106–11.
3. Thatcher N, *et al.* UK Erlotinib Skin Toxicity Management Consensus Group. Expert consensus on the management of erlotinib-associated cutaneous toxicity in the UK *Oncologist* 2009; 14: 840–7.
4. Bidoli P, *et al.* Isotretinoin plus clindamycin seem highly effective against severe erlotinib-induced skin rash in advanced non-small cell lung cancer. *J Thorac Oncol* 2010; 5: 1662–3.
5. Vincenzi B, *et al.* Aprepitant for erlotinib-induced pruritus. *N Engl J Med* 2010; 363: 397–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies erlotinib 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 27/09/11)

Interactions

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, can increase erlotinib concentrations and use with potent inhibitors should be avoided as increased toxicity may occur. Conversely, CYP3A4 inducers, such as rifampicin, can reduce erlotinib concentrations and may reduce its efficacy. Dose adjustments may be required (see Uses and Administration, p. 788.3). Caution is also required with ciprofloxacin or potent inhibitors of CYP1A2, as erlotinib exposure may be increased, and dose reductions may be needed if adverse effects occur. Use with P-glycoprotein inhibitors such as ciclosporin and verapamil may cause altered distribution or elimination of erlotinib. Drugs that increase the pH of the gastrointestinal tract such as antacids, H_2-receptor antagonists, or proton pump inhibitors may reduce the solubility of erlotinib and hence lower its bioavailability. Use of proton pump inhibitors with erlotinib should be avoided. If the use of antacids or H_2-receptor antagonists cannot be avoided, dosing should be staggered; licensed product information recommends that antacids should be taken at least 4 hours before or 2 hours after erlotinib, and erlotinib at least 2 hours before or 10 hours after ranitidine. Exposure to erlotinib is reduced in smokers compared with non-smokers. Exposure to erlotinib may be increased by capecitabine.

Erlotinib is a strong inhibitor of glucuronidation by the uridine diphosphate glucuronosyltransferase isoenzyme UGT1A1 *in vitro* and may affect exposure to UGT1A1 substrates. Increased INR and bleeding events have been reported with erlotinib, some associated with the use of warfarin and some with the use of NSAIDs, see p. 1532.2 and p. 107.3, respectively.

Fibrates. Progression of lung adenocarcinoma in a patient treated with erlotinib was attributed to suboptimal exposure to erlotinib, and the dose was increased. Concomitant medications included escitalopram, alprazolam, and *fenofibrate*. Given the potential induction of cytochrome P450 isoenzyme CYP3A4 by fenofibrate, this was withdrawn; a reduction in erlotinib dosage was subsequently needed.

1. Mir O, *et al.* Drug-induced effects on erlotinib metabolism. *N Engl J Med* 2011; 365: 379–80.

Tobacco smoking. Exposure to erlotinib is reduced in smokers (see Interactions, above). A study determined that the maximum tolerated dose of oral erlotinib was 300 mg daily in lung cancer patients who were also current smokers. Steady-state trough plasma concentrations and incidence of rash and diarrhoea were similar to those in other studies of former smokers or those who had never smoked, who were taking the usual recommended dose of 150 mg daily.[1]

1. Hughes AN, *et al.* Overcoming CYP1A1/1A2 mediated induction of metabolism by escalating erlotinib dose in current smokers. *J Clin Oncol* 2009; 27: 1220–6.

Pharmacokinetics

Erlotinib is absorbed from the gastrointestinal tract, with a bioavailability of about 60%; this may increase up to almost 100% in the presence of food. Peak plasma concentrations occur about 4 hours after a dose, and it is about 93% bound to plasma proteins. Erlotinib is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP1A2. Metabolic pathways include demethylation, to metabolites OSI-420 and OSI-413, oxidation, and aromatic hydroxylation. Erlotinib has an elimination half-life of

about 36 hours. More than 80% of a dose is excreted as metabolites in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tarceva; *Austral.*: Tarceva; *Austria*: Tarceva; *Belg.*: Tarceva; *Braz.*: Tarceva; *Canad.*: Tarceva; *Chile*: Tarceva; *China*: Tarceva (特罗凯); *Cz.*: Tarceva; *Denm.*: Tarceva; *Fin.*: Tarceva; *Fr.*: Tarceva; *Ger.*: Tarceva; *Gr.*: Tarceva; *Hong Kong*: Tarceva; *Hung.*: Tarceva; *Indon.*: Tarceva; *Irl.*: Tarceva; *Israel*: Tarceva; *Ital.*: Tarceva; *Jpn*: Tarceva; *Malaysia*: Tarceva; *Mex.*: Tarceva; *Neth.*: Tarceva; *Norw.*: Tarceva; *NZ*: Tarceva; *Philipp.*: Tarceva; *Pol.*: Tarceva; *Port.*: Tarceva; *Rus.*: Tarceva (Тарцева); *S.Afr.*: Tarceva; *Singapore*: Tarceva; *Spain*: Tarceva; *Swed.*: Tarceva; *Switz.*: Tarceva; *Thai.*: Tarceva; *Turk.*: Tarceva; *UK*: Tarceva; *Ukr.*: Tarceva (Тарцева); *USA*: Tarceva.

Estramustine Sodium Phosphate

(BANM, rINNM)

Estramustin Fosfat Sodyum; Estramustina, fosfato sódico de; Estramustine, Phosphate Sodique de; Estramustine Phosphate Sodium (USAN); Fosfato sódico de estramustina; Natrii Estramustini Phosphas; NSC-89199 (estramustine phosphate); Ro-22-2296/000 (estramustine); Ro-21-8837/001; Натрия Эстрамустина Фосфат.

Estra-1,3,5(10)-triene-3,17β-diol 3-[bis(2-chloroethyl)carbamate] 17-(disodium phosphate); Disodium 3-[bis(2-chloroethyl)-carbamoyloxy]estra-1,3,5(10)-trien-17β-yl orthophosphate.

$C_{23}H_{30}Cl_2NNa_2O_6P$=564.3

CAS — 2998-57-4 (estramustine); 4891-15-0 (estramustine phosphate); 52205-73-9 (estramustine sodium phosphate).

ATC — L01XX11.

ATC Vet — QL01XX11.

UNII — 75F375MT2N.

Pharmacopoeias. In *Br.*

BP 2014: (Estramustine Sodium Phosphate). A white or almost white powder. Freely soluble in water and in methyl alcohol; very slightly soluble in dehydrated alcohol and in chloroform. A 0.5% solution in water has a pH of 8.5 to 10.0. Protect from light.

Uses and Administration

Estramustine is a combination of estradiol and normustine, a homologue of chlormethine (p. 765.1). It has weaker oestrogenic activity than estradiol and weaker antineoplastic activity than most other alkylating agents. Estramustine phosphate is given orally as the disodium salt. Doses are calculated in terms of estramustine phosphate; 108 mg of estramustine sodium phosphate is equivalent to about 100 mg of estramustine phosphate. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Estramustine phosphate with meglumine has been given by intravenous injection.

Estramustine sodium phosphate is licensed for use in the treatment of advanced prostatic carcinoma (p. 712.3). An estramustine phosphate dose of about 14 mg/kg daily in divided doses is used. The usual initial dose is 560 to 840 mg daily, which may be adjusted to between 140 mg and 1.4 g daily according to the response and gastrointestinal tolerance. It should be given not less than 1 hour before or 2 hours after meals.

References.

1. Bergenheim AT, Henriksson R. Pharmacokinetics and pharmacodynamics of estramustine phosphate. *Clin Pharmacokinet* 1998; 34: 163–72.
2. Sangrajrang S, *et al.* Estramustine resistance. *Gen Pharmacol* 1999; 33: 107–13.
3. Kreis W, Budman D. Daily oral estramustine and intermittent intravenous docetaxel (Taxotere) as chemotherapeutic treatment for metastatic, hormone-refractory prostate cancer. *Semin Oncol* 1999; 26 (suppl 17): 34–8.
4. Kitamura T. Necessity of re-evaluation of estramustine phosphate sodium (EMP) as a treatment option for first-line monotherapy in advanced prostate cancer. *Int J Urol* 2001; 8: 33–6.
5. Hamilton A, Muggia F. Estramustine potentiates taxane in prostate and refractory breast cancers. *Oncology (Huntingt)* 2001; 15 (suppl 7): 40–3.
6. Kitamura T, *et al.* EMP combination chemotherapy and low-dose monotherapy in advanced prostate cancer. *Expert Rev Anticancer Ther* 2002; 2: 59–71.
7. Petrylak DP, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; 351: 1513–20.
8. Fizazi K, *et al.* Meta-analysis of Estramustine in Prostate Cancer (MECaP) Trialists' Collaborative Group. Addition of estramustine to chemotherapy and survival of patients with castration-refractory prostate cancer: a meta-analysis of individual patient data. *Lancet Oncol* 2007; 8: 994–1000.

Adverse Effects, Treatment, and Precautions

Oestrogenic adverse effects with estramustine are fairly common, and may include gynaecomastia, fluid retention, and cardiovascular effects. Gastrointestinal disturbances, hepatic dysfunction, loss of libido, hypersensitivity reactions, and occasionally leucopenia and thrombocytopenia may occur. Estramustine is contra-indicated in patients with peptic ulceration and severe hepatic or cardiovascular disease. Diabetes mellitus may be exacerbated, and the drug should be given with care to patients with disorders such as congestive heart failure, epilepsy, hypertension, migraine, and renal impairment which may be adversely affected by additional fluid retention. Care is also required in patients with conditions predisposing to hypercalcaemia, and serum calcium should be monitored in hypercalcaemic patients.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies estramustine 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 28/09/11)

Interactions

Estramustine sodium phosphate should not be given with milk products or products high in calcium, which may interfere with its absorption. Hypersensitivity reactions including angioedema have occurred rarely in patients given estramustine who were also receiving an ACE inhibitor.

Pharmacokinetics

Up to 75% of a dose of estramustine sodium phosphate is absorbed from the gastrointestinal tract and rapidly dephosphorylated. Estramustine is found in the body mainly as its oxidised isomer estromustine; both forms accumulate in the prostate. Some hydrolysis of the carbamate linkage occurs in the liver, releasing estradiol, estrone, and the normustine group. Estramustine and estromustine have plasma half-lives of 10 to 20 hours, and are excreted with their metabolites mainly in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Estracyt; Estranovag; Suloprost; Tratina†; *Austria*: Estracyt; *Belg.*: Estracyt; *Canad.*: Emcyt; *Chile*: Estracyt; *China*: Estracyt (艾去适); *Cz.*: Estracyt; *Denm.*: Estracyt; *Fin.*: Estracyt; *Fr.*: Estracyt; *Ger.*: cellmustin; Estracyt; Medactin†; Multosin; *Gr.*: Estracyt; *Hong Kong*: Estracyt; *Hung.*: Estracyt; *India*: Estramin; X-Trant; *Irl.*: Estracyt†; *Israel*: Estracyt; *Ital.*: Estracyt; *Jpn*: Estracyt; *Malaysia*: Estracyt; *Mex.*: Emcyt; *Neth.*: Estracyt; *Norw.*: Estracyt†; *Pol.*: Estracyt; *Port.*: Estracyt; *Rus.*: Estracyt (Эстрацит); *S.Afr.*: Estracyt; *Singapore*: Estracyt; *Spain*: Estracyt; *Swed.*: Estracyt; *Switz.*: Estracyt; *Turk.*: Estracyt; *UK*: Estracyt; *Ukr.*: Estracyt (Эстрацит); *USA*: Emcyt; *Venez.*: Estracyt.

Pharmacopoeial Preparations

BP 2014: Estramustine Phosphate Capsules.

Etanidazole *(USAN, rINN)*

Etanidazol; Étanidazole; Etanidazolum; NSC-301467; SR-2508; Этанидазол.

N-(2-Hydroxyethyl)-2-nitroimidazole-1-acetamide.

$C_7H_{10}N_4O_4$=214.2

CAS — 22668-01-5.

UNII — 30DKA3Q1HL

Profile

Etanidazole is a radiosensitiser, structurally related to metronidazole, that is under investigation as an adjunct to radiotherapy in the treatment of cancer. Peripheral neuropathy may be dose-limiting.

References.

1. Lee DJ, *et al.* Results of an RTOG phase III trial (RTOG 85-27) comparing radiotherapy plus etanidazole with radiotherapy alone for locally advanced head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1995; 32: 567–76.
2. Eschwege F, *et al.* Results of a European randomized trial of etanidazole combined with radiotherapy in head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1997; 39: 275–81.
3. Marcus KJ, *et al.* A phase I trial of etanidazole and hyperfractionated radiotherapy in children with diffuse brainstem glioma. *Int J Radiat Oncol Biol Phys* 2003; 55: 1182–5.
4. Drzymala RE, *et al.* Radiation Therapy Oncology Group. A phase I-B trial of the radiosensitizer: etanidazole (SR-2508) with radiosurgery for the treatment of recurrent previously irradiated primary brain tumors or brain metastases (RTOG Study 95-02). *Radiother Oncol* 2008; 87: 89–92.

Etoposide *(BAN, USAN, rINN)*

EPEG; Etoposid; Étoposide; Etoposidi; Etoposido; Etopósido; Etoposidum; Etopozid; Etopozidas; Etopozyd; NSC-141540; VP-16; VP-16-213; Этопозид.

4′-Demethylepipodophyllotoxin 9-[4,6-*O*-(*R*)-ethylidene-β-D-glucopyranoside]; (5*S*,5a*R*,8a*S*,9*R*)-9-(4,6-*O*-Ethylidene-β-D-glucopyranosyloxy)-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-isobenzofuro[5,6-*f*][1,3]benzodioxol-6(5a*H*)-one.

$C_{29}H_{32}O_{13}$=588.6

CAS — 33419-42-0.

ATC — L01CB01.

ATC Vet — QL01CB01.

UNII — 6PLQ3CP4P3.

NOTE. The trivial name epipodophyllotoxin has occasionally been used incorrectly for etoposide.

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

Ph. Eur. 8: (Etoposide). A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers.

USP 36: (Etoposide). A fine, white to off-white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol, in chloroform, in dichloromethane, and in ethyl acetate; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Etoposide Phosphate *(USAN)*

BMY-40481; Etopósido, fosfato de.

[5*R*-[5α,5aβ,8aα,9β(*R**)]]-5-[3,5-Dimethoxy-4-(phosphonooxy)phenyl]-9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydrofuro-[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one; 4′-Demethylepipodophyllotoxin 9-(4,6-*O*-ethylidene-β-D-glucopyranoside) 4′-(dihydrogen phosphate).

$C_{29}H_{33}O_{16}P$=668.5

CAS — 117091-64-2.

ATC — L01CB01.

ATC Vet — QL01CB01.

UNII — 528XYJ8L1N.

Incompatibility. For reference to precipitation when mannitol or potassium chloride was added to mixtures of etoposide and cisplatin in sodium chloride injection see Cisplatin, p. 766.1.

For incompatibility of etoposide formulations with various plastics see Administration, p. 791.1.

Stability. UK licensed product information states that etoposide (diluted to a concentration of 200 or 400 micrograms/mL) has been shown to be physically and chemically stable for 24 hours at 15 degrees to 25 degrees. For microbiological reasons, the diluted solution should be used immediately; if not immediately used, the solution should not be stored longer than 12 hours at 15 degrees to 25 degrees, unless it has been diluted under aseptic conditions.

US licensed product information states that etoposide, diluted to a concentration of 200 or 400 micrograms/mL, is stable for 96 and 24 hours, respectively, at room temperature (25 degrees) under normal fluorescent light in either glass or plastic containers.

Etoposide phosphate, after reconstitution and further dilution, can be stored under refrigeration (at 2 degrees to 8 degrees) or at room temperature (20 degrees to 25 degrees) for 24 hours.

Uses and Administration

Etoposide is a semisynthetic derivative of podophyllotoxin with antineoplastic properties; it interferes with the function of topoisomerase II thus inhibiting DNA synthesis, and is most active against cells in the late S and G_2 phases of the cell cycle.

It is used, usually with other antineoplastics, in the treatment of tumours of the testis, small cell cancer of the lung, and in acute leukaemias. It has also been tried in other solid tumours including those of the brain, gastrointestinal tract, ovary, and thymus, and some childhood neoplasms; in lymphomas, and in the treatment of Kaposi's sarcoma associated with AIDS. For further discussion, see the cross-references indicated under Malignant Neoplasms, p. 791.2.

Etoposide may be given orally or intravenously. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Etoposide is given by slow intravenous infusion over at least 30 minutes, as a solution in sodium chloride 0.9% or glucose 5% injection. In general, the concentration of the infusion should be between 200 to 400 micrograms/mL, although recommendations vary depending on the preparation; precipitation may occur at higher concentrations. Etoposide phosphate, a prodrug, has improved solubility in water. 113.6 mg of etoposide phosphate is equivalent to 100 mg of etoposide. Intravenous doses are calculated in terms of etoposide, and are identical to those of the base, but it may be given in concentrations up to the

equivalent of etoposide 20 mg/mL. Etoposide phosphate solutions may be infused over 5 minutes to 3.5 hours.

Regimens vary; the usual *intravenous* dose of etoposide ranges from 50 to 120 mg/m² daily for 5 days. Somewhat lower doses have been suggested in lung cancer. Alternatively, 100 mg/m² has been given on alternate days to a total of 300 mg/m². The usual *oral* dose of etoposide is 100 to 240 mg/m² daily for 5 consecutive days. Courses may be repeated after 3 to 4 weeks. Doses should be reduced in renal impairment (see below).

Administration. Although precipitation of etoposide may occur at high infusion concentrations (see Uses and Administration, p. 790.3), high doses of etoposide have been infused undiluted to avoid giving large volumes of fluid to the patient.[1-3] Etoposide was infused through a central line, and this method has been reported to be safe and effective;[2] pharmacokinetic studies suggested unaltered systemic bioavailability when compared with diluted infusions.[3] However, cracking of plastic syringes and infusion cassettes has been reported, possibly due to the polyethylene glycol component of the formulation. This appears particularly problematic when devices containing ABS plastic (a polymer produced from acrylonitrile, butadiene, and styrene) are used; alternative devices may be preferable.[1] Leaching of the plasticiser diethylhexyl phthalate (which is potentially toxic and carcinogenic) from PVC bags and tubing has been reported with etoposide, and it has been suggested that these should also not be used if possible when preparing and giving the drug.[4]

Etoposide has been injected into the ventricles of the brain in the treatment of patients with neoplastic meningitis.[5]

1. Schwinghammer TL, *et al.* Cracking of ABS plastic devices used to infuse undiluted etoposide injection. *Am J Hosp Pharm* 1988; 45: 1277.
2. Creger RJ, *et al.* Infusion of high doses of undiluted etoposide through central venous catheters during preparation for bone marrow transplantation. *Cancer Invest* 1990; 8: 13–16.
3. Ehninger G, *et al.* Unaltered pharmacokinetics after the administration of high-dose etoposide without prior dilution. *Cancer Chemother Pharmacol* 1991; 28: 214–16.
4. de Lemos ML, *et al.* Leaching of diethylhexyl phthalate from polyvinyl chloride materials into etoposide intravenous solutions. *J Oncol Pharm Pract* 2005; 11: 155–7.
5. Chamberlain MC, *et al.* Phase II trial of intracerebrospinal fluid etoposide in the treatment of neoplastic meningitis. *Cancer* 2006; 106: 2021–7.

Administration in the elderly. Increasing age was reported to correlate with higher etoposide concentrations during oral therapy; increasing age and higher etoposide concentrations also correlated with lower white blood cell and absolute neutrophil counts.[1] A review noted that, compared with intravenous etoposide, there is more variability in the pharmacokinetics and toxicity of oral etoposide, and the oral route may appear less effective and more toxic as a result. In elderly patients taking etoposide, a small dose reduction and careful monitoring has thus been advised, even in those with normal renal and hepatic function.[2]

1. Miller AA, *et al.* Pharmacology of 21-day oral etoposide given in combination with i.v. cisplatin in patients with extensive-stage small cell lung cancer: a cancer and leukemia group B study (CALGB 9062). *Clin Cancer Res* 1997; 3: 719–25.
2. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in renal impairment. Some licensed product information for etoposide or etoposide phosphate recommends that patients with a creatinine clearance of between 15 and 50 mL/minute be given 75% of the recommended dose. No recommendations are given for those patients having a creatinine clearance of below 15 mL/minute, although one product (*Vepesid; BMS, USA*) suggests that further dose reduction in these patients be considered.

Histiocytic syndromes. Systemic chemotherapy is often tried in patients with extensive Langerhans-cell histiocytosis (p. 692.1), although its value is uncertain. Etoposide is one of the drugs widely used for this purpose.

Hypereosinophilic syndrome. Etoposide has been reported to produce clinical responses in patients with the hypereosinophilic syndrome.[1]

1. Bourrat E, *et al.* Etoposide for treating the hypereosinophilic syndrome. *Ann Intern Med* 1994; 121: 899–900.

Influenza. A patient was diagnosed with pandemic (H1N1) 2009 influenza infection (p. 960.2). During the course of this, he developed secondary haemophagocytic lymphohistiocytosis, and was treated with etoposide and betamethasone. He had a prompt clinical response within one week. It has been hypothesised that cytotoxic therapy might be beneficial for severe influenza infection, and the authors suggested that further studies in this area are needed.[1]

1. Henter J-I, *et al.* Cytotoxic therapy for severe swine flu A/H1N1. *Lancet* 2010; 376: 2116.

Malignant neoplasms. Etoposide has been used for a variety of solid tumours: in particular it is part of curative regimens used in the treatment of testicular cancer and germ-cell tumours of the ovary (see p. 715.1 and p. 711.2), and is used with cisplatin and other drugs in the treatment of lung cancer (p. 710.2). Other solid neoplasms in which it is sometimes employed include those of the brain (p. 701.2), stomach (p. 706.1), and thymus (p. 715.3), as well as in neuroblastoma (p. 716.2), Wilms' tumour (p. 709.1), retinoblastoma (p. 717.2), and rhabdomyosarcoma (p. 718.2); it has also formed part of systemic regimens for bone sarcomas (p. 717.3), disseminated Kaposi's sarcoma (see p. 718.1), and gestational trophoblastic tumours (p. 691.2). Etoposide is used in regimens for Hodgkin's disease (see p. 696.1); it is also sometimes used in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p. 696.3), and may produce short-term responses in mycosis fungoides (p. 698.3). It is also used in Burkitt's lymphoma (p. 697.3). Etoposide may have benefits when added to induction protocols for acute myeloid leukaemia (p. 693.1), and when used as part of intensification therapy in acute lymphoblastic leukaemia (p. 692.3). It has formed part of salvage regimens in multiple myeloma (p. 699.2).

Vasculitic syndromes. For mention of the use of etoposide to induce remission in patients with Wegener's granulomatosis resistant to standard therapy with cyclophosphamide and corticosteroids, see p. 1615.2.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The dose-limiting toxicity of etoposide is myelosuppression, mainly seen as leucopenia, but also thrombocytopenia, and sometimes anaemia. The nadir of the granulocyte count usually occurs 7 to 14 days after a dose, with recovery by about 21 days. Nausea and vomiting are common; there may also be anorexia, diarrhoea, and mucositis. Gastrointestinal toxicity may be more common after oral dosage. Reversible alopecia occurs in about two-thirds of all patients. Hypersensitivity or anaphylactoid reactions can occur, characterised by flushing, chills, fever, tachycardia, bronchospasm, dyspnoea, and hypotension. Apnoea and fatal reactions associated with bronchospasm have been reported. Peripheral or central neuropathies, including transient cortical blindness, have been reported rarely, as have weakness, fatigue, somnolence, aftertaste, fever, rashes, urticaria, skin pigmentation, pruritus, and dysphagia. Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely. Tumour lysis syndrome, sometimes fatal, has been reported after use of etoposide with other chemotherapeutic drugs. Disturbances of liver function have been reported, mainly at high doses. There have been occasional reports of cardiotoxicity. Local irritation and thrombophlebitis may occur at the site of injection. Care should be taken to avoid extravasation although tissue damage (possibly associated with the vehicle) is rare.

Rapid intravenous doses may cause hypotension; etoposide should be given by infusion over at least 30 minutes. Etoposide should not be given to patients with severe hepatic impairment nor by the intracavitary route.

Some adverse effects associated with intravenous etoposide may be due to the formulation of the vehicle.

There is evidence that etoposide may be associated with the development of secondary leukaemias—see Carcinogenicity, p. 726.2.

Breast feeding. Some licensed product information states that it is unknown whether etoposide is excreted into breast milk. However, in breast milk samples from a woman given consolidation therapy, including etoposide,[1] for acute promyelocytic leukaemia, etoposide concentrations were maximal just after a dose, but decreased rapidly to undetectable levels within 24 hours on each of three days. She started to breast feed her baby 3 weeks after the completion of therapy, and no abnormalities were seen in the infant up to 16 months of age. It has been suggested[2] that breast feeding be withheld for 24 to 36 hours after a dose.

1. Azuno Y, *et al.* Mitoxantrone and etoposide in breast milk. *Am J Hematol* 1995; 48: 131–2.
2. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Effects on the gastrointestinal tract. Pneumatosis intestinalis (the presence of gas within the bowel wall), a rare condition, has been reported after intravenous[1] and oral[2] etoposide. It is supposed that myelosuppressive drugs might interfere with the mucosal integrity of the intestinal tract, and that the intestinal mucosa might be highly sensitive to etoposide.

1. Hashimoto S, *et al.* Pneumatosis cystoides intestinalis after chemotherapy for hematological malignancies: report of 4 cases. *Intern Med* 1995; 34: 212–15.
2. Shih I-L, *et al.* Pneumatosis coli after etoposide chemotherapy for breast cancer. *J Clin Oncol* 2007; 25: 1623–5.

Effects on the nervous system. A report of an acute dystonic reaction in a child given etoposide as part of a combined maintenance regimen for acute lymphoblastic leukaemia;[1] the patient had been receiving the same regimen uneventfully for over a year but symptoms (which responded to diphenhydramine) recurred on rechallenge with etoposide.

1. Ascher DP, Delaney RA. Acute dystonia from etoposide. *Drug Intell Clin Pharm* 1988; 22: 41–2.

Handling and disposal. *Urine and faeces* produced for up to 4 and 7 days respectively after a dose of etoposide should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Hypersensitivity. Hypersensitivity reactions to intravenous etoposide are characterised by one or more of: hypotension, bronchospasm, flushing, exanthema, dyspnoea, fever, chills, tachycardia, tightness in the chest, cyanosis, and hypertension. Although originally thought rare, some investigators[1] have reported an incidence of up to about 50%, particularly in younger patients. The mechanism is uncertain, but a literature review[1] supported the hypothesis that it might not be antibody-mediated, since reducing the rate of infusion can prevent reactions, as can reducing etoposide concentration in the infusion solution. However, an immunogenic mechanism cannot be excluded as hypersensitivity appears to have been reported less frequently with the oral formulation, which unlike the infusion does not contain polysorbate 80. In addition, there are reports[2-4] of successful use of etoposide phosphate formulations (which do not contain polysorbate 80) after hypersensitivity reactions to etoposide, suggesting that the solvent may be responsible. Successful desensitisation in a patient hypersensitive to etoposide has been reported.[5]

1. Hoetelmans RMW, *et al.* Hypersensitivity reactions to etoposide. *Ann Pharmacother* 1996; 30: 367–71.
2. Bernstein BJ, Troner MB. Successful rechallenge with etoposide phosphate after an acute hypersensitivity reaction to etoposide. *Pharmacotherapy* 1999; 19: 989–91.
3. Siderov J, *et al.* Safe administration of etoposide phosphate after hypersensitivity reaction to intravenous etoposide. *Br J Cancer* 2002; 86: 12–13.
4. Collier K, *et al.* Successful treatment with etoposide phosphate in patients with previous etoposide hypersensitivity. *J Oncol Pharm Pract* 2008; 14: 51–5.
5. Alvarez Cardona A, *et al.* Desensibilización para etopósido: comunicación de un caso. *Rev Alerg Mex* 2010; 57: 33–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etoposide 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 26/08/11)

Pregnancy. A 22-year-old woman, who was diagnosed with acute myelogenous leukaemia at 20 weeks of gestation, was treated with combination chemotherapy including cytarabine and daunorubicin at 22 weeks, but the response was unsatisfactory, and the regimen was altered to cytarabine, mitoxantrone, and etoposide at 31 weeks. After the second course of chemotherapy was completed, an intermittent sinusoidal fetal heart rate pattern was detected, along with intra-uterine fetal growth retardation. Complete remission was achieved at 35 weeks and a caesarean section was performed a week later due to fetal distress. The neonate was underweight and had pancytopenia requiring blood transfusion and antibacterial therapy; he was discharged at 2 months of age in good health. The authors concluded that the fetal sinusoidal heart rate pattern may have been induced by tissue hypoxia due to severe anaemia, and that the leucopenia and thrombocytopenia resulted from bone marrow suppression caused by the transplacental effects of maternal chemotherapy; they considered that mitoxantrone and etoposide might be responsible for the neonatal pancytopenia.[1]

For a report of hair loss in an infant, attributed to etoposide given to the mother before delivery, see Pregnancy, under Cisplatin, p. 768.2.

1. Hsu K-F, *et al.* Sinusoidal fetal heart rate pattern during chemotherapy in a pregnant woman with acute myelogenous leukemia. *J Formos Med Assoc* 1995; 94: 562–5.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Phenylbutazone, salicylic acid, and sodium salicylate can affect the protein binding of etoposide.

Caution is advised when etoposide phosphate is given with drugs such as levamisole hydrochloride that are known to inhibit phosphatase activities.

Antineoplastics. Giving etoposide 2 days after a dose of *cisplatin* was associated with a marked decrease in etoposide clearance and more toxicity, compared with the same dose given 21 days after a dose of cisplatin, in a study involving 17 children.[1] There was no evidence of a persistent decrease in etoposide clearance associated with the cumulative dose of cisplatin, however. In a randomised, crossover study,[2] cisplatin or *carboplatin* were given alternately during 2 courses of etoposide. Although increases in the area under the concentration-time curve of etoposide were seen in the second course, effects were modest and, given the pharmacokinetic variability seen with etoposide, the authors considered any clinical impact to be small.

1. Relling MV, *et al.* Etoposide pharmacokinetics and pharmacodynamics after acute and chronic exposure to cisplatin. *Clin Pharmacol Ther* 1994; 56: 503–11.
2. Thomas HD, *et al.* Randomized cross-over clinical trial to study potential pharmacokinetic interactions between cisplatin or carboplatin and etoposide. *Br J Clin Pharmacol* 2002; 53: 83–91.

Ciclosporin. High-dose ciclosporin therapy was found to increase the exposure to etoposide by 80%, and to reduce etoposide clearance by 38%. Leucopenia was increased. Etoposide doses should be halved when the drug is given with high-dose ciclosporin.[1] In a study[2] of children who received etoposide and mitoxantrone for acute myeloid leukaemia, the addition of ciclosporin with a 40% reduction in the doses of the antineoplastics still resulted in a 71% reduction in the clearance of etoposide, and a 42% reduction for mitoxantrone. However, there was wide interpatient variability, and the rates of stomatitis and infection were similar between the groups, with or without ciclosporin.

1. Lum BL, *et al.* Alteration of etoposide pharmacokinetics and pharmacodynamics by cyclosporine in a phase I trial to modulate drug resistance. *J Clin Oncol* 1992; 10: 1635–42.
2. Lacayo NJ, *et al.* Pharmacokinetic interactions of cyclosporine with etoposide and mitoxantrone in children with acute myeloid leukemia. *Leukemia* 2002; 16: 920–7.

Grapefruit juice. In a randomised crossover study[1] of 6 patients, grapefruit juice appeared to reduce the oral bioavailability of etoposide. Initially the authors had expected the opposite since etoposide is demethylated by cytochrome P450 isoenzyme CYP3A4. Although no definite conclusions could be made due to the small number of patients studied, a possible mechanism might have been alteration of P-glycoprotein mediated transport.

1. Reif S, *et al.* Effect of grapefruit juice intake on etoposide bioavailability. *Eur J Clin Pharmacol* 2002; 58: 491–4.

Pharmacokinetics

Absorption after oral doses is variable, but on average about 50% of the dose of etoposide is absorbed. The pharmacokinetics of etoposide are subject to considerable interindividual variation. It is rapidly distributed, and concentrations in plasma fall in a biphasic manner, with a terminal half-life of 4 to 11 hours. Etoposide is about 94% bound to plasma protein. It is metabolised by the cytochrome P450 isoenzyme CYP3A4. Etoposide is excreted in urine and faeces as unchanged drug and metabolites: about 45% of a dose is reported to be excreted in urine over 72 hours. It crosses the blood-brain barrier poorly; concentrations in CSF are 1 to 10% of those in plasma. It is distributed into breast milk (see Breast Feeding, p. 791.2).

References.

1. Toffoli G, *et al.* Pharmacokinetic optimisation of treatment with oral etoposide. *Clin Pharmacokinet* 2004; 43: 441–66.
2. Schieveen PG, *et al.* Suivi thérapeutique pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique de l'étoposide administré par voie orale. *Therapie* 2010; 65: 207–12.

Metabolism. Studies *in vitro* suggested that metabolic activation of etoposide by oxidation into the *O*-quinone derivative might play an essential role in its activity against DNA.[1]

1. van Maanen JMS, *et al.* Metabolic activation of anti-tumour agent VP 16-213. *Hum Toxicol* 1986; 5: 136.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Citodox†; Etocris; Euvaxon; Neoplaxol; Percas†; Vepesid; VP-Gen; ***Austral.***: Etopophos; Vepesid; ***Austria***: Etopofos; Vepesid; ***Belg.***: Celltop; Eposin; Vepesid; ***Braz.***: Eposido; Etomorase; Etosin†; Eunades; Nexvep; Posidon; Tevaetopo; Vepesid; ***Canad.***: Vepesid; ***Chile***: Epsidox; ***China***: Bo Rui (泊瑞); Etopophos (凡毕复); Lastet (拉司太特); Vepesid (凡毕士); Wei Ke (威克); ***Cz.***: Lastet†; Vepesid†; ***Denm.***: Eposid; Etopofos†; Vepesid; ***Fin.***: Eposin; Etopofos†; Vepesid; ***Fr.***: Celltop; Etopophos; Vepeside†; ***Ger.***: Eto-cell; Eto-Gry; Etomedac Etopophos; Lastet; Neoposid†; Riboposid; Vepesid; ***Gr.***: Celltop; Etobion; Etopofos; Vepesid; ***Hong Kong***: Sintopozid; Vepesid†; ***Hung.***: Lastet†; Sintopozid; Vepesid†; ***India***: Acitop; Beposid; Bioposide; Eside; Ethopul; Etolon; Etosid; Fytop; Fytosid; Lastet; Oncosid; Posid; ***Indon.***: Etopul; Posyd; ***Irl.***: Etopophos; Vepesid; ***Ital.***: Lastet†; Vepesid; ***Jpn***: Lastet; ***Malaysia***: Eposin; Lastet; ***Mex.***: Cryosid; Etoncot†; Etopost†; Kenazol†; Tosuben; Vepesid; VP-Tec; ***Neth.***: Eposin; Etomedac; Toposin; Vepesid; ***Norw.***: Eposin; Etopofos†; Vepesid; ***NZ***: Etopophos; Vepesid; ***Philipp.***: Etopoxan†; Etopul; Fytosid; Lastet; Posid; Topresid; Vepesid†; ***Pol.***: Lastet†; Sintopozid†; Vepesid; ***Port.***: Eposin; Vepesid†; ***Rus.***: Cytoposid (Цитопозид); Fytosid (Фитозид); Lastet (Ластет); Vepesid (Вепезид); ***S.Afr.***: Eposin; Etopophos†; Vepesid; ***Singapore***: Ebeposide; Lastet; Vepesid; ***Spain***: Vepesid; ***Swed.***: Eposin; Etopofos; Vepesid; ***Switz.***: Etopophos; Vepesid; ***Thai.***: Eposin; Etopos; Fytosid; Lastet; Topo; Vepesid†; ***Turk.***: Eposin; Etosid; Lastet; Vepesid; ***UK***: Eposin; Etopophos; Vepesid; ***USA***: Etopophos; Toposar; Vepesid; ***Venez.***: Etonolver; Etosid; Fytosid.

Pharmacopoeial Preparations

BP 2014: Etoposide Capsules; Etoposide Infusion;
USP 36: Etoposide Capsules; Etoposide Injection.

Exemestane *(BAN, USAN, rINN)* ⊗

Eksemestaani; Eksemestan; Exemestan; Exémestane; Exemestano; Exemestanum; FCE-24304; Экземестан.

6-Methyleneandrosta-1,4-diene-3,17-dione.

$C_{20}H_{24}O_2$=296.4

CAS — 107868-30-4.

ATC — L02BG06.

ATC Vet — QL02BG06.

UNII — NY22HMQ4BX.

Uses and Administration

Exemestane is a selective inhibitor of the aromatase (oestrogen synthetase) system responsible for the conversion of androgens to oestrogens in peripheral tissues, but unlike anastrozole (p. 742.2) or letrozole (p. 817.2) it has a steroidal structure. It is used in the treatment of advanced breast cancer (p. 702.1), in postmenopausal women who are no longer responsive to anti-oestrogen therapy. It is also used for adjuvant treatment of postmenopausal women with oestrogen-receptor positive early breast cancer, after 2 to 3 years of initial adjuvant tamoxifen treatment; a total of 5 years of adjuvant hormonal therapy should be given. The recommended oral dose is 25 mg once daily, preferably after a meal.

In patients receiving potent inducers of the cytochrome P450 isoenzyme CYP3A4 (such as rifampicin or phenytoin), the recommended oral dose of exemestane is 50 mg once daily, after a meal.

References.

1. Coombes RC, *et al.* A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; 350: 1081–92. Corrections. *ibid.*; 351: 2461 and *ibid.* 2006; 355: 1746.
2. Bertelli G, *et al.* Sequential treatment with exemestane and non-steroidal aromatase inhibitors in advanced breast cancer. *Oncology* 2006; 69: 471–7.
3. Bundred N. The evolving role of exemestane in the management of breast cancer. *Br J Hosp Med* 2006; 67: 427–30.
4. Coombes RC, *et al.* Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; 369: 559–70. Correction. *ibid.*; 906.
5. Paridaens RJ, *et al.* Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol* 2008; 26: 4883–90.
6. Deeks ED, Scott LJ. Exemestane: a review of its use in postmenopausal women with breast cancer. *Drugs* 2009; 69: 889–918.
7. Nabholtz JM, *et al.* Comparative review of anastrozole, letrozole and exemestane in the management of early breast cancer. *Expert Opin Pharmacother* 2009; 10: 1435–47.
8. Glück S. Exemestane as first-line therapy in postmenopausal women with recurrent or metastatic breast cancer. *Am J Clin Oncol* 2010; 33: 314–19.
9. Bertelli G, Gangadbara S. Exemestane in postmenopausal women with early or advanced breast cancer: a review. *Expert Opin Pharmacother* 2010; 11: 1933–42.
10. Goss PE, *et al.* NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011; 364: 2381–91.

Adverse Effects and Precautions

The adverse effects of exemestane are similar to those seen with other aromatase inhibitors such as anastrozole (p. 742.3), and similar precautions should be taken. Fatigue and increased sweating are common with exemestane. Visual disturbances have been reported. Thrombocytopenia and leucopenia have been reported rarely. For the suggestion that exemestane may have more pro-atherogenic effects on blood lipids than anastrozole or letrozole, see below.

Breast feeding. Studies show that exemestane is distributed into the milk of *rats*. Licensed product information states that it is unknown whether exemestane is excreted into human milk; in the UK use during breast feeding is contra-indicated while in the USA a decision may be made based on clinical judgement. It has been suggested[1] that breast feeding be stopped if using multiple doses of exemestane, and to withhold breast feeding for at least 5 days after the last dose.

1. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Effects on blood lipids. A comparison of the adverse effects of letrozole, anastrozole, and exemestane in postmenopausal women indicated[1] that although all had similar effects on markers of bone turnover, exemestane was associated with a markedly greater decrease in high-density lipoprotein (HDL) cholesterol. This resulted in an increase in the atherogenic ratio of low-density (LDL) to HDL-cholesterol. Since some studies have suggested that low HDL-cholesterol may be a more important risk factor for cardiovascular disease in women than men it was suggested that further study was needed to see if this difference had clinical significance.

1. McCloskey EV, *et al.* Effects of third generation aromatase inhibitors on bone health and other safety parameters: results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. *Eur J Cancer* 2007; 43: 2523–31.

Effects on the musculoskeletal system. Exemestane therapy has been found to decrease bone mineral density (BMD) in postmenopausal women with early breast cancer.[1,2] In one study, the decrease in BMD was seen within 6 months of switching therapy from tamoxifen, and was significant at the lumbar spine and hip.[2] In a Scandinavian study, BMD loss with exemestane compared with placebo was modest from the femoral neck, and not significant at the lumbar spine;[1] however, it was noted that the changes in the placebo group were greater than expected, possibly due to the lack of calcium and vitamin D supplementation, and that there is a high incidence of hip fracture in Scandinavia. Patients starting exemestane therapy should be assessed for baseline BMD;[1] while those with normal BMD are considered to not need further assessment beyond lifestyle advice, those with osteopenia should have their BMD monitored, and therapeutic interventions made as appropriate.[2]

See also Effects on the Musculoskeletal System, under Anastrozole, p. 743.1.

1. Lønning PE, *et al.* Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol* 2005; 23: 5126–37.
2. Coleman RE, *et al.* Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007; 8: 119–27.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies exemestane 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 05/09/11)

Interactions

The metabolism of exemestane is mediated by the cytochrome P450 isoenzyme CYP3A4. Rifampicin, a potent inducer of CYP isoenzymes, can decrease plasma concentrations of exemestane. Use with other drugs that induce this isoenzyme may reduce the efficacy of exemestane; dose adjustments are recommended in these patients (see Uses and Administration, above). Exemestane should also be used cautiously with drugs that are substrates for CYP3A4 and that have a narrow therapeutic index. Significant effects on exemestane clearance by cytochrome P450 isoenzyme inhibitors are considered unlikely. Exemestane should not be given with oestrogen-containing drugs as these would negate its pharmacological action

Pharmacokinetics

Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, and is 90% bound to plasma proteins. It is metabolised via oxidation by the cytochrome P450 isoenzyme CYP3A4, and via reduction by aldoketoreductase. Metabolites are excreted in the urine and faeces, and less than 1% of a dose is excreted unchanged in the urine. Exemestane has a terminal elimination half-life of about 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aromasin; Noxetol; *Austral.*: Aromasin; *Austria*: Aromasin; *Belg.*: Aromasin; *Braz.*: Aromasin; *Canad.*: Aromasin; *Chile*: Aromasin; *China*: Ao Qi (澳奇); Aromasin (阿诺新); Ke Yi (可怡); Ru Su Mei (如苏美); Su Lai (速莱); Yi Si Tan (依斯坦); You Ke Yi (优可依); *Cz.*: Aromasin; Astexana; Exestea; Funamel; Greca; Mexinat; Netamise; Sarivanil; *Denm.*: Aremedan; Aromasin; Exemasin; Glandex; Memelin†; Nosteron†; *Fin.*: Aromasin; Xemestan; *Fr.*: Aromasine; *Ger.*: Aromasin; Exemed; Exemedac; Exestan; *Gr.*: Aromasin; *Hong Kong*: Aromasin; *Hung.*: Aromasin; Exemin; Mexezon; *Indon.*: Aromasin; *Irl.*: Aromasin; *Israel*: Aromasin; *Ital.*: Aromasin; Exegen; Plextane; *Malaysia*: Aromasin; *Mex.*: Aromasin; *Neth.*: Aromasin; Exanidon; Exemedica; Exeregio; Memelin†; Nateran; *Norw.*: Aromasin; *NZ*: Aromasin; Exaccord; Mestane; *Philipp.*: Aromasin; *Pol.*: Aromasin; Nosteron; *Port.*: Aromasin; *Rus.*: Aromasin (Аромазин); Aromeston (Ароместон); *S.Afr.*: Aromasin; *Singapore*: Aromasin; *Spain*: Aromasil; Gepex; *Swed.*: Aromasin; *Switz.*: Aromasin; *Thai.*: Aromasin; *Turk.*: Aromasin; *UK*: Aromasin; *Ukr.*: Aromasin (Аромазин); *USA*: Aromasin; *Venez.*: Aromasin.

Exisulind *(rINN)*

Exisulindum; FGN-1; Sulfona de sulindac; Sulindac Sulfone; Эксисулинд.

5-Fluoro-2-methyl-1-[(*Z*)-*p*-(methylsulfonyl)benzylidene] indene-3-acetic acid.

$C_{20}H_{17}FO_4S$=372.4

CAS — 59973-80-7.

UNII — K619IIG2R9.

NOTE. The names Aptosyn and Prevatec have been used as trade marks for exisulind.

Profile

Exisulind is a sulfone metabolite of sulindac (p. 134.2) that is reported to induce apoptosis in cancerous and precancerous cells. It has been studied for the treatment of familial adenomatous polyposis, with variable results. It is also being investigated for the prevention and treatment of malignant neoplasms, including those of the breast, prostate, and lung.

References.

1. Goluboff ET. Exisulind, a selective apoptotic antineoplastic drug. *Expert Opin Invest Drugs* 2001; **10**: 1875–82.
2. Webster WS, Leibovich BC. Exisulind in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2005; **5**: 957–62.
3. Arber N, *et al.* Sporadic adenomatous polyp regression with exisulind is effective but toxic: a randomised, double blind, placebo controlled, dose-response study. *Gut* 2006; **55**: 367–73.

Ezatiostat Hydrochloride *(USAN, rINNM)*

Ezatiostat, Chlorhydrate d'; Ezatiostati Hydrochloridum; Hidrocloruro de ezatiostat; TER-199; TLK-199; Эзатиостата Гидрохлорид.

Ethyl (2*R*)-[(4*S*)-4-amino-5-ethoxy-5-oxopentanoyl]-*S*-benzyl-L-cysteinyl-2-phenylglycinate hydrochloride.

$C_{27}H_{35}N_3O_6S$,HCl=566.1

CAS — 286942-97-0.

UNII — D59N834676.

NOTE. The name Telintra has been used as a trade mark for ezatiostat.

Profile

Ezatiostat hydrochloride is an inhibitor of glutathione S-transferase P1-1. It is under investigation in the treatment of myelodysplastic syndrome and has been granted orphan drug status in the USA. Ezatiostat has been given orally and intravenously. Adverse effects following oral use have included nausea, diarrhoea, vomiting; chills, back pain, and flushing were seen following intravenous use. Ezatiostat has also been investigated in the treatment of idiopathic chronic neutropenia.

References.

1. Quddus F, *et al.* Oral ezatiostat HCl (TLK199) and myelodysplastic syndrome: a case report of sustained hematologic response following an abbreviated exposure. *J Hematol Oncol* 2010; **3**: 16.
2. Raza A, *et al.* A phase 2 randomized multicenter study of 2 extended dosing schedules of oral ezatiostat in low to intermediate-1 risk myelodysplastic syndrome. *Cancer* 2012; **118**: 2138–47.
3. Lyons RM, *et al.* Oral ezatiostat HCl (Telintra, TLK199) and idiopathic chronic neutropenia (ICN): a case report of complete response of a patient with G-CSF resistant ICN following treatment with ezatiostat, a glutathione S-transferase P1-1 (GSTP1-1) inhibitor. *J Hematol Oncol* 2011; **4**: 43.

Fadrozole Hydrochloride *(USAN, rINNM)* ⊗

CGS-16949 (fadrozole); CGS-16949A; Fadrozol, hidrocloruro de; Fadrozole, Chlorhydrate de; Fadrozoli Hydrochloridum; Hidrocloruro de fadrozol; Фадрозола Гидрохлорид.

(±)-*p*-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitrile monohydrochloride.

$C_{14}H_{13}N_3$,HCl=259.7

CAS — 102676-47-1 (fadrozole); 102676-96-0 (fadrozole hydrochloride).

UNII — H0Q44H4ECQ.

Profile

Fadrozole hydrochloride is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p. 742.1). It has been used for the treatment of breast cancer.

References.

1. Buzdar AU, *et al.* Fadrozole HCl (CGS-16949A) versus megestrol acetate treatment of postmenopausal patients with metastatic breast carcinoma: results of two randomized double blind controlled multiinstitutional trials. *Cancer* 1996; **77**: 2503–13.
2. Miller AA, *et al.* Fadrozole hydrochloride in postmenopausal patients with metastatic breast carcinoma. *Cancer* 1996; **78**: 789–93.
3. Falkson CI, Falkson HC. A randomised study of CGS 16949A (fadrozole) versus tamoxifen in previously untreated postmenopausal patients with metastatic breast cancer. *Ann Oncol* 1996; **7**: 465–9.
4. Thurlimann B, *et al.* First-line fadrozole HCl (CGS 16949A) versus tamoxifen in postmenopausal women with advanced breast cancer: prospective randomised trial of the Swiss Group for Clinical Cancer Research SAKK 20/88. *Ann Oncol* 1996; **7**: 471–9.
5. Tominaga T, *et al.* Double-blind randomised trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. *Ann Oncol* 2003; **14**: 62–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Afema.

Farletuzumab *(USAN, rINN)*

Farletuzumabum; MORAb-003; Фарлетузумаб.

CAS — 896723-44-7.

UNII — 2O09BG0OWA.

Profile

Farletuzumab is a humanised monoclonal antibody that binds to and blocks the function of folate receptor alpha (FRA), a cell surface protein that is over-expressed in ovarian and other cancers. Farletuzumab is under investigation for the treatment of ovarian cancer.

References.

1. Spannuth WA, *et al.* Farletuzumab in epithelial ovarian carcinoma. *Expert Opin Biol Ther* 2010; **10**: 431–7.
2. Konner JA, *et al.* Farletuzumab, a humanized monoclonal antibody against folate receptor α, in epithelial ovarian cancer: a phase I study. *Clin Cancer Res* 2010; **16**: 5288–95.

Fenretinide *(USAN, rINN)*

Fenretinida; Fenrétinide; Fenretinidum; 4-HPR; 4-Hydroxyphenylretinamide; McN-R-1967; Фенретинид.

all-trans-4′-Hydroxyretinanilide.

$C_{26}H_{33}NO_2$=391.6

CAS — 65646-68-6.

UNII — 187EJ7QEXL.

Profile

Fenretinide is a retinoid derivative that is given orally and is being studied in the management of haematological malignancies such as lymphoma and solid malignancies such as brain and bone tumours, Ewing's sarcoma, and breast, prostate, ovarian, and cervical cancer. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Fenretinide has also been tried in oral lichen planus and leucoplakia. It is also under investigation as an adjunct to antipsychotic treatment in schizophrenia, for atrophy in age-related macular degeneration, and for insulin resistance in obese patients. It has been tried in the treatment of psoriasis, but was associated with unacceptable adverse effects such as night blindness and severe toxic erythema.

Fenretinide has been studied for the treatment of breast cancer and cutaneous malignancies but early results were disappointing and night blindness and mucocutaneous effects have been associated with this use.[1] Fenretinide has been investigated for the prevention of breast cancer (p. 703.2), but a large randomised study of secondary prevention failed to show any benefit.[2] A follow-up of the same study[3] found that patients receiving fenretinide had a lower incidence of ovarian carcinoma during the 5-year treatment period, but that this apparently protective effect disappeared after treatment was stopped. Combinations of tamoxifen and fenretinide, given intermittently (for treatment or prevention), have been reported to be well tolerated.[4-6] Its actions may be due to anti-angiogenic properties.[7]

1. Modiano MR, *et al.* Phase II study of fenretinide (*N*-[4-hydroxyphenyl] retinamide) in advanced breast cancer and melanoma. *Invest New Drugs* 1990; **8**: 317–19.
2. Veronesi U, *et al.* Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst* 1999; **91**: 1847–56.
3. De Palo G, *et al.* Effect of fenretinide on ovarian carcinoma occurrence. *Gynecol Oncol* 2002; **86**: 24–7.
4. Cobleigh MA, *et al.* Phase I/II trial of tamoxifen with or without fenretinide, an analog of vitamin A, in women with metastatic breast cancer. *J Clin Oncol* 1993; **11**: 474–7.
5. Conley B, *et al.* Pilot trial of the safety, tolerability, and retinoid levels of N-(4-hydroxyphenyl) retinamide in combination with tamoxifen in patients at high risk for developing invasive breast cancer. *J Clin Oncol* 2000; **18**: 275–83.
6. Guerrieri-Gonzaga A, *et al.* Preliminary results on safety and activity of a randomized, double-blind, 2 x 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in premenopausal women. *J Clin Oncol* 2006; **24**: 129–35.
7. Sogno I, *et al.* Anti-angiogenic properties of chemopreventive drugs: fenretinide as a prototype. *Recent Results Cancer Res* 2009; **181**: 71–6.

Floxuridine *(USAN, rINN)*

Floxuridina; Floxuridinum; 5-Fluorouracil Deoxyriboside; FUDR; NSC-27640; WR-138720; Флоксуридин.

2′-Deoxy-5-fluorouridine; 5-Fluoro-2′-deoxyuridine; 1-(2-Deoxy-β-D-ribofuranosyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione.

$C_9H_{11}FN_2O_5$=246.2

CAS — 50-91-9.

UNII — 039LU44I5M.

Pharmacopoeias. In *US.*

USP 36: (Floxuridine). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Floxuridine is an antineoplastic which acts as an antimetabolite, either by conversion to fluorouracil (after rapid injection), or, when given by slow intra-arterial infusion, partly via floxuridine monophosphate (F-dUMP), which produces greater inhibition of DNA synthesis.

Floxuridine is used in the palliative treatment of hepatic metastases of colorectal cancer (p. 706.3). It has been tried in some other solid neoplasms. Doses of 100 to 600 micrograms/kg daily are given by continuous hepatic arterial infusion, usually with the aid of an infusion pump, until toxicity occurs.

White cell and platelet counts should be carried out regularly during therapy and treatment should be stopped if the white cell count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p. 730.3), or if major adverse effects occur.

References.

1. Fordy C, *et al.* Hepatic arterial floxuridine as second-line treatment for systemic fluorouracil-resistant colorectal liver metastases. *Br J Cancer* 1998; **78**: 1058–60.
2. Kemeny N, *et al.* Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341**: 2039–48.
3. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2000; **18**: 243–54.
4. Fiorentini G, *et al.* Locoregional therapy for liver metastases from colorectal cancer: the possibilities of intraarterial chemotherapy, and new hepatic-directed modalities. *Hepatogastroenterology* 2001; **48**: 305–12.
5. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; **352**: 734–5.
6. Power DG, Kemeny NE. The role of floxuridine in metastatic liver disease. *Mol Cancer Ther* 2009; **8**: 1015–25.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p. 797.1. Adverse reactions after intra-arterial infusion often include local reactions, thromboembolic complications, and infection or bleeding at the catheter site, or blockage of the catheter. Erythema, stomatitis, and gastrointestinal disturbances are relatively common. There have also been signs of liver dysfunction.

Effects on the liver. Serious biliary toxicity has been reported in over half of all patients receiving hepatic arterial infusions of floxuridine, usually manifesting as sclerosing cholangitis or acalculous cholecystitis;[1] as a result some surgeons routinely remove the gallbladder at the time of infusion pump implantation.[2] Extrahepatic biliary stenosis with jaundice and cholestasis has also been described;[3] the authors suggest that this could lead to intrahepatic biliary damage from bile stasis and infection, recurrent cholangitis, and biliary sclerosis. Floxuridine infusions have also been associated with a case of fatal progressive cirrhosis of the liver in the absence of overt cholestasis.[4] Pseudoaneurysms of the hepatic artery, lead-

ing to serious retroperitoneal or gastrointestinal bleeding, have also been described.[3]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; ii: 440–4.
2. Anonymous. An implanted infusion pump for chemotherapy of liver metastases. *Med Lett Drugs Ther* 1984; 26: 89–90.
3. Aldrighetti L, *et al.* Extrahepatic biliary stenoses after hepatic arterial infusion (HAI) of floxuridine (FUdR) for liver metastases from colorectal cancer. *Hepatogastroenterology* 2001; 48: 1302–7.
4. Pettavel J, *et al.* Fatal liver cirrhosis associated with long-term arterial infusion of floxuridine. *Lancet* 1986; ii: 1162–3.
5. Samaras P, *et al.* Hemorrhage associated with hepatic artery pseudoaneurysms after regional chemotherapy with floxuridine: case report. *Int Semin Surg Oncol* 2008; 5: 17.

Interactions

As for Fluorouracil, p. 797.3.

Pharmacokinetics

Floxuridine is poorly absorbed from the gastrointestinal tract and it is usually given by injection. Floxuridine is metabolised mainly in the liver to fluorouracil after rapid injection. When given by slow intra-arterial infusion, more of the drug is metabolised to floxuridine monophosphate (F-dUMP). It is excreted as carbon dioxide via the lungs; some is excreted, as unchanged drug and metabolites, in urine. Floxuridine crosses the blood-brain barrier to some extent and is found in CSF.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: FUDR; *Turk.*: Floxudem; *USA*: FUDR†.

Pharmacopoeial Preparations
USP 36: Floxuridine for Injection.

Fludarabine Phosphate

(BAN, USAN, rINNM)

2-F-ara-AMP; Fludarabiinifosfaatti; Fludarabin Fosfat; Fludarabina, fosfato de; Fludarabine Monophosphate; Fludarabine, phosphate de; Fludarabinfosfat; Fludarabin-fosfát; Fludarabini Phosphas; Fludarabino fosfatas; Fludarabinphosphat; 2-Fluoro-ara-AMP; Fosfato de fludarabina; NSC-312887; Флударабина Фосфат.

9-β-D-Arabinofuranosyl-2-fluoroadenine 5′-dihydrogenphosphate.

$C_{10}H_{13}FN_5O_7P$=365.2

CAS — 21679-14-1 (fludarabine); 75607-67-9 (fludarabine phosphate).

ATC — L01BB05.

ATC Vet — QL01BB05.

UNII — 1X9VK9O1SC.

NOTE. The name FluCam has been used for a regimen of fludarabine with alemtuzumab. Distinguish from Flucam, which is a proprietary name for ampiroxicam (p. 21.1).

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

Ph. Eur. 8: (Fludarabine Phosphate). A white or almost white, hygroscopic, crystalline powder. Slightly soluble in water; very slightly soluble in dehydrated alcohol; freely soluble in dimethylformamide. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Fludarabine Phosphate). A white to off-white, hygroscopic, crystalline powder. Slightly soluble in water and in 0.1M hydrochloric acid; practically insoluble in dehydrated alcohol; freely soluble in dimethylformamide. Store at 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Fludarabine phosphate is a fluorinated nucleotide analogue of the antiviral vidarabine (p. 1023.1); it is a purine analogue that acts as an antimetabolite antineoplastic to inhibit DNA synthesis. Fludarabine is used for the treatment of B-cell chronic lymphocytic leukaemia (p. 693.3). Fludarabine phosphate is given intravenously or orally. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* For intravenous use, fludarabine phosphate is either given by bolus injection, usually in 10 mL sodium chloride 0.9%, or by infusion over 30 minutes, usually in 100 mL sodium chloride 0.9%. The usual *intravenous* dose is 25 mg/m² daily for 5 consecutive days. Alternatively it may be given *orally* in a dose of 40 mg/m² daily for 5 consecutive days. Courses may be repeated every 28 days, usually for up to 6 cycles.

Haematological function should be monitored regularly; the dosage may need to be reduced, or further courses delayed, if blood counts indicate severe or persistent myelosuppression (see Administration in Subsequent Cycles, below). Doses should be reduced in renal impairment (see below).

General references.

1. Adkins JC, *et al.* Fludarabine: an update of its pharmacology and use in the treatment of haematological malignancies. *Drugs* 1997; 53: 1005–37.
2. Plosker GL, Figgitt DP. Oral fludarabine. *Drugs* 2003; 63: 2317–23.

Administration in the elderly. US licensed product information states that patients of advanced age are predisposed to increased toxicity from fludarabine, and that such patients should be monitored closely, and the dose modified accordingly. UK licensed product information states that data are limited for patients over the age of 75 years; in patients over the age of 65 years, creatinine clearance (CC) should be measured and patients treated accordingly, see Administration in Renal Impairment, below.

A review[1] stated that fludarabine may be used safely and effectively in older patients, but that supportive measures were important. Response rates tend to be lower in older patients, and dose reductions are recommended in the setting of reduced CC in an effort to minimise treatment-related toxicity.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in renal impairment. US licensed product information for intravenous fludarabine recommends that patients with moderate renal impairment, defined as creatinine clearance (CC) of 30 to 70 mL/min per 1.73 m² should have a 20% dose reduction of fludarabine. Fludarabine should not be given to those with severe renal impairment (CC less than 30 mL/min per 1.73 m²).

UK licensed product information for intravenous and oral fludarabine states that for those patients with a CC of between 30 and 70 mL/min, the dose should be reduced by up to 50% and close haematological monitoring used to assess toxicity; the drug is contra-indicated in those with CC less than 30 mL/min.

Administration in subsequent cycles. US licensed product information for *intravenous* fludarabine states that the dose may need to be decreased or treatment delayed based on haematological or non-haematological toxicity; if neurotoxicity occurs, therapy may need to be delayed, or stopped.

UK licensed product information for *oral* fludarabine states that if cell numbers are too low at the start of a subsequent cycle and there is evidence of treatment-related myelosuppression, the planned treatment cycle should be postponed until the granulocyte count is above 1000 cells/mm³ and the platelet count is above 100 000 cells/mm³. Treatment should only be postponed up to a maximum of 2 weeks; if the counts have not recovered after 2 weeks, the daily dose of fludarabine phosphate should be reduced accordingly to the following:

- granulocytes 500 to 1000 cells/mm³ and/or platelets 50 000 to 100 000 cells/mm³: 30 mg/m²
- granulocytes less than 500 cells/mm³ and/or platelets less than 50 000 cells/mm³: 20 mg/m²

The dose is not reduced if thrombocytopenia is disease related. If the patient does not respond to treatment after 2 cycles and shows little or no haematological toxicity, the dose may be increased cautiously in subsequent cycles.

Malignant neoplasms. Fludarabine is the preferred second-line therapy for chronic lymphocytic leukaemia once initial alkylating agent therapy fails,[1] and may also be used for initial therapy (see p. 693.3). It has also been tried in other malignancies. Listed below are some references to the use of fludarabine phosphate for the treatment of chronic lymphocytic leukaemia,[2-4] and its potential activity against a variety of other malignancies, including indolent low-grade non-Hodgkin's lymphoma[5,6] (p. 696.3), mycosis fungoides,[7] heavy chain disease,[8] prolymphocytic leukaemia,[9,10] hairy cell leukaemia,[11] and Waldenström's macroglobulinaemia.[12-14]

1. NICE. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (issued September 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/NICEfludarab_E_29guidance.pdf (accessed 31/07/08)
2. Zhu Q, *et al.* Fludarabine in comparison to alkylator-based regimen as induction therapy for chronic lymphocytic leukemia: a systematic review and meta-analysis. *Leuk Lymphoma* 2004; 45: 2239–45.
3. Richards S. Fludarabine increases complete response but not survival compared with conventional alkylator-based regimens for previously untreated chronic lymphocytic leukaemia. *Cancer Treat Rev* 2005; 31: 332–5.
4. Ricci F, *et al.* Fludarabine in the treatment of chronic lymphocytic leukemia: a review. *Ther Clin Risk Manag* 2009; 5: 187–207.
5. Hiddemann W, Pott-Hoeck C. Fludarabine in the management of malignant lymphomas. *Drugs* 1994; 47 (suppl 6): 50–6.
6. Anderson VR, Perry CM. Fludarabine: a review of its use in non-Hodgkin's lymphoma. *Drugs* 2007; 67: 1633–55.
7. Scarisbrick JJ, *et al.* A trial of fludarabine and cyclophosphamide combination chemotherapy in the treatment of advanced refractory primary cutaneous T-cell lymphoma. *Br J Dermatol* 2001; 144: 1010–15.
8. Agrawal S, *et al.* First report of fludarabine in gamma-heavy chain disease. *Br J Haematol* 1994; 88: 653–5.
9. Smith OP, Mehta AB. Fludarabine monophosphate for prolymphocytic leukaemia. *Lancet* 1990; 336: 820.
10. Kantarjian HM, *et al.* Efficacy of fludarabine, a new adenine nucleoside analogue, in patients with prolymphocytic leukemia and the prolymphocytoid variant of chronic lymphocytic leukemia. *Am J Med* 1991; 90: 223–8.
11. Kantarjian HM, *et al.* Fludarabine therapy in hairy cell leukemia. *Cancer* 1991; 67: 1291–3.
12. Dhodapkar MV, *et al.* Prognostic factors and response to fludarabine therapy in patients with Waldenström macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). *Blood* 2001; 98: 41–8.
13. Leblond V, *et al.* Multicenter, randomized comparative trial of fludarabine and the combination of cyclophosphamide-doxorubicin-prednisone in 92 patients with Waldenström macroglobulinemia in first relapse or with primary refractory disease. *Blood* 2001; 98: 2640–4.
14. Tedeschi A, *et al.* Fludarabine-based combination therapies for Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma* 2009; 9: 67–70.

Organ and tissue transplantation. Fludarabine is commonly used in non-myeloablative or reduced-intensity conditioning regimens before haematopoietic stem cell transplantation (p. 1937.1).[1,2] Fludarabine-based conditioning appears to be most effective in slowly proliferating malignancies, which give time for a graft-versus-leukaemia effect to develop. Although toxicity is generally mild with fludarabine, graft-versus-host disease is still a significant problem and the optimal conditioning regimen remains to be determined.[1]

1. Carella AM. Treatment of hematological malignancies with allogeneic nonmyeloablative stem cell transplantation: conditioning regimens with fludarabine. *Hematol J* 2004; 5 (suppl 1): S68–S75.
2. Blaise D, *et al.* Current status of reduced-intensity-conditioning allogeneic stem cell transplantation for acute myeloid leukemia. *Haematologica* 2007; 92: 533–41.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow suppression from fludarabine is very common and dose-limiting, manifesting as neutropenia, thrombocytopenia, and anaemia; the nadir of the white cell and platelet counts usually occurs after about 13 and 6 days, respectively. Myelosuppression can be severe and cumulative; prolonged lymphopenia with concomitant risk of opportunistic infections may occur. Bone marrow hypoplasia or aplasia resulting in pancytopenia may sometimes be fatal. Careful haematological monitoring is required. Infections can be severe and sometimes fatal; these include opportunistic infections and reactivations of latent viral infections such as herpes zoster, Epstein-Barr virus, and JC virus (causing progressive multifocal leukoencephalopathy). Hepatitis B has been reported; in hepatitis B virus carriers, aggravation of hepatitis or fulminant hepatitis can occur.

Auto-immune disorders (including auto-immune haemolytic anaemia, thrombocytopenic purpura, acquired haemophilia, and Evan's syndrome) have been reported, and may be life-threatening or fatal. Patients should be monitored for signs of haemolysis and therapy stopped if it occurs. Use of fludarabine should be avoided in patients with decompensated haemolytic anaemia.

Peripheral neuropathy is common with fludarabine. Other neurological disturbances include agitation, confusion, visual disturbances, and seizures; high intravenous doses of fludarabine have been associated with severe neurological effects, including blindness, coma, and death.

Other common adverse effects include fever, fatigue, chills, cough, weakness, malaise, anorexia, gastrointestinal disturbances, mucositis, stomatitis, oedema, and rashes. Less commonly, pulmonary toxicity (including pulmonary fibrosis, pneumonitis, and dyspnoea), gastrointestinal haemorrhage, and abnormalities in hepatic or pancreatic enzymes can occur. Tumour lysis syndrome has been reported, especially in patients with large tumour burdens. Rarely reported effects include heart failure, arrhythmias, pemphigus, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Cerebral haemorrhage, pulmonary haemorrhage, and haemorrhagic cystitis can occur.

Exacerbation of existing skin cancer lesions as well as new onset of skin cancer has been reported in some patients. Transfusion-associated graft-versus-host disease has been seen after transfusion of non-irradiated blood in patients treated with fludarabine, and fatalities have occurred; patients should only receive irradiated blood.

Dosage should be reduced in renal impairment (see above).

Carcinogenicity. A study in patients with chronic lymphocytic leukaemia who were treated with fludarabine found that there was no significantly increased risk of secondary malignancy after therapy, despite the immunosuppressive properties of this drug.[1] A review[2] of this and other studies concluded that no significant increase in the risk of secondary malignancy had been shown, but also that long-

term follow-up of patients treated with fludarabine was needed.

1. Cheson BD, *et al.* Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukaemias. *J Clin Oncol* 1999; 17: 2454–60.
2. Van Den Neste E, *et al.* Second primary tumors and immune phenomena after fludarabine or 2-chloro-2′-deoxyadenosine treatment. *Leuk Lymphoma* 2001; 40: 541–50.

Effects on the eyes. See Effects on the Nervous System, below.

Effects on the lungs. Pulmonary toxicity manifest as dyspnoea, fever, hypoxaemia, and radiographic evidence of interstitial and alveolar infiltrates was diagnosed in 9 patients of a cohort of 105 treated with fludarabine.[1] Lung biopsies were performed in 6 patients and showed diffuse chronic interstitial inflammation and fibrosis. Patients with chronic lymphocytic leukaemia appeared to be at greater risk of developing this complication than those with non-Hodgkin's lymphoma.

1. Helman DL, *et al.* Fludarabine-related pulmonary toxicity: a distinct clinical entity in chronic lymphoproliferative syndromes. *Chest* 2002; 122: 785–90.

Effects on the nervous system. High doses (of the order of 100 mg/m^2 daily intravenously) of fludarabine are associated with severe, life-threatening neurotoxicity. However, a few cases of progressive multifocal leukoencephalopathy have also been reported in patients given fludarabine in usual doses.[1-4] The prolonged immunosuppression caused by fludarabine might increase the risk of developing this fatal demyelinating disease, which is caused by opportunistic JC virus infection. Ocular toxicity, including irreversible loss of vision, has also been reported occasionally, including with low-dose regimens.[5]

1. Zabernigg A, *et al.* Late-onset fatal neurological toxicity of fludarabine. *Lancet* 1994; 344: 1780.
2. Gonzalez H, *et al.* Progressive multifocal leukoencephalitis (PML) in three patients treated with standard-dose fludarabine (FAMP). *Hematol Cell Ther* 1999; 41: 183–6.
3. Cid J, *et al.* Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. *Ann Hematol* 2000; 79: 392–5.
4. Vidarsson B, *et al.* Progressive multifocal leukoencephalopathy after fludarabine therapy for low-grade lymphoproliferative disease. *Am J Hematol* 2002; 70: 51–4.
5. Ding X, *et al.* Ocular toxicity of fludarabine: a purine analog. *Expert Rev Ophthalmol* 2008; 3: 97–109.

Graft-versus-host disease. Transfusion-associated graft-versus-host disease has been reported when blood products were used in patients treated with fludarabine.[1] Fludarabine-treated patients should receive irradiated red cells and platelets (to inactivate any viable T-cells) if they require a transfusion.

1. Williamson LM, *et al.* Fludarabine treatment and transfusion-associated graft-versus-host disease. *Lancet* 1996; 348: 472–3.

Infection. A review[1] of patients treated with fludarabine-containing regimens showed that therapy was associated with serious infections including listeriosis, pneumocystis pneumonia, mycobacterial infections, and opportunistic fungal and viral infections. The risk was exacerbated by previous or current corticosteroid therapy. Prophylactic therapy with co-trimoxazole, triazole antifungals, aciclovir, and colony-stimulating factors was recommended in at-risk patients. A high incidence of herpesvirus infections was also found in another review[2] of patients treated with fludarabine. Combination therapy using chlorambucil and fludarabine resulted in more infections than when either was used alone,[3] but single-agent fludarabine was associated with more major infections and herpesvirus infections than chlorambucil alone. The frequency of serious infection has also been reported[4] to be increased in patients after their conditions became refractory to fludarabine and they were being treated with conventional chemotherapy.

For reports of progressive multifocal leukoencephalopathy caused by opportunistic JC virus infection in patients receiving fludarabine, see Effects on the Nervous System, above.

1. Anaissie EJ, *et al.* Infections in patients with chronic lymphocytic leukemia treated with fludarabine. *Ann Intern Med* 1998; 129: 559–66.
2. Byrd JC, *et al.* Herpes virus infections occur frequently following treatment with fludarabine: results of a prospective natural history study. *Br J Haematol* 1999; 105: 445–7.
3. Morrison VA, *et al.* Impact of therapy with chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia: Intergroup Study Cancer and Leukemia Group B 9011. *J Clin Oncol* 2001; 19: 3611–21.
4. Perkins JG, *et al.* Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population. *Cancer* 2002; 94: 2033–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fludarabine 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 29/09/11)

Psoriasis. Although incidental resolution of psoriatic lesions has been reported[1,2] in a few patients being treated with fludarabine, there is also a report[3] of a patient with fulminant exacerbation of psoriatic plaques and generalised erythroderma after starting fludarabine therapy. Symptoms resolved on stopping the drug and treatment with corticosteroids, emollients, and phototherapy.

1. Karadoğan I, *et al.* Resolution of psoriatic skin lesions with fludarabine. *Am J Med* 1999; 107: 300–1.
2. Smith OP, *et al.* Fludarabine and psoriasis. *N Engl J Med* 1994; 330: 1540–1.
3. Jordan J, *et al.* Paradoxical exacerbation of psoriasis during therapy with fludarabine. *Eur J Dermatol* 2008; 18: 365–6.

Interactions

Increased pulmonary toxicity, sometimes fatal, has been reported in patients given fludarabine with pentostatin. Pretreatment with cytarabine may reduce the metabolic activation of fludarabine, but pretreatment with fludarabine results in increased intracellular concentrations of cytarabine—see p. 775.3. The therapeutic efficacy of fludarabine may also be reduced by dipyridamole and other inhibitors of adenosine uptake.

Aminoglycosides. Severe ototoxicity occurred when a short course of *gentamicin* was given to a patient who had recently completed a course of fludarabine.[1]

1. O'Brien RK, Sparling TG. Gentamicin and fludarabine ototoxicity. *Ann Pharmacother* 1995; 29: 200–1.

Corticosteroids. For a suggestion that use of fludarabine with corticosteroids may increase the risk of infection, see Infection, above.

Pharmacokinetics

Intravenous fludarabine phosphate is rapidly dephosphorylated to fludarabine which is taken up by lymphocytes and rephosphorylated via the enzyme deoxycytidine kinase to the active triphosphate nucleotide. Peak intracellular concentrations of fludarabine triphosphate occur about 4 hours after a dose. Fludarabine has a bioavailability of about 50 to 65% after oral doses of the phosphate.

Clearance of fludarabine from the plasma is triphasic with a terminal half-life of about 20 hours. Elimination is mostly via renal excretion: 40 to 60% of an intravenous dose is excreted in the urine. The pharmacokinetics of fludarabine show considerable interindividual variation.

References.

1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; 39: 5–26.
2. Gandhi V, Plunkett W. Cellular and clinical pharmacology of fludarabine. *Clin Pharmacokinet* 2002; 41: 93–103.
3. Lichtman SM, *et al.* The pharmacokinetics and pharmacodynamics of fludarabine phosphate in patients with renal impairment: a prospective dose adjustment study. *Cancer Invest* 2002; 20: 904–13.
4. Ogawa Y, *et al.* Phase I and pharmacokinetic study of oral fludarabine phosphate in relapsed indolent B-cell non-Hodgkin's lymphoma. *Ann Oncol* 2006; 17: 330–3.
5. Salinger DH, *et al.* A limited sampling schedule to estimate individual pharmacokinetic parameters of fludarabine in hematopoietic cell transplant patients. *Clin Cancer Res* 2009; 15: 5280–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Fludakebir; Fludara; Fluradosa; Forclina; ***Austral.***: Fludara; ***Austria***: Fludara; Neoflubin; ***Belg.***: Fludara; ***Braz.***: Fludalibbs; Fludara; ***Canad.***: Fludara; ***Chile***: Fludara; ***China***: Fludara (福达华); ***Cz.***: Fludara; Tazumara†; ***Denm.***: Fludara; ***Fin.***: Fludara; ***Fr.***: Fludara; ***Ger.***: Bendarabin; Fludara; Neoflubin†; ***Gr.***: Fludara; ***Hong Kong***: Fludara; ***Hung.***: Fludara; ***India***: Fludabine; Fludacel; Fludara; Fludarin; Naprobin; ***Indon.***: Fludara; ***Irl.***: Fludara; ***Israel***: Fludara; ***Ital.***: Fludara; ***Malaysia***: Fludara; ***Mex.***: Beneflur; Fludara†; ***Neth.***: Fludara; ***Norw.***: Fludara; ***NZ***: Fludara; ***Philipp.***: Fludara; ***Pol.***: Fludalym; Fludara; ***Port.***: Fludara; ***Rus.***: Fludara (Флудара); Flugarda (Флугарда); ***S.Afr.***: Fludara; ***Singapore***: Fludara; ***Spain***: Beneflur; ***Swed.***: Fludara; ***Switz.***: Fludara†; ***Thai.***: Fludara; ***Turk.***: Fludara; Flumen; ***UK***: Fludara; ***USA***: Fludara†; Oforta†; ***Venez.***: Fludara.

Pharmacopoeial Preparations

USP 36: Fludarabine Phosphate for Injection; Fludarabine Phosphate Injection.

Fluorouracil *(BAN, USAN, rINN)*

5-Fluorouracil; Fluorouracilas; Fluorouracile; Fluorouracilo; Fluorouracilum; Fluoruracyl; Fluorourasill; 5-Fluorourasil; Fluorourasil; Fluouracil; 5-FU; NSC-19893; Ro-2-9757; WR-69596; Фторурацил.

5-Fluoropyrimidine-2,4(1*H*,3*H*)-dione.

$C_4H_3FN_2O_2$=130.1.

CAS — 51-21-8.
ATC — L01BC02.
ATC Vet — QL01BC02.
UNII — U3P01618RT.

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

Ph. Eur. 8: (Fluorouracil). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.0. Protect from light.

USP 36: (Fluorouracil). A white to practically white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Incompatibility. Preparations of fluorouracil are alkaline, and compatibility problems may be expected with acidic drugs and preparations, or those which are unstable in the presence of alkali. Fluorouracil is reported to be incompatible with cytarabine,[1] diazepam,[2] doxorubicin[2] (and presumably other anthracyclines that are unstable at alkaline pH), and calcium folinate.[3] Although fluorouracil has been stated to be incompatible with methotrexate[4] a study of the long-term stability of an admixture of the 2 drugs in sodium chloride 0.9% injection suggests otherwise.[4]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; 33: 1010–13.
2. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; 6: 42–52.
3. Trissel LA, *et al.* Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium. *Am J Health-Syst Pharm* 1995; 52: 710–15.
4. Vincké BJ, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; 54: 181–9.

Stability. Despite one report[1] that fluorouracil had limited stability when dissolved in glucose 5% at room temperature (10% loss from solution in 43 hours when stored in PVC and in only 7 hours when stored in glass), others[2] found such a solution to be stable for at least 16 weeks when stored in PVC at 5 degrees. When stored at room temperature in PVC, solutions of fluorouracil may lose water by evaporation, which slowly increases their concentration.[2,3] Results of a study of fluorouracil and methotrexate admixtures in sodium chloride 0.9% suggest that extended stability (up to 13 weeks) is possible in this diluent at 5 degrees in PVC bags.[3] Commercial solutions of fluorouracil for injection have been reported to be stable for 7 days at 37 degrees in a portable infusion pump, although at 25 degrees one brand showed evidence of precipitation.[4] Fluorouracil solutions may be incompatible with synthetic elastomers: microscopic precipitation has been reported as soon as 4 hours after placement into polyisoprene reservoirs of elastomeric infusers and in polypropylene syringes with an elastomeric joint.[5] Some have questioned the validity of this finding.[6,7]

1. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; 38: 1914–18.
2. Quebbeman EJ, *et al.* Stability of fluorouracil in plastic containers used for continuous infusion at home. *Am J Hosp Pharm* 1984; 41: 1153–6.
3. Vincké B, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; 54: 181–9.
4. Stiles ML, *et al.* Stability of fluorouracil administered through four portable infusion pumps. *Am J Hosp Pharm* 1989; 46: 2036–40.
5. Corbrion V, *et al.* Precipitation of fluorouracil in elastomeric infusers with a polyisoprene reservoir and in polypropylene syringes with an elastomeric joint. *Am J Health-Syst Pharm* 1997; 54: 1845–8.
6. Trissel LA. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; 55: 1314–15.
7. Allwood MC. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; 55: 1315–16.

Uses and Administration

Fluorouracil, an analogue of the pyrimidine uracil, is an antineoplastic that acts as an antimetabolite. After intracellular conversion to the active deoxynucleotide it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. It can also interfere with RNA synthesis.

Fluorouracil is used alone or in combination in the adjuvant and palliative treatment of gastrointestinal cancer. In this setting it may be combined with folinic acid (see Administration, p. 796.1). Fluorouracil is often given with cyclophosphamide and methotrexate or doxorubicin in the adjuvant treatment of breast cancer. It may also be used in the palliation of other malignant neoplasms such as those of the head and neck, liver, and pancreas. In addition, it may be used topically for treating malignant or premalignant lesions of the skin. Its use in these malignancies is further discussed under Choice of Antineoplastic as indicated by the cross-references given below.

Many dosage regimens have been used. Although it is most often given in combination regimens for the treatment of malignancy, many of the licensed dosage regimens relate to single-agent use. Such licensed regimens include:

- by *intravenous injection*, usual doses of 12 mg/kg daily (to a maximum of 0.8 to 1 g daily) for 3 or 4 days. If there is

no evidence of toxicity, this may be followed after 1 day by 6 mg/kg on alternate days for 3 or 4 further doses. An alternative schedule is to give 15 mg/kg intravenously once a week throughout the course. The course may be repeated after 4 to 6 weeks or maintenance doses of 5 to 15 mg/kg to a maximum of 1 g may be given weekly.

- by *intravenous infusion*, usual doses of 15 mg/kg daily (to a maximum of 1 g daily) being infused in 500 mL of sodium chloride 0.9% or glucose 5% over 4 hours and repeated on successive days until toxicity occurs or a total of 12 to 15 g has been given. *Continuous infusion* may also be used. The course may be repeated after 4 to 6 weeks.
- by continuous *intra-arterial infusion*, in doses of 5 to 7.5 mg/kg daily (regional perfusion).
- by *mouth*, although the parenteral route is generally preferred, a dose of 15 mg/kg, to a maximum of 1 g in one day, has been given once weekly for maintenance. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Suggested regimens with folinic acid include:

- 200 mg/m^2 of folinic acid (as calcium folinate) by slow intravenous injection followed immediately by an intravenous bolus of fluorouracil 370 mg/m^2; the treatment is given daily for 5 consecutive days, and may be repeated every 4 to 5 weeks
- lower doses of folinic acid (20 mg/m^2) followed by fluorouracil 425 mg/m^2 for 5 consecutive days, repeated every 4 to 5 weeks (the Mayo regimen)
- an initial dose of 200 mg/m^2 of folinic acid, followed by fluorouracil 400 mg/m^2 as an initial intravenous bolus injection and then 600 mg/m^2 by continuous intravenous infusion. This dosage is given for 2 consecutive days every 2 weeks (the de Gramont regimen)

The white cell count should be determined frequently during treatment with fluorouracil and therapy stopped immediately if the count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p. 730.3) or if severe adverse effects occur. Doses should be reduced by up to half in patients with poor nutritional status, impaired bone-marrow, hepatic, or renal function, and within 30 days of major surgery.

Fluorouracil is used *topically* in the treatment of solar (actinic) keratoses and other superficial tumours and premalignant conditions of the skin including Bowen's disease and superficial basal cell carcinomas. For actinic keratosis it is usually applied as a 0.5 to 5% cream or as a 1 to 5% solution in propylene glycol once or twice daily for 2 to 4 weeks; the higher strength may be applied for at least 3 to 6 weeks for superficial basal cell carcinomas.

Administration. For reference to sequence-specific toxicity when fluorouracil and folinic acid were given before capecitabine, see Administration, under Capecitabine, p. 758.1.

MODULATION. Modulation of fluorouracil by other drugs has been tried in an effort to enhance its effects, particularly in the treatment of colorectal cancer (p. 706.3).

Folinic acid has been extensively used to modulate the effects of fluorouracil, and has become the agent of choice. Various regimens have been used, modifying the fluorouracil schedule (continuous infusion versus bolus), folinic acid dose (low-dose versus high-dose) and the regimen frequency (monthly, bimonthly, or weekly). Despite many studies, the optimum regimen in terms of efficacy and tolerability has yet to be determined.

In the adjuvant setting, a large-scale randomised study[1] found low-dose folinic acid was as effective as high-dose when added to fluorouracil given either once weekly for 30 doses, or for 5 consecutive days per month over 6 months.

In the palliation of advanced disease, meta-analyses have revealed the value of the addition of folinic acid to fluorouracil,[2] and the use of infusions rather than bolus fluorouracil,[3] in terms of response rates. An updated meta-analysis confirmed the benefit of addition of folinic acid to fluorouracil in terms of response rate, and found a small but statistically significant advantage in terms of overall survival. Survival benefit was restricted to studies using the same dose of fluorouracil in the treatment arms (fluorouracil alone versus fluorouracil and folinic acid), suggesting that the benefit of modulation with folinic acid could be compensated by an increase of fluorouracil dose in the fluorouracil alone arm. However, increased toxicity from high-dose fluorouracil might occur.[4] The data for low-dose folinic acid versus high-dose are less clear.[5] In 1 randomised study,[6] a bimonthly infusion regimen of fluorouracil plus high-dose folinic acid (the de Gramont regimen[7]) was more effective than a monthly bolus regimen of fluorouracil plus low-dose folinic acid. Further studies comparing the effect of high- and low-dose folinic acid added to the same schedule of continuous infusion fluorouracil are required.

1. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; 355: 1588–96.
2. Advanced Colorectal Cancer Meta-analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; 10: 896–903.
3. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; 16: 301–8.
4. The Meta-Analysis Group in Cancer. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004; 22: 3766–75. Correction. *ibid.* 2005; 23: 1337–8.
5. Rustum YM, *et al.* Rationale for treatment design: biochemical modulation of 5-fluorouracil by leucovorin. *Cancer J Sci Am* 1998; 4: 12–18.
6. de Gramont A, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997; 15: 808–15.
7. de Gramont A, *et al.* A review of GERCOD trials of bimonthly leucovorin plus 5-fluorouracil 48-h continuous infusion in advanced colorectal cancer: evolution of a regimen. *Eur J Cancer* 1998; 34: 619–26.
8. Makower D, Wadler S. Interferons as biomodulators of fluoropyrimidines in the treatment of colorectal cancer. *Semin Oncol* 1999; 26: 663–71.
9. Wolmark N, *et al.* Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; 17: 3553–9.
10. Advanced Colorectal Cancer Meta-analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. *J Clin Oncol* 1994; 12: 960–9.

Interferon alfa also appears to modify[8] the actions of fluorouracil (see also under Interactions, p. 797.3), and has been investigated with fluorouracil and folinic acid. Although some early results were promising, later randomised controlled studies failed to show any benefit for the addition of interferon alfa to fluorouracil or fluorouracil plus folinic acid.[8] It is not clear whether interferon beta will prove of any greater benefit.

Based on the results of early adjuvant studies, *levamisole* was used as standard therapy to modulate fluorouracil, particularly in the USA. However, more recent studies indicate that levamisole is no more effective than placebo when added to fluorouracil,[1] or to fluorouracil plus folinic acid.[9]

Methotrexate has also been used to modulate fluorouracil. Meta-analysis of several studies of fluorouracil preceded by methotrexate found that the combination doubled the response rate to fluorouracil in metastatic colorectal cancer and produced some survival benefits.[10] (Combination in the reverse order, i.e. methotrexate preceded by fluorouracil, may reduce methotrexate toxicity—see Other Drugs, under Treatment of Adverse Effects, p. 827.1.)

ROUTE. Fluorouracil can be given orally, parenterally, or topically (see Uses and Administration, p. 795.3); it has also been used intralesionally and intraurethrally in the treatment of condyloma acuminata, see Warts, below.

Administration in the elderly. A review[1] concluded that there is no pharmacokinetic basis for dose modification of fluorouracil based on age alone; data are conflicting as to whether toxicity is likely to be increased in elderly patients.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Darier's disease. Two patients with resistant Darier's disease (p. 1683.2) receiving long-term oral retinoid therapy responded to treatment with topical fluorouracil applied as a 1% cream once daily.[1] There was complete clearance of skin lesions after 3 weeks of treatment. In another case,[2] topical fluorouracil 1% cream applied every second day, alternating with clobetasol ointment, dramatically improved hyperkeratosis after 1 month; improvement persisted for 2 months after the end of treatment. Fluorouracil 1% cream has also been used as monotherapy,[3,4] leading to marked improvement or complete remission after about 4 weeks of therapy.

1. Knulst AC, *et al.* Topical 5-fluorouracil in the treatment of Darier's disease. *Br J Dermatol* 1995; 133: 463–6.
2. Velasco S, Guillet G. Amélioration d'une maladie de Darier traitée par 5-fluorouracil topique. *Ann Dermatol Venereol* 2006; 133: 366–8.
3. Yoon TY, *et al.* Successful treatment of Darier disease with topical 5-fluorouracil. *Br J Dermatol* 2006; 154: 1210–12.
4. Schmidt H, *et al.* Topical 5-fluorouracil in Darier disease. *Br J Dermatol* 2008; 158: 1393–6.

Eye disorders. Aside from its use in glaucoma surgery (below), fluorouracil has been used adjunctively in other ocular surgery. It has also shown promising results in the treatment of ocular surface malignancies.[1]

1. Abraham LM, *et al.* The clinical applications of fluorouracil in ophthalmic practice. *Drugs* 2007; 67: 237–55.

Glaucoma. A regimen of subconjunctival injections of fluorouracil is effective in improving the outcome of glaucoma filtering surgery[1-3] in selected patients when used as an adjunct to prevent the formation of scar tissue (see p. 1999.1). However, in view of the increased risk of late-onset conjunctival wound leaks caution has been suggested in its use in eyes with a good prognosis.[3] Although one study[4] found that fluorouracil improved the success of combined glaucoma filtering surgery and cataract surgery earlier studies had failed to find any advantage.[5,6] A systematic review[7] of these and 2 other studies concluded that fluorouracil reduced the risk of surgical failure of trabeculectomy in eyes at high risk of failure, and in those undergoing surgery for the first time, but noted that the methodological quality of the studies was not high, and that this practice has largely been superseded by the use of intra-operative mitomycin. However, a later survey[8] in the UK found that the use of antimetabolites in glaucoma surgery was much less common than in the USA or Japan, and that fluorouracil was strongly preferred to mitomycin.

Intra-operative topical application of fluorouracil has been tried as an alternative to subconjunctival injection with conflicting results.[9-11]

1. Ophir A, Ticho U. A randomized study of trabeculectomy and subconjunctival administration of fluorouracil in primary glaucomas. *Arch Ophthalmol* 1992; 110: 1072–5.
2. Goldenfeld M, *et al.* 5-Fluorouracil in initial trabeculectomy: a prospective, randomized, multicenter study. *Ophthalmology* 1994; 101: 1024–9.
3. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the Fluorouracil Filtering Surgery Study. *Am J Ophthalmol* 1996; 121: 349–66.
4. Gandolfi SA, Vecchi M. 5-Fluorouracil in combined trabeculectomy and clear-cornea phacoemulsification with posterior chamber intraocular lens implantation: a one-year randomized, controlled clinical trial. *Ophthalmology* 1997; 104: 181–6.
5. Wong PC, *et al.* 5-Fluorouracil after primary combined filtration surgery. *Am J Ophthalmol* 1994; 117: 149–54.
6. O'Grady JM, *et al.* Trabeculectomy, phacoemulsification, and posterior chamber lens implantation with and without 5-fluorouracil. *Am J Ophthalmol* 1993; 116: 594–9.
7. Wormald R, *et al.* Post-operative 5-fluorouracil for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 12/05/05).
8. Siriwardena D, *et al.* National survey of antimetabolite use in glaucoma surgery in the United Kingdom. *Br J Ophthalmol* 2004; 88: 873–6.
9. Egbert PR, *et al.* A prospective trial of intraoperative fluorouracil during trabeculectomy in a black population. *Am J Ophthalmol* 1993; 116: 612–16.
10. Lachkar Y, *et al.* Trabeculectomy with intraoperative sponge 5-fluorouracil in Afro-Caribbeans. *Br J Ophthalmol* 1997; 81: 555–8.
11. Yorston D, Khaw PT. A randomised trial of the effect of intraoperative 5-FU on the outcome of trabeculectomy in east Africa. *Br J Ophthalmol* 2001; 85: 1028–30.

Malignant neoplasms. Fluorouracil plays an important role in the adjuvant treatment of gastrointestinal cancer, as discussed on p. 705.2, and has been widely used in adjuvant regimens for early breast cancer (p. 702.1). It may also be employed in the management of several other malignancies including pancreatic endocrine tumours (p. 716.3), cancers of the cervix (p. 704.2) and head and neck (p. 708.1), liver metastases (p. 709.3), and tumours of the exocrine pancreas (p. 712.1). It is reported to have only modest activity in neoplasms of the kidney (p. 708.3). In addition, it is sometimes applied topically as part of the management of malignant or pre-malignant lesions of the skin (see Basal Cell and Squamous Cell Carcinoma, p. 714.2), or surface neoplasia of the eye (p. 705.1).

The role of fluorouracil in chemoradiotherapy of various malignancies has been reviewed.[1]

1. Rich TA, *et al.* Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. *J Clin Oncol* 2004; 22: 2214–32.

Toxoplasmosis. For mention of the use of fluorouracil with clindamycin to treat cerebral toxoplasmosis, see p. 271.1.

Warts. Fluorouracil has been used, as a 1% or, more usually, a 5% cream or solution in the treatment of genital warts (condylomata acuminata).[1-3] It has been tried as an adjuvant to laser therapy in severe papilloma virus-associated vulvar disease,[4] with variable results, and in men with subclinical or clinically apparent penile lesions.[5] A preparation of fluorouracil 3% in a collagen gel basis, with adrenaline as a local vasoconstrictor, has been tried by injection into genital warts.[6] Fluorouracil has also been used intraurethrally to treat intraurethral warts; preparations have included instillation of a 1% solution, 5% cream, or a 5% suppository; urethral instillation of 250 mg fluorouracil injection mixed with 0.18% lidocaine hydrochloride gel has been reported to reduce the size and number of intraurethral condyloma acuminata in 1 patient, and no new growth was seen after 6 months of follow-up.[7] A combination of fluorouracil 0.5% and salicylic acid 10% has also been stated to be effective in the topical treatment of common and plantar warts.[8] Although the evidence was weak, a systematic review found fluorouracil to be better at curing genital warts than placebo, no treatment, or podophyllum resin; use with interferon alfa-2a, or with interferon alfa-2a and carbon dioxide laser

treatment may have a better outcome.[9] For a discussion of the various agents, including cytotoxics such as fluorouracil, used to destroy warts, see p. 1689.3.

1. Kling AR. Genital warts—therapy. *Semin Dermatol* 1992; 11: 247–55.
2. Stone KM. Human papillomavirus infection and genital warts: update on epidemiology and treatment. *Clin Infect Dis* 1995; 20 (suppl 1): S91–7.
3. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med* 1997; 102: 28–37.
4. Reid R. *et al.* Superficial laser vulvectomy IV: extended laser vaporization and adjunctive 5-fluorouracil therapy of human papillomavirus-associated vulvar disease. *Obstet Gynecol* 1990; 76: 439–48.
5. Bergman A, Nalick R. Genital human papillomavirus infection in men: diagnosis and treatment with a laser and 5-fluorouracil. *J Reprod Med* 1991; 36: 363–6.
6. Swinehart JM. *et al.* Intralesional fluorouracil/epinephrine injectable gel for treatment of condylomata acuminata: a phase 3 clinical study. *Arch Dermatol* 1997; 133: 67–73.
7. Gammon DC. *et al.* Intraurethral fluorouracil and lidocaine for intraurethral condyloma acuminata. *Am J Health-Syst Pharm* 2008; 65: 1830–3.
8. Zschocke I. *et al.* Wirksamkeit und Nutzen eines 5-FU-/Salicylsäure-haltigen Präparates in der Therapie vulgärer und plantarer Warzen—systematische Literaturübersicht und Metaanalyse. *J Dtsch Dermatol Ges* 2004; 2: 187–93.
9. Batista CS, *et al.* 5-FU for genital warts in non-immunocompromised individuals. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 21/06/10).

Adverse Effects and Treatment

For general discussions see Antineoplastics, p. 726.1 and p. 730.2. The main adverse effects of fluorouracil are on the bone marrow and the gastrointestinal tract, and may be dose-limiting. Toxicity is also schedule dependent: a 5-day regimen is commonly associated with bone marrow suppression, diarrhoea, and mucositis, a weekly schedule with neutropenia. With protracted continuous infusion or high-dose boluses, the palmar-plantar erythrodysesthesia syndrome (erythema and painful desquamation of the hands and feet) may occur. Gastrointestinal toxicity may be exacerbated if fluorouracil is given with folinic acid.

Treatment should be stopped at the first sign of oral ulceration or if there is evidence of stomatitis, gastrointestinal ulceration and bleeding, diarrhoea, or haemorrhage from any site. Leucopenia is common; the nadir of the white cell count may occur from 7 to 20 days after a dose, and counts usually return to normal after about 30 days. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. It is recommended that treatment should also be stopped if falling blood counts go below 100 000 cells/mm^3 for platelets or below 3500 cells/mm^3 for white cells, but see also Bone Marrow Depression, p. 730.3. Anaemia may also occur. Nausea and vomiting are common, and may be treated with an antiemetic. Alopecia may be seen especially in females, but is generally reversible. Other adverse effects include dermatitis, changes in pigmentation, changes in the nails, ataxia, and fever. Thrombophlebitis has been reported. Ocular toxicity, including excessive lachrymation, dacryostenosis, visual changes, and photophobia can occur. A transient reversible cerebellar syndrome has been reported, and a reversible confusional state can occur rarely. Cases of leukoencephalopathy have also been reported. There have been reports of chest pain, tachycardia, breathlessness, and ECG changes after use of fluorouracil. Anaphylaxis has also occurred.

Local inflammatory reactions such as erythema, pain, pruritus, burning, irritation, and photosensitivity reactions have occurred after topical use. Telangiectasia, hyperpigmentation, and scarring have also been reported. Dermatitis and, rarely, erythema multiforme have occurred. Ocular irritation has also been reported after topical use.

Effects on the eyes. Systemic fluorouracil therapy has been associated with various types of ocular toxicity including several cases of excessive lachrymation and watering of the eyes.[1] In one patient this was associated with symptoms suggesting fibrosis of the tear duct,[1] and possibly representing local irritation due to the presence of fluorouracil in tear fluid,[2] although symptoms have not always resolved on stopping the drug.[1] More seriously a case of bilateral total corneal epithelial erosion has been described.[3] Optic neuropathy, culminating in near blindness, has also occurred in a patient given fluorouracil as part of a combination regimen.[4] Severe ulceration and corneal abscess with hypopyon has followed local injection of fluorouracil into the eye in a diabetic patient with idiopathic band keratopathy.[5]

1. Haidak DJ, *et al.* Tear-duct fibrosis (dacryostenosis) due to 5-fluorouracil. *Ann Intern Med* 1978; 88: 657.
2. Christophidis N. *et al.* Lacrimation and 5-fluorouracil. *Ann Intern Med* 1978; 89: 574.
3. Hirsh A. *et al.* Bilateral total corneal epithelial erosion as a side effect of cytotoxic therapy. *Br J Ophthalmol* 1990; 74: 638.
4. Adams JW. *et al.* Recurrent acute toxic optic neuropathy secondary to 5-FU. *Cancer Treat Rep* 1984; 68: 565–6.
5. Hickey-Dwyer M, Wishart PK. Serious corneal complication of 5-fluorouracil. *Br J Ophthalmol* 1993; 77: 250–1.

Effects on the heart. Life-threatening cardiotoxicity (arrhythmias, ventricular tachycardia, and cardiac arrest, secondary to transmural ischaemia) has been reported to occur in 0.55% of patients given fluorouracil,[1] although the incidence of angina and less severe cardiotoxicity associated with coronary artery spasm may be higher.[1-3] Possible risk factors include pre-existing heart disease or mediastinal radiotherapy, and prolonged infusion of the drug, but symptoms can also occur in patients without these risk factors.[2-5] Therefore, at present, it is not possible to reliably predict patients at risk.[6] Some suggest that the use of a trometamol buffer in the fluorouracil formulation may contribute to the formation of cardiotoxic degradation products.[7]

1. Keefe DL. *et al.* Clinical cardiotoxicity of 5-fluorouracil. *J Clin Pharmacol* 1993; 33: 1060–70.
2. McLachlan SA. *et al.* The spectrum of 5-fluorouracil cardiotoxicity. *Med J Aust* 1994; 161: 207–9.
3. Anand AJ. Fluorouracil cardiotoxicity. *Ann Pharmacother* 1994; 28: 374–8.
4. Hannaford R. Sudden death associated with 5-fluorouracil. *Med J Aust* 1994; 161: 225.
5. Dalzell JR, Samuel LM. The spectrum of 5-fluorouracil cardiotoxicity. *Anticancer Drugs* 2009; 20: 79–80.
6. Becker K. *et al.* Cardiotoxicity of the antiproliferative compound fluorouracil. *Drugs* 1999; 57: 475–84.
7. Lukaschek J. *et al.* Cardiotoxicity and neurotoxicity of high-dose continuous fluorouracil as a result of degradation compounds in the drug vials. *J Clin Oncol* 2004; 22: 5022–5.

Effects on the nervous system. Central neurotoxicity, including cerebellar ataxia, confusion, disorientation, and emotional lability is reported to occur rarely in patients receiving fluorouracil, although the incidence may be increased with high-dose or intensive regimens. The dihydropyrimidine dehydrogenase gene may exist in variant forms[1] and patients with polymorphisms of this or other disorders of pyrimidine metabolism may be at increased risk of neurotoxicity.[2-4] It has also been suggested that fluorouracil may produce neurotoxicity by causing thiamine deficiency.[5] (Wernicke's encephalopathy has been reported[6]) and that thiamine may be used to treat it.[5,6]

1. Amstutz U, *et al.* Dihydropyrimidine dehydrogenase gene variation and severe 5-fluorouracil toxicity: a haplotype assessment. *Pharmacogenomics* 2009; 10: 931–44.
2. Tuchman M. *et al.* Familial pyrimidinemia and pyrimidinuria associated with severe fluorouracil toxicity. *N Engl J Med* 1985; 313: 245–9.
3. Stéphan F. *et al.* Depressed hepatic dihydropyrimidine dehydrogenase activity and fluorouracil-related toxicities. *Am J Med* 1995; 99: 685–8.
4. Takimoto C. *et al.* Reversible 5-fluorouracil-associated encephalopathy in a dihydropyrimidine dehydrogenase (DPD) deficient patient. *Clin Pharmacol Ther* 1996; 59: 161.
5. Pirzada NA. *et al.* Fluorouracil-induced neurotoxicity. *Ann Pharmacother* 2000; 34: 35–8.
6. Cho U. *et al.* A case of Wernicke's encephalopathy following fluorouracil-based chemotherapy. *J Korean Med Sci* 2009; 24: 747–50.

Effects on the skin. In addition to reports of fluorouracil-associated dermatitis and photosensitivity a syndrome of erythema, pain, and desquamation of the skin of palms and soles has been reported[1-6] (the palmar-plantar erythrodysesthesia syndrome, p. 730.1). Although particularly associated with continuous infusion[1,2] the syndrome can also occur after bolus doses.[3,4] Symptoms generally respond to stopping the drug, but addition of oral pyridoxine to chemotherapy regimens has been reported to prevent or resolve symptoms,[5] as has application of a nicotine patch in one patient.[6]

Rash and confusion developing in an elderly man with malabsorption and poor nutritional intake who received fluorouracil for a biliary-tract tumour were diagnosed as pellagra.[7] Symptoms responded to nicotinic acid therapy.

1. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; 101: 798–800.
2. Feldman LD, Ajani JA. Fluorouracil-associated dermatitis of the hands and feet. *JAMA* 1985; 254: 3479.
3. Atkins JN. Fluorouracil and the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1985; 102: 419.
4. Curran CF, Luce JK. Fluorouracil and palmar-plantar erythrodysesthesia. *Ann Intern Med* 1989; 111: 858.
5. Vukelja SJ. *et al.* Pyridoxine for the palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1989; 111: 688–9.
6. Kingsley EC. 5-Fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med* 1994; 120: 813.
7. Stevens HP. *et al.* Pellagra secondary to 5-fluorouracil. *Br J Dermatol* 1993; 128: 578–80.

Hypersensitivity. Although local hypersensitivity reactions are included in licensed product information as potential adverse effects of topical fluorouracil, hypersensitivity reactions to systemic fluorouracil have been reported very rarely.[1-6] For a report of the successful use of fluorouracil in a patient allergic to capecitabine, suggesting that cross-sensitivity does not occur between the two, see p. 758.2.

1. Reed WP, Morris DM. Maculopapular eruption resulting from systemic administration of 5-fluorouracil. *Cutis* 1984; 33: 381–2.
2. Sridhar KS. Allergic reaction to 5-fluorouracil infusion. *Cancer* 1986; 58: 862–4.
3. Milla Santos A, Sanchiz Medina F. Anaphylactic reaction following iv administration of 5-fluorouracil. *Cancer Treat Rep* 1986; 70: 1346.
4. Duley JA, Nethersell AB. Delayed hypersensitivity to 5-fluorouracil associated with reduced dihydropyrimidine dehydrogenase (DPD) activity. *Adv Exp Med Biol* 1998; 431: 147–50.
5. Eppinger T, Sperber K. Desensitization to 5-fluorouracil. *Allergy Asthma Proc* 1999; 20: 189–91.
6. Biswal BM. Anaphylaxis following continuous 5-fluorouracil infusion chemotherapy. *Aust N Z J Med* 1999; 29: 743–4.

Precautions

For general discussions see Antineoplastics, p. 732.2. Fluorouracil should be given with care to weak or malnourished patients, to those with a history of heart disease, or to those with hepatic or renal insufficiency. Patients with a history of high-dose pelvic irradiation or treatment with alkylating agents, and those with widespread metastases to the bone marrow should also be treated with extreme caution. Blood cell counts should be determined frequently during therapy. Fluorouracil should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency as this can lead to increased toxicity.

Topical fluorouracil should not be used on mucous membranes. There is a possibility of increased absorption if used excessively or on ulcerated or inflamed skin. Occlusive dressings may increase inflammatory actions. Exposure to UV light during treatment should be avoided. Creams are preferably applied using a nonmetal applicator or gloved hand; if bare fingertips are used the hands must be washed immediately afterwards.

Handling and disposal. Fluorouracil is irritant; avoid contact with skin and mucous membranes.

Urine and faeces produced for up to 48 hours and 5 days respectively after an oral dose of fluorouracil should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Metabolic disorders. For reference to increased risk of neurotoxicity in patients with a defect of pyrimidine metabolism given fluorouracil, see under Effects on the Nervous System, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluorouracil 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 29/09/11)

Interactions

For a general discussion of antineoplastic drug interactions, see p. 733.3. The actions of fluorouracil may be modified by other drugs including allopurinol, cimetidine, folinic acid, methotrexate, and metronidazole (see also under Administration, p. 796.1). Fluorouracil and fluorouracil prodrugs should not be given with brivudine, sorivudine, and analogues as these are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD) which degrades fluorouracil, and increased fluoropyrimidine toxicity can occur (see also Precautions, above, and Antivirals, below).

References.

1. Jansman FGA. *et al.* Assessing the clinical significance of drug interactions with fluorouracil in patients with colorectal cancer. *Am J Health-Syst Pharm* 2005; 62: 1788–93.

Antineoplastics. *Oxaliplatin*, which is given with fluorouracil and folinic acid in the treatment of colorectal cancer, reduced fluorouracil clearance in a study[1] of 29 patients with colorectal cancer. The effect was delayed and prolonged, lasting about 15 days, and an increase in toxicity correlated with raised fluorouracil concentrations. The mechanism of this interaction is unclear. In contrast, however, another study[2] found no effect of oxaliplatin on fluorouracil pharmacokinetics; the study was not designed to investigate a delayed effect and the dose of oxaliplatin was lower than that used in the first study.

Sorafenib has been reported to have variable effects on fluorouracil exposure.

For reference to the effect of fluorouracil on the action of *paclitaxel*, see Antineoplastics, p. 842.2. For the increased risk of haemolytic-uraemic syndrome that may be seen if fluorouracil is used with *mitomycin*, see Effects on the Kidneys, p. 831.3.

1. Boisdron-Celle M. *et al.* Influence of oxaliplatin on 5-fluorouracil plasma clearance and clinical consequences. *Cancer Chemother Pharmacol* 2002; 49: 235–43.
2. Joel SP. *et al.* Lack of pharmacokinetic interaction between 5-fluorouracil and oxaliplatin. *Clin Pharmacol Ther* 2004; 76: 45–54.

Antiprotozoals. *Metronidazole* increased the toxicity of fluorouracil in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic. No enhanced antineoplastic effect was seen with the combination *in vitro*.[1]

1. Bardakji Z. *et al.* 5-Fluorouracil–metronidazole combination therapy in metastatic colorectal cancer. *Cancer Chemother Pharmacol* 1986; 18: 140–4.

Antivirals. Giving *interferon alfa-2b* with fluorouracil has produced a marked increase in the initial plasma concentration of fluorouracil and a decrease in fluorouracil clearance.[1]

Severe leucopenia, fatal in some cases, has been reported in patients given fluorouracil or fluorouracil prodrugs (such as tegafur) with *sorivudine*.[2,3] A metabolite of sorivudine appears to inhibit dihydropyrimidine dehydrogenase, the primary enzyme responsible for the inactivation of fluorouracil.[3] A fatality has also been reported in a patient treated with the oral prodrug capecitabine who was also given *brivudine*.[4]

1. Czejka MJ, *et al.* Clinical pharmacokinetics of 5-fluorouracil: influence of the biomodulating agents interferon, dipyridamole and folic acid alone and in combination. *Arzneimittelforschung* 1993; **43**: 387–90.
2. Yawata M. Deaths due to drug interaction. *Lancet* 1993; **342**: 1166.
3. 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.
4. Rätz Bravo AE, *et al.* Fatal drug-drug interaction of brivudine and capecitabine. *Acta Oncol* 2009; **48**: 631–3.

Gastrointestinal drugs. Pretreatment with *cimetidine* for 4 weeks increased plasma concentrations of fluorouracil after intravenous and oral doses in 6 patients.[1] The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow. No such effect was seen after single doses of cimetidine in 5 patients or pretreatment for just 1 week in 6. Care is required in patients given both drugs together.

1. Harvey VJ, *et al.* The influence of cimetidine on the pharmacokinetics of 5-fluorouracil. *Br J Clin Pharmacol* 1984; **18**: 421–30.

Pharmacokinetics

Absorption of fluorouracil from the gastrointestinal tract is unpredictable and fluorouracil is usually given intravenously. Little is absorbed when fluorouracil is applied to healthy skin.

After intravenous injection fluorouracil is cleared rapidly from plasma with a mean half-life of about 16 minutes. It is distributed throughout body tissues and fluids (including crossing the blood-brain barrier to appear in the CSF), and disappears from the plasma within about 3 hours. Within the target cell fluorouracil is converted to 5-fluorouridine monophosphate and floxuridine monophosphate (5-fluorodeoxyuridine monophosphate), the former undergoing conversion to the triphosphate which can be incorporated into RNA while the latter inhibits thymidylate synthetase. About 15% of an intravenous dose is excreted unchanged in the urine within 6 hours. The remainder is inactivated mainly in the liver and is catabolised via dihydropyrimidine dehydrogenase (DPD) similarly to endogenous uracil. A large amount is excreted as respiratory carbon dioxide; urea and other metabolites are also produced.

References.

1. Ploylearnsaeng S-A, *et al.* How may anticancer chemotherapy with fluorouracil be individualised? *Clin Pharmacokinet* 2006; **45**: 567–92.

Chronopharmacology. Plasma concentrations of fluorouracil during continuous intravenous infusion are reported to undergo circadian variations of as much as 50% of the mean, peak concentrations occurring in the middle of the night.[1] The variation may be due to a circadian variation in the activity of the enzyme dihydropyrimidine dehydrogenase in blood,[2] but striking interpatient variations in peak concentrations of fluorouracil and peak enzyme activity suggest that any adjustment of infusion times would need to be individualised.[2] It has been suggested that pharmacokinetic monitoring should be investigated as a means of individualising fluorouracil doses with the aim of improving efficacy and reducing toxicity.[3]

1. Petit E, *et al.* Circadian rhythm-varying plasma concentration of 5-fluorouracil during a five-day continuous venous infusion at a constant rate in cancer patients. *Cancer Res* 1988; **48**: 1676–9.
2. Harris BE, *et al.* Relationship between dihydropyrimidine dehydrogenase activity and plasma 5-fluorouracil levels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. *Cancer Res* 1990; **50**: 197–201.
3. Young AM, *et al.* Can pharmacokinetic monitoring improve clinical use of fluorouracil. *Clin Pharmacokinet* 1999; **36**: 391–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ader; Efudix; Oncofu†; Triosules; *Austral.*: Efudix; *Belg.*: Efudix; Fluracedyl; Fluroblastine; *Braz.*: Efurix; Fauldfluor; Neugrast; *Canad.*: Efudex; Fluoroplex†; *Chile*: Efudix; Fluoracilo†; *China*: An Te Fan (安特凡); Fu Ke (福可); Fu Mi Te (弗米特); Fu Ruo Xin (福若欣); Fu Shi Ke (扶时可); Gefente (格芬特); Hua Kang Da (华康达); Ning Lan Xin (宁兰欣); Pu Li Da (普力达); Sen Ting (森汀); Sinofuan (中人氟安); Zuo Ding (佐定); *Cz.*: La-Fu†; *Denm.*: Flurablastin; *Fin.*: Flurablastin; *Fr.*: Efudix; *Ger.*: Benda; Efudix; Haemato-fu†; Neofluor†; Onkofluor†; Ribofluor; *Gr.*: Fluracedyl; Fluroblastin; Uraciflor; *Hong Kong*: Efudix; *Hung.*: Efudix; *India*: Fivefluro†; Fivocil; Fivoflu; Flocil; Flonida; Florac; Flucil; Fludin; Fluonco; Fluracil; Flutas; Kucil; Oncofluor; Oncourcil; *Indon.*: Curacil; Fluracedyl; *Irl.*: Efudix; *Israel*: Efudix; *Malaysia*: Fluracedyl; *Mex.*: Acoflut; Carebin; Efudix; Flurox; Tecflu; *Neth.*: Efudix; Fluracedyl; *Norw.*: Flurablastin; *NZ*: Efudix; *Philipp.*: Fivoflu; Fluonco; Fluoxan†; Fluracedyl; Fluroblastin; Uflahex†; Utoral; *Pol.*: Efudix; *Port.*: Cinkef-U; *Rus.*: Flurox (Флурокс); *S.Afr.*: Efudix; Floracor; Fluracedyl; Fluroblastin; *Singapore*: Efudix†; *Swed.*: Flurablastin†; *Switz.*: Efudix; *Thal.*: Effcil; Fivoflut†; Fluroxt†; *Turk.*: Fluro-5; Oncosil; Oncouracil†; *UK*: Efudix; *USA*: Adrucil; Carac; Efudex; Fluoroplex; *Venez.*: Fivoflu; Fluroblastin.

Multi-ingredient Preparations. *Austria*: Verrumal; *Cz.*: Verrumal; *Ger.*: Actikerall; Verrumal; *Gr.*: Verruca Hermal; *Hong Kong*: Verrumal; *Hung.*: Verrumal; *Israel*: Verrumal; *Malaysia*: Verrumal; *Pol.*: Verrumal; *Port.*: Verrucare; Verrumal; *Singapore*: Verrumal; *Switz.*: Actikerall; Verrumal; *Thai.*: Verrumal; *Turk.*: Verrutol; *UK*: Actikerall.

Pharmacopoeial Preparations

BP 2014: Fluorouracil Cream; Fluorouracil Injection;
USP 36: Fluorouracil Cream; Fluorouracil Injection; Fluorouracil Topical Solution.

Flutamide *(BAN, USAN, rINN)*

Flutamid; Flutamida; Flutamidas; Flutamidi; Flutamidum; Sch-13521; Флутамид.

α′,α′,α′-Trifluoro-4′-nitroisobutyro-*m*-toluidide; α,α,α-Trifluoro-2-methyl-4′-nitro-*m*-propionotoluidide.

$C_{11}H_{11}F_3N_2O_3$=276.2

CAS — 13311-84-7.

ATC — L02BB01.

ATC Vet — QL02BB01.

UNII — 76W6J0943E.

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

Ph. Eur. 8: (Flutamide). A pale yellow, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; practically insoluble in heptane. Protect from light.

USP 36: (Flutamide). A pale yellow, crystalline powder. Practically insoluble in water, in liquid paraffin, and in petroleum spirit; freely soluble in acetone, in ethyl acetate, and in methyl alcohol; soluble in chloroform and in ether. Store in airtight containers. Protect from light.

Uses and Administration

Flutamide is a nonsteroidal compound with anti-androgenic properties which appears to act by inhibiting the uptake and/or binding of androgens in target tissues. It is used, usually with gonadorelin analogues, in the palliative treatment of prostatic carcinoma (p. 712.3). The usual oral dose is 250 mg three times daily. When used in combination therapy UK licensed product information recommends that flutamide treatment should be started at least 3 days before the gonadorelin analogue to suppress any 'flare' reaction; however, in some other countries it is recommended that treatment with both agents be begun simultaneously for optimum effect.

Congenital adrenal hyperplasia. For mention of the use of flutamide with testolactone to block androgenic effects in congenital adrenal hyperplasia, see p. 1603.2.

Hirsutism and alopecia. Anti-androgens (usually cyproterone or spironolactone) are widely used for the drug treatment of hirsutism (p. 2262.1). Flutamide has no particular advantage in this context;[1,2] one study has found flutamide to be more effective than spironolactone in inhibiting hirsutism,[3] but others found them to be of similar efficacy,[4,5] and the risk of hepatotoxicity with flutamide is a problem.[2] Nonetheless, flutamide has continued to be investigated.[6-10]

Flutamide has also been investigated[11] in women with female-pattern hair loss (female androgenetic alopecia).

1. Rittmaster RS. Hyperandrogenism—what is normal? *N Engl J Med* 1992; **327**: 194–6.
2. Rittmaster RS. Hirsutism. *Lancet* 1997; **349**: 191–5.
3. Cusan L, *et al.* Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. *Fertil Steril* 1994; **61**: 281–7.
4. Erenus M, *et al.* Comparison of the efficacy of spironolactone versus flutamide in the treatment of hirsutism. *Fertil Steril* 1994; **61**: 613–6.
5. Moghetti P, *et al.* Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2000; **85**: 89–94.
6. Muderris II, *et al.* Treatment of hirsutism with lowest-dose flutamide (62.5 mg/day). *Gynecol Endocrinol* 2000; **14**: 38–41.
7. Venturoli S, *et al.* Low-dose flutamide (125 mg/day) as maintenance therapy in the treatment of hirsutism. *Horm Res* 2001; **56**: 25–31.
8. Gambineri A, *et al.* Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60**: 241–9.
9. Calaf J, *et al.* Spanish Working Group for Hirsutism. Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. *J Clin Endocrinol Metab* 2007; **92**: 3446–52.
10. Unluhizarci K, *et al.* A comparison between finasteride, flutamide, and finasteride plus flutamide combination in the treatment of hirsutism. *J Endocrinol Invest* 2009; **32**: 37–40.
11. Paradisi R, *et al.* Prospective cohort study on the effects and tolerability of flutamide in patients with female pattern hair loss. *Ann Pharmacother* 2011; **45**: 469–75.

Polycystic ovary syndrome. Flutamide has been used, usually with metformin, in the management of polycystic ovary syndrome (p. 2253.3);[1-5] additive effects have been reported with this combination.

1. Ibáñez L, *et al.* Additive effects of insulin-sensitizing and anti-androgen treatment in young nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 2002; **87**: 2870–4.
2. Ibáñez L, *et al.* Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in nonobese adolescents with ovarian hyperandrogenism. *J Clin Endocrinol Metab* 2003; **88**: 2600–6.
3. Gambineri A, *et al.* Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60**: 241–9.
4. Gambineri A, *et al.* Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. *J Clin Endocrinol Metab* 2006; **91**: 3970–80.
5. Ibáñez L, *et al.* Low-dose pioglitazone, flutamide, metformin plus an estro-progestagen for non-obese young women with polycystic ovary syndrome: increasing efficacy and persistent safety over 30 months. *Gynecol Endocrinol* 2010; **26**: 869–73.

Adverse Effects and Precautions

The most frequently reported adverse effects with flutamide are hot flushes and reversible gynaecomastia or breast tenderness, sometimes accompanied by galactorrhoea. Nausea, vomiting, diarrhoea, increased appetite, anorexia, and sleep disturbances may occur. There have been reports of skin reactions, including epidermal necrolysis, and of liver damage, sometimes fatal. Other adverse effects reported in patients receiving flutamide include anaemias, haemolysis, headache, dizziness, malaise, blurred vision, anxiety, depression, decreased libido, impotence, and hypertension. Abdominal pain, chest pain, dyspnoea, and cough have been reported rarely. Discoloration of the urine to amber or yellow-green can be caused by the presence of flutamide and/or its metabolites.

Flutamide should be used with care in patients with cardiovascular disease because of the possibility of fluid retention. It should also be used with caution in patients with hepatic impairment and is contra-indicated in those with severe impairment. Regular liver function testing is recommended in all patients: therapy should be stopped or dosage reduced if there is evidence of hepatotoxicity.

Effects on the blood. A report[1] of methaemoglobinaemia in an elderly man was attributed to flutamide. A study[2] of 45 patients given flutamide found no cases of methaemoglobinaemia, but the authors noted a further 3 published case reports.

1. Schott AM, *et al.* Flutamide-induced methemoglobinemia. *DICP Ann Pharmacother* 1991; **25**: 600–1.
2. Schulz M, *et al.* Lack of methemoglobinemia with flutamide. *Ann Pharmacother* 2001; **35**: 21–5.

Effects on the liver. Hepatitis occurred in a 79-year old man taking flutamide 750 mg daily as sole therapy after a prostatectomy,[1] but a subsequent study[2] in 1091 patients given flutamide 250 mg three times daily as part of a regimen for prostate cancer found marked signs of liver damage only in 4, of whom only 2 had clinical evidence of hepatotoxicity. In the USA, the FDA had 46 reports of patients with hepatotoxicity associated with flutamide up to December 1994. Of these patients, 20 died from progressive liver disease.[3] Further cases have continued to be reported,[4-7] including in women receiving low doses for hirsutism.[7,8] Early tapering of the dose, stopping therapy, or switching to another anti-androgen may resolve hepatotoxic effects.[9] Patients with chronic viral hepatitis may be at higher risk of developing hepatotoxicity with anti-androgen therapy.[10]

1. Hart W, Stricker BHC. Flutamide and hepatitis. *Ann Intern Med* 1989; **110**: 943–4.
2. Gomez J-L, *et al.* Incidence of liver toxicity associated with the use of flutamide in prostate cancer patients. *Am J Med* 1992; **92**: 465–70.
3. Wysowski DK, Fourcroy JL. Flutamide hepatotoxicity. *J Urol (Baltim ort)* 1996; **155**: 209–12. Correction *ibid.* 396.
4. Garcia Cortes M, *et al.* Flutamide-induced hepatotoxicity: report of a case series. *Rev Esp Enferm Dig* 2001; **93**: 423–32. Correction. *ibid.*; 634.
5. Lubbert C, *et al.* Ikterus und schwere Leberfunktionsstorung bei der hormonablativen Behandlung des Prostatakarzinoms. *Internist (Berl)* 2004; **45**: 333–40.
6. Osculati A, Castiglioni C. Fatal liver complications with flutamide. *Lancet* 2006; **367**: 1140–1.
7. Brahm J, *et al.* Acute and fulminant hepatitis induced by flutamide: case series report and review of the literature. *Ann Hepatol* 2011; **10**: 93–8.
8. Castelo-Branco C, Del Pino M. Hepatotoxicity during low-dose flutamide treatment for hirsutism. *Gynecol Endocrinol* 2009; **25**: 419–22.
9. Lin ADY, *et al.* Antiandrogen-associated hepatotoxicity in the management of advanced prostate cancer. *J Chin Med Assoc* 2003; **66**: 735–40.
10. Pu Y-S, *et al.* Antiandrogen hepatotoxicity in patients with chronic viral hepatitis. *Eur Urol* 1999; **36**: 293–7.

Effects on the lungs. In a review[1] of 78 cases of pneumonitis reported to the FDA between 1998 and 2000 that were associated with bicalutamide, flutamide, or nilutamide, it was found that 14 patients had died of respiratory failure. It was estimated that the incidence of pneumonitis

was highest for nilutamide (0.77%), but lower for flutamide (0.04%) and bicalutamide (0.01%).

1. Bennett CL, *et al.* Pneumonitis associated with nonsteroidal antiandrogens: presumptive evidence of a class effect. *Ann Intern Med* 2002; 137: 625.

Effects on the skin. Photosensitivity reactions have been reported in patients receiving flutamide.[1,2] Some consider it to be an early manifestation of SLE.[2]

1. Fujimoto M, *et al.* Photosensitive dermatitis induced by flutamide. *Br J Dermatol* 1996; 135: 496–7.
2. Kaur C, Thami GP. Flutamide-induced photosensitivity: is it a forme fruste of lupus? *Br J Dermatol* 2003; 148: 603–4.

Gynaecomastia. Gynaecomastia (p. 2264.3) and breast pain are frequent adverse effects of nonsteroidal anti-androgens used to treat prostate cancer. Nearly 90% of patients treated with bicalutamide in the Early Prostate Cancer programme had breast pain, gynaecomastia, or both.[1] Some patients will accept gynaecomastia as a tolerable adverse effect of therapy but others will require specific treatment. The risk of breast changes can be reduced by the use of prophylactic low-dose irradiation of the breast area before nonsteroidal anti-androgen therapy is started. However, skin irritation can occur, and the long-term risk for development of breast cancer is unknown. Irradiation is unlikely to be effective once breast enlargement has occurred but it can help to reduce pain. Empirical use of oral analgesics or topical local anaesthetics may be considered for breast pain. Specific surgical treatment to reduce breast tissue includes liposuction and breast tissue excision.[2,3]

Hormonal therapy using tamoxifen or anastrozole has been suggested, largely based on reports of benefit in various patient groups with gynaecomastia.[1,2] Two randomised controlled studies[4,5] of men who were treated with bicalutamide for prostate cancer found that prophylactic tamoxifen was effective for the prevention of gynaecomastia and breast pain, but that anastrozole was no better than placebo. One of these studies[5] also assessed the use of these drugs as treatment and found that gynaecomastia and breast pain resolved in at least 65% of patients treated with tamoxifen, but only in about 18% of those treated with anastrozole. Tamoxifen is considered to be more effective than radiotherapy for prevention of gynaecomastia.[3]

1. Sieber PR. Treatment of bicalutamide-induced breast events. *Expert Rev Anticancer Ther* 2007; 7: 1773–9.
2. Leibovitch I, *et al.* Management options for gynaecomastia and breast pain associated with nonsteroidal antiandrogen therapy: case studies in context. *Clin Drug Invest* 2003; 23: 205–15.
3. Di Lorenzo G, *et al.* Management of gynaecomastia in patients with prostate cancer: a systematic review. *Lancet Oncol* 2005; 6: 972–9.
4. Boccardo F, *et al.* Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol* 2005; 23: 808–15.
5. Saltzstein D, *et al.* Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; 8: 75–83.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flutamide 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 05/09/11)

Interactions

Flutamide may increase the effect of warfarin, see Antineoplastics, p. 1532.2.

Pharmacokinetics

Flutamide is reported to be rapidly and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 hour after a dose. It is rapidly and extensively metabolised; the major metabolite (2-hydroxyflutamide) possesses anti-androgenic properties. The half-life of the metabolite is about 6 hours. Both flutamide and 2-hydroxyflutamide are more than 90% bound to plasma proteins. Excretion is mainly in the urine with only minor amounts appearing in the faeces.

References.

1. Radwanski E, *et al.* Single and multiple dose pharmacokinetic evaluation of flutamide in normal geriatric volunteers. *J Clin Pharmacol* 1989; 29: 554–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Asoflut; Dedile; Flutaplex; Flutepan; Flutrax; *Austral.*: Eulexin; Flutamin; *Austria*: Flutabene; Flutastad; Fugerel; *Belg.*: Eulexin; Flutaplex; *Braz.*: Eulexin; Tecnoflut; Teflut; *Canad.*: Euflex; *Chile*: Drogenil†; Etaconil; Flulem†; Ilidar; *China*: Fugerel (福至尔); *Cz.*: Andraxan†; Flucinom; Flumed; Flutaplex; Prostandril†; *Denm.*: Eulexin†; Fluprosin; Profamid; *Fin.*: Eulexin†; Profamid; *Fr.*: Eulexine; Prostadirex; *Ger.*: Flumid†; Fluta; Fugerel†; Prostica†; *Gr.*: Adiprost†; Andraxan; Antipros; Elbat; Flucinom; Flutaplex; Palistop; Prostamide; Rikital; Rosiniol; Tremexal; *Hong Kong*: Codalan†; Fugerel; *Hung.*: Fluprost; Flutam; Flutasin; Fugerel; Prosztika; *India*: Cytomid; Drogenil; Flutam; Flutide; Prostamid; *Indon.*: Flutaplex; Fugerel; *Irl.*: Androstat†; Drogenil; *Ital.*: Eulexin; Fluprost; Ricalide; *Malaysia*: Eumide; Fluta-Cell; Flutaplex; *Mex.*: Eulexin†; Flimutal; Flulem; Tafenil; *Neth.*: Flutaplex†; *Norw.*: Eulexin; *NZ*: Eulexin; Flutamin; *Philipp.*: Fugerel; Prostanon; *Pol.*: Apo-Flutam; Fugerel†; Prostandril†; *Port.*: Drogenil; Eulexin; Prosneo; *Rus.*: Flucinom (Флуцином); Flutamid (Флутамид); Flutaplex (Флутаплекс); Frugyl (фругил); *S. Afr.*: Eulexin; Flutahexal; Flutaplex; *Singapore*: Flutan; Fugerel; *Spain*: Eulexin; Grisetin; Oncosal†; Prostacur; *Swed.*: Eulexin; *Switz.*: Flucinome†; *Thai.*: Andraxan; Flulem; Flutan; Flutaplex; Fugerel; *Turk.*: Andraxan; Eulexin; *UK*: Chimax; Drogenil†; *Ukr.*: Flutafarm (Флутафарм); *Venez.*: Etaconil; Eulexin.

Pharmacopoeial Preparations
USP 36: Flutamide Capsules.

Formestane *(BAN, rINN)* ⊗

CGP-32349; Formestaani; Formestan; Formestano; Formestanum; 4-Hydroxyandrostenedione; 4-OHA; 4-OHAD; Форместан.

4-Hydroxyandrost-4-ene-3,17-dione.

$C_{19}H_{26}O_3$=302.4

CAS — 566-48-3.

ATC — L02BG02.

ATC Vet — QL02BG02.

UNII — PUB9T8T355.

Profile

Formestane, like exemestane (p. 792.2), is a steroidal inhibitor of the aromatase (oestrogen synthetase) system responsible for the production of oestrogens from androgens. It has been used for its anti-oestrogenic properties in the endocrine treatment of advanced breast cancer in postmenopausal women.

Irritation and pain at the site of intramuscular injection have been reported; injection into or near the sciatic nerve has resulted in pain and nerve trauma. Hypersensitivity reactions have occurred.

Reviews.

1. Wiseman LR, McTavish D. Formestane: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of breast cancer and prostatic cancer. *Drugs* 1993; 45: 66–84.
2. Anonymous. Formestane for advanced breast cancer in postmenopausal women. *Drug Ther Bull* 1993; 31: 85–7.
3. Carlini P, *et al.* Formestane, a steroidal aromatase inhibitor after failure of non-steroidal aromatase inhibitors (anastrozole and letrozole): is a clinical benefit still achievable? *Ann Oncol* 2001; 12: 1539–43.

Effects on carbohydrate metabolism. Recurrent hypoglycaemic episodes developed in a diabetic patient previously well maintained on gliclazide after addition of formestane to treatment for metastatic breast cancer.[1] Episodic hypoglycaemia continued after dosage reduction, and eventually withdrawal, of gliclazide, suggesting that the effect was not simply an interaction with the sulfonylurea.

1. Brankin E, *et al.* Hypoglycaemia associated with formestane treatment. *BMJ* 1997; 314: 869.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Lentaron†; *Turk.*: Lentaron†.

Forodesine Hydrochloride *(USAN, rINNM)*

BCX-1777 (forodesine or forodesine hydrochloride); Forodésine, Chlorhydrate de; Forodesini Hydrochloridum; Hidrocloruro de forodesina; Фородезина Гидрохлорид.

(-)-7-[(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-yl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one hydrochloride.

$C_{11}H_{14}N_4O_4$,HCl=302.7

CAS — 209799-67-7 (forodesine); 284490-13-7 (forodesine hydrochloride).

UNII — 65N82Y9U73.

Profile

Forodesine is an inhibitor of purine nucleoside phosphorylase. It is under investigation in the treatment of T-cell lymphomas, chronic lymphocytic leukaemia, and acute lymphoblastic leukaemia.

Fosbretabulin *(rINN)*

CA4P; Combretastatin A4 Phosphate; CS-A4 (combretastatin A4); Fosbretabulina; Fosbrétabuline; Fosbretabulinum; NSC-348103 (combretastatin); Фосбретабулин.

2-Methoxy-5-[(1*Z*)-2-(3,4,5-trimethoxyphenyl)ethenyl]-phenyl dihydrogen phosphate.

$C_{18}H_{21}O_8P$=396.3

CAS — 82855-09-2 (combretastatin); 117048-59-6 (combretastatin A4); 222030-63-9 (combretastatin A4 phosphate); 168555-66-6 (combretastatin A4 disodium phosphate).

UNII — I5590ES2QZ.

NOTE. The name Zybrestat has been used as a trade mark for fosbretabulin.

Profile

Fosbretabulin is a synthetic derivative of combretastatin compounds originally isolated from the African bush-willow tree (Cape bush-willow; *Combretum caffrum*). It is described as a vascular targeting agent that reduces blood flow to tumours by disrupting the endothelial cells of newly formed blood vessels, and is under investigation for the treatment of thyroid, ovarian, and non-small cell lung cancer. It is also being investigated topically for ophthalmological disease, particularly age-related macular degeneration.

Fotemustine *(BAN, rINN)*

Fotemustin; Fotemustina; Fotémustine; Fotemustinum; S-10036; Фотемустин.

(±)-Diethyl {1-[3-(2-chloroethyl)-3-nitrosoureido]ethyl}phosphonate.

$C_9H_{19}ClN_3O_5P$=315.7

CAS — 92118-27-9.

ATC — L01AD05.

ATC Vet — QL01AD05.

UNII — GQ7JL9P5I2.

Profile

Fotemustine is a nitrosourea derivative and alkylating agent with actions similar to those of carmustine (p. 761.2). It is used in the treatment of disseminated malignant melanoma (p. 714.3), particularly where cerebral metastases are present, and has been tried in primary malignancies of the brain (p. 701.2). When used as a single agent it is licensed for intravenous or intra-arterial infusion in usual doses of 100 mg/m² weekly for 3 weeks to induce remission, followed after 4 to 5 weeks, if blood counts permit, by maintenance dosage with 100 mg/m² every 3 weeks. Intravenous infusions are given over 1 hour and intra-arterial infusions over 4 hours. Liver function should be monitored regularly during induction treatment. Regular blood counts should be taken and dosage should be reduced or withheld if white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p. 730.3). Bone-marrow suppression may be delayed, with the nadir of the white cell counts 5 or 6 weeks after dosing. Solutions for infusion must be freshly prepared and protected from light.

References.

1. Marzolini C, *et al.* Pharmacokinetics of temozolomide in association with fotemustine in malignant melanoma and malignant glioma patients: comparison of oral, intravenous, and hepatic intra-arterial administration. *Cancer Chemother Pharmacol* 1998; 42: 433–40.
2. Fazeny-Dorner B, *et al.* Second-line chemotherapy with dacarbazine and fotemustine in nitrosourea-pretreated patients with recurrent glioblastoma multiforme. *Anticancer Drugs* 2003; 14: 437–42.
3. Avril MF, *et al.* Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clin Oncol* 2004; 22: 1118–25.
4. Ozkan M, *et al.* Post-operative sequential chemo-radiotherapy in high-grade cerebral gliomas with fotemustine. *J Chemother* 2004; 16: 298–302.
5. Bonenkamp JJ, *et al.* Isolated limb infusion with fotemustine after dacarbazine chemosensitisation for inoperable loco-regional melanoma recurrence. *Eur J Surg Oncol* 2004; 30: 1107–12.
6. Peters S, *et al.* Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. *Ann Oncol* 2006; 17: 578–83.
7. Gill S, *et al.* Long-term survival and secondary acute leukemia after fotemustine therapy for metastatic melanoma. *J Clin Oncol* 2007; 25: 4493–4.
8. Scoccianti S, *et al.* Second-line chemotherapy with fotemustine in temozolomide-pretreated patients with relapsing glioblastoma: a single institution experience. *Anticancer Drugs* 2008; 19: 613–20.
9. Mangiacavalli S, *et al.* Efficacy and safety of fotemustine for the treatment of relapsed and refractory multiple myeloma patients. *Eur J Haematol* 2009; 82: 240–1.
10. Addeo R, *et al.* Fotemustine and recurrent glioblastoma: possible new opportunities for an old drug. *Cancer Chemother Pharmacol* 2009; 64: 863–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Muforan; *Austral.*: Muphoran; *Austria*: Muphoran; *Belg.*: Muphoran; *Braz.*:

Muphoran; *China*: Muphoran (武活龙); *Cz.*: Mustophoran; *Fr.*: Muphoran; *Gr.*: Muphoran†; *Hung.*: Mustophoran; *Israel*: Muphoran; *Ital.*: Muphoran; *NZ*: Muphoran; *Pol.*: Mustophoran; *Port.*: Muphoran; *Rus.*: Mustophoran (Мюстофоран); *Spain*: Mustoforan; *Turk.*: Muphoran; *Ukr.*: Mustophoran (Мюстофоран).

Fulvestrant *(BAN, USAN, rINN)* ⊗

Fulvestrantum; ICI-182780; ZD-9238; ZM-182780; Фульвестрант.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol.

$C_{32}H_{47}F_5O_3S$=606.8

CAS — 129453-61-8.

ATC — L02BA03.

ATC Vet — QL02BA03.

UNII — 22X328QOC4.

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

Ph. Eur. 8: (Fulvestrant). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane. Store at a temperature of 2 degrees to 8 degrees. Protect from light. If the substance is sterile, store in airtight containers.

USP 36: (Fulvestrant). A mixture of the diastereoisomers A and B. A white powder. Freely soluble in alcohol. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Fulvestrant is an oestrogen antagonist that downregulates the oestrogen receptor and is used for the treatment of oestrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women (p. 702.1); it is given when disease has relapsed or progressed during or after treatment with anti-oestrogens. Fulvestrant is given intramuscularly in a dose of 500 mg every 2 weeks for the first 3 doses, then every month thereafter. Half the dose (250 mg) is injected into each buttock concurrently. For doses in hepatic impairment, see Administration in Hepatic Impairment, below.

References.

1. Buzdar AU. Fulvestrant: a new type of estrogen receptor antagonist for the treatment of advanced breast cancer. *Drugs Today* 2004; **40**: 751–64.
2. Bundred N. Preclinical and clinical experience with fulvestrant (Faslodex) in postmenopausal women with hormone receptor-positive advanced breast cancer. *Cancer Invest* 2005; **23**: 173–81.
3. Buzdar AU, Robertson JFR. Fulvestrant: pharmacologic profile versus existing endocrine agents for the treatment of breast cancer. *Ann Pharmacother* 2006; **40**: 1572–83.
4. Flemming J, *et al.* Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: a systematic review. *Breast Cancer Res Treat* 2009; **115**: 255–68.
5. de la Haba Rodríguez JR, *et al.* Fulvestrant in advanced male breast cancer. *Ann Oncol* 2009; **20**: 1896–7.
6. Argenta PA, *et al.* A phase II study of fulvestrant in the treatment of multiply-recurrent epithelial ovarian cancer. *Gynecol Oncol* 2009; **113**: 205–9.
7. Valachis A, *et al.* Fulvestrant in the treatment of advanced breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Oncol Hematol* 2010; **73**: 220–7.
8. Kabos P, Borges VF. Fulvestrant: a unique antiendocrine agent for estrogen-sensitive breast cancer. *Expert Opin Pharmacother* 2010; **11**: 807–16.
9. Johnston SJ, Cheung KL. Fulvestrant—a novel endocrine therapy for breast cancer. *Curr Med Chem* 2010; **17**: 902–14.
10. Gasent Blesa JM, *et al.* Experience with fulvestrant acetate in castration-resistant prostate cancer patients. *Ann Oncol* 2010; **21**: 1131–2.
11. Di Leo A, *et al.* Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol* 2010; **28**: 4594–4600.
12. Warm M, *et al.* Benefits of early and prolonged fulvestrant treatment in 848 postmenopausal advanced breast cancer patients. *Breast Cancer Res Treat* 2011; **125**: 127–36.
13. Masci G, *et al.* Fulvestrant for advanced male breast cancer patients: a case series. *Ann Oncol* 2011; **22**: 985.
14. Oakman C, *et al.* Fulvestrant in the management of postmenopausal women with advanced, endocrine-responsive breast cancer. *Future Oncol* 2011; **7**: 173–86.
15. Croxtall JD, McKeage K. Fulvestrant: a review of its use in the management of hormone receptor-positive metastatic breast cancer in postmenopausal women. *Drugs* 2011; **71**: 363–80.

Administration in hepatic impairment. Exposure to fulvestrant is increased in patients with moderate hepatic impairment (Child-Pugh class B), and so in the USA a reduced dose of 250 mg as a single intramuscular injection into one buttock is given every 2 weeks for the first 3 doses and monthly thereafter; however, such dose adjustment is not recommended in the UK. Fulvestrant has not been studied in those with severe hepatic impairment (Child-Pugh class C).

Adverse Effects and Precautions

The most commonly reported adverse effects of fulvestrant are gastrointestinal disturbances, headache, musculoskeletal and abdominal pain, hot flushes, cough, dyspnoea, asthenia, and increases in liver enzymes. Injection site reactions can occur. Other common adverse effects include rash, urinary-tract infections, and thromboembolic events. Hypersensitivity reactions, including angioedema and urticaria, can occur. Vaginal bleeding or infection, vertigo and leucopenia have been reported rarely.

There is a lack of data on the use of fulvestrant in those with severe hepatic impairment (Child-Pugh class C), and use in these patients is not recommended in some countries. It should be used with caution in those with lesser degrees of hepatic impairment; a reduction in dose may be required (see Administration in Hepatic Impairment, above). Fulvestrant should also be used with caution in those with severe renal impairment (creatinine clearance less than 30 mL/minute). Because it must be given by intramuscular injection, fulvestrant should be used with caution in patients with bleeding tendencies, thrombocytopenia, or who are taking anticoagulants.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fulvestrant 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 05/09/11)

Pharmacokinetics

Fulvestrant is slowly absorbed after intramuscular injection and peak plasma concentrations occur after about 7 days. Steady-state concentrations are reached after about 3 to 6 doses (given monthly). Fulvestrant is highly bound to plasma proteins. It is metabolised mainly in the liver to several metabolites, some of which have oestrogen antagonist activity, and is excreted in the faeces. After intramuscular injection fulvestrant has a half-life of about 40 to 50 days.

References.

1. Robertson JFR, *et al.* Pharmacokinetic profile of intramuscular fulvestrant in advanced breast cancer. *Clin Pharmacokinet* 2004; **43**: 529–38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Faslodex; *Austral.*: Faslodex; *Austria*: Faslodex; *Belg.*: Faslodex; *Braz.*: Faslodex; *Canad.*: Faslodex; *Chile*: Faslodex; *China*: Faslodex (芙仕得); *Cz.*: Faslodex; *Denm.*: Faslodex; *Fin.*: Faslodex; *Fr.*: Faslodex; *Ger.*: Faslodex; *Gr.*: Faslodex; *Hong Kong*: Faslodex; *Hung.*: Faslodex; *India*: Faslodex; *Irl.*: Faslodex; *Israel*: Faslodex; *Ital.*: Faslodex; *Jpn*: Faslodex; *Malaysia*: Faslodex; *Mex.*: Faslodex; *Neth.*: Faslodex; *Norw.*: Faslodex; *NZ*: Faslodex†; *Philipp.*: Faslodex; *Pol.*: Faslodex; *Port.*: Faslodex; *Rus.*: Faslodex (Фаслодекс); *S.Afr.*: Faslodex; *Singapore*: Faslodex; *Spain*: Faslodex; *Swed.*: Faslodex; *Switz.*: Faslodex; *Thai.*: Faslodex; *Turk.*: Faslodex; *UK*: Faslodex; *Ukr.*: Faslodex (Фаслодекс); *USA*: Faslodex; *Venez.*: Faslodex.

Gefitinib *(BAN, USAN, rINN)*

Gefitinib; Gefitinibum; ZD-1839; Гефитиниб.

N-(3-Chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine.

$C_{22}H_{24}ClFN_4O_3$=446.9

CAS — 184475-35-2.

ATC — L01XE02.

ATC Vet — QL01XE02.

UNII — S65743JHBS.

Uses and Administration

Gefitinib is a selective inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR). EGFR is expressed on the surface of cells and is implicated in the process of cell growth and proliferation. Gefitinib is used for the management of locally advanced or metastatic non-small cell lung cancer (NSCLC; p. 710.2) in adults. In the UK and EU, gefitinib is indicated for those patients with tumours with activating mutations of the EGFR tyrosine kinase. In the USA, use is restricted to those patients who are currently receiving and benefiting from gefitinib, or to those who have previously benefited from therapy; it is only used after failure of both platinum-based and docetaxel chemotherapy regimens.

The recommended dose of gefitinib is 250 mg orally once daily. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For patients with diarrhoea or cutaneous adverse reactions, gefitinib therapy may be interrupted for up to 14 days, after which it may be re-instated at the same dose; if therapy is not tolerated after such an interruption, gefitinib should be stopped, and alternative treatment considered.

In patients who are given a potent CYP3A4 inducer, a dose increase of gefitinib to 500 mg orally once daily should be considered; clinical response and adverse effects should be carefully monitored.

Caution is advised in some patients with hepatic or renal impairment (see below).

References.

1. Culy CR, Faulds D. Gefitinib. *Drugs* 2002; **62**: 2237–48.
2. Kris MG, *et al.* Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003; **290**: 2149–58.
3. Liu CY, Seen S. Gefitinib therapy for advanced non-small-cell lung cancer. *Ann Pharmacother* 2003; **37**: 1644–53.
4. Cersosimo RJ. Gefitinib: a new antineoplastic for advanced non-small-cell lung cancer. *Am J Health-Syst Pharm* 2004; **61**: 889–98.
5. Tanovic A, Alfaro V. Gefitinib: current status in the treatment of non-small cell lung cancer. *Drugs Today* 2004; **40**: 809–27.
6. Birnbaum A, Ready N. Gefitinib therapy for non-small cell lung cancer. *Curr Treat Options Oncol* 2005; **6**: 75–81.
7. Shah NT, *et al.* Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol* 2005; **23**: 165–74.
8. Blackhall F, *et al.* Where next for gefitinib in patients with lung cancer? *Lancet Oncol* 2006; **7**: 499–507.
9. Maruyama R, *et al.* Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol* 2008; **26**: 4244–52.
10. Kim ES, *et al.* Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008; **372**: 1809–18.
11. Sanford M, Scott LJ. Gefitinib: a review of its use in the treatment of locally advanced/metastatic non-small cell lung cancer. *Drugs* 2009; **69**: 2303–28.

Administration. Gefitinib tablets may be taken with or without food, and are preferably swallowed whole. However, for those patients who have difficulty swallowing a whole tablet may be dispersed in half a glass of non-carbonated water; the tablet should not be crushed, and the glass of water should be swirled or stirred until the tablet is fully dispersed (this may take 10 to 20 minutes). The dispersion should be consumed immediately (UK licensed product information specifies this as being within 1 hour), and the glass rinsed with some more water, which should also be consumed.

This dispersion is also suitable for use through a nasogastric or gastrostomy tube.

Administration in children. For reference to the use of gefitinib with irinotecan in the treatment of children with refractory solid tumours, see Administration, under Irinotecan, p. 813.1.

Administration in hepatic impairment. UK licensed product information states that, compared with healthy control subjects, exposure to gefitinib was tripled in patients with moderate or severe hepatic impairment (classified according to Child-Pugh criteria) due to cirrhosis. In patients with tumours, gefitinib pharmacokinetics in those with hepatic impairment were similar to those patients with normal hepatic function.

US licensed product information states that no dosage adjustment is needed in patients with moderate to severe hepatic impairment due to liver metastases: in the UK, patients with moderate to severe impairment (Child-Pugh B or C) due to cirrhosis should be closely monitored for adverse effects.

Administration in renal impairment. UK licensed product information states that no dose adjustment of gefitinib is needed in patients with a creatinine clearance (CC) greater than 20 mL/minute. Caution is advised in those patients with a CC of 20 mL/minute or less, due to limited data in these patients.

US licensed product information states that, while no studies have been conducted in patients with severe renal impairment, gefitinib and its metabolites are not significantly excreted via the kidney, and no dose adjustment is required on the basis of renal function.

Adverse Effects, Treatment, and Precautions

The adverse effects of gefitinib are similar to those of erlotinib (p. 789.2), although severe hepatic and renal toxicity seems to be rare. Haemorrhage, such as epistaxis or haematuria, is common. There are also reports of tumour haemorrhage, sometimes fatal, after use of gefitinib in patients with head and neck cancer.

Other common adverse effects include nausea, vomiting, stomatitis, dry mouth, alopecia, nail disorders, asthenia, pyrexia, proteinuria, and elevations in blood creatinine.

References.

1. Inoue A, *et al.* Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; **361**: 137–9.
2. Forsythe B, Faulkner K. Overview of the tolerability of gefitinib (IRESSA®) monotherapy: clinical experience in non-small-cell lung cancer. *Drug Safety* 2004; **27**: 1081–92.

Effects on survival. In chemotherapy-naive patients with advanced non-small cell lung cancer, gefitinib, given with gemcitabine plus cisplatin,[1] or paclitaxel plus carboplatin,[2] showed no survival advantage over chemotherapy

without gefitinib. In a large study in patients with non-small cell lung cancer given gefitinib or placebo, after failure of one or two previous treatment regimens, no survival benefit was shown with gefitinib;[3] recommendations restricting the use of gefitinib to selected patients have been made in the USA (see Uses and Administration, p. 800.2).[4] However, a subset analysis of study data found an improvement in survival in a subgroup of patients of Asian origin.[5] In reports of the IMEX study in patients with head and neck cancer, no survival advantage for gefitinib was found when compared with methotrexate; an increased incidence of tumour haemorrhage was seen in those treated with gefitinib.[6] Studies have suggested that there are subgroups of patients with non-small cell lung cancer who have specific biomarkers or mutations in the epidermal growth factor receptor (EGFR) gene which correlate with clinical response to gefitinib.[7-10] A subsequent study established EGFR mutation status as the most important independent predictor of survival benefit with gefitinib treatment.[11]

A small retrospective study found that further treatment with gefitinib prolonged survival in patients who were initially responsive, but who had subsequent disease progression upon stopping therapy.[12]

1. Giaccone G, *et al.* Gefitinib in combination with gemcitabine and cisplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol* 2004; **22:** 777–84.
2. Herbst RS, *et al.* Gefitinib in combination with paclitaxel and carboplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol* 2004; **22:** 785–94.
3. Thatcher N, *et al.* Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; **366:** 1527–37.
4. FDA Public Health Advisory. New labeling and distribution program for gefitinib (Iressa) (issued 17/06/05). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm163112.htm (accessed 21/07/10)
5. Chang A, *et al.* Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. *J Thorac Oncol* 2006; **1:** 847–55.
6. AstraZeneca, Canada. Health Canada endorsed important safety information on Iressa (gefitinib): lack of survival benefit and increased incidence of tumour haemorrhage in association with IRESSA in patients with squamous cell carcinoma of the head and neck (SCCHN) (issued 1st December 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/Iressa_4_hpc-cps-eng.php (accessed 23/09/09)
7. Lynch TJ, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350:** 2129–39.
8. Paez JG, *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304:** 1497–1500.
9. Pao W, Miller VA. Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non–small-cell lung cancer: current knowledge and future directions. *J Clin Oncol* 2005; **23:** 2556–68.
10. Hirsch FR, *et al.* Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 5034–42.
11. Satouchi M, *et al.* Predictive factors associated with prolonged survival in patients with advanced non-small-cell lung cancer (NSCLC) treated with gefitinib. *Br J Cancer* 2007; **96:** 1191–6.
12. Yokouchi H, *et al.* Clinical benefit of readministration of gefitinib for initial gefitinib-responders with non-small cell lung cancer. *BMC Cancer* 2007; **7:** 51.

Interactions

Gefitinib is metabolised via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Inhibitors of CYP3A4, such as itraconazole, can decrease the clearance of gefitinib and increase exposure. The increase in gefitinib plasma concentration caused by potent CYP3A4 inhibitors may be higher in patients with CYP2D6 poor-metaboliser genotype. In CYP2D6 extensive metabolisers, use of gefitinib with potent CYP2D6 inhibitors may double gefitinib concentrations. Patients taking gefitinib who are also treated with potent CYP3A4 or CYP2D6 inhibitors should be closely monitored for adverse reactions.

Conversely, CYP3A4 inducers, such as rifampicin, can reduce exposure to gefitinib. Use with potent CYP3A4 inhibitors should be avoided, but if not, dose adjustment is recommended (see Uses and Administration, p. 800.2), and the patient's response should be carefully monitored.

Substances that cause a significant and sustained elevation in gastric pH may reduce gefitinib bioavailability; high doses of short-acting antacids may have a similar effect if taken regularly and at the same time as gefitinib, and ranitidine, with or without sodium bicarbonate, decreased exposure to gefitinib by over 40%.

Elevations in INR or bleeding events have been reported in patients taking gefitinib with warfarin.

Gefitinib also has limited potential to inhibit the cytochrome P450 isoenzyme CYP2D6; substrates of CYP2D6 may need dose modification when given with gefitinib (such as metoprolol, see p. 1322.1).

1. Swaisland HC, *et al.* Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet* 2005; **44:** 1067–81.

Pharmacokinetics

Gefitinib is slowly absorbed, and peak plasma concentrations occur 3 to 7 hours after an oral dose. Bioavailability is about 60%, and is not significantly altered by food. Gefitinib is extensively distributed throughout the body. Plasma protein binding is about 90%. Gefitinib is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6; the major metabolite is *O*-desmethylgefitinib, which is much less potent than gefitinib, and unlikely to contribute to its clinical activity. Gefitinib is excreted mainly as metabolites via the faeces; renal elimination of gefitinib and its metabolites accounts for less than 4% of the dose given. The elimination half-life is reported to be about 41 to 48 hours.

1. Swaisland HC, *et al.* Single-dose clinical pharmacokinetic studies of gefitinib. *Clin Pharmacokinet* 2005; **44:** 1165–77.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Iressa; *Austral.*: Iressa; *Austria*: Iressa; *Belg.*: Iressa; *Braz.*: Iressa; *Canad.*: Iressa; *Chile*: Iressa; *China*: Iressa (易瑞沙); *Cz.*: Iressa; *Denm.*: Iressa; *Fr.*: Iressa; *Ger.*: Iressa; *Gr.*: Iressa; *Hong Kong*: Iressa; *Hung.*: Iressa; *India*: Gefitero; Gefonib; Geftib; Geftilon; Geftinat; *Indon.*: Iressa; *Irl.*: Iressa; *Israel*: Iressa; *Malaysia*: Iressa; *Mex.*: Iressa; *Neth.*: Iressa; *Norw.*: Iressa; *NZ*: Iressa; *Philipp.*: Iressa; *Pol.*: Iressa; *Port.*: Iressa; *Rus.*: Iressa (Иресса); *Singapore*: Iressa; *Spain*: Iressa; *Swed.*: Iressa; *Switz.*: Iressa; *Thai.*: Iressa; *UK*: Iressa; *USA*: Iressa†; *Venez.*: Iressa.

Gemcitabine Hydrochloride

(BANM, USAN, rINNM)

Gemcitabina, hidrocloruro de; Gemcitabine, Chlorhydrate de; Gemcitabinhydrochlorid; Gemcitabini Hydrochloridum; Hidrocloruro de gemcitabina; LY-188011 (gemcitabine); Гемцитабина Гидрохлорид.

4-Amino-1-(2-deoxy-2,2-difluoro-β-D-ribofuranosyl)pyrimidin-2(1*H*)-one hydrochloride; 2′-Deoxy-2′,2′-difluorocytidine hydrochloride.

$C_9H_{11}F_2N_3O_4HCl$=299.7

CAS — 95058-81-4 (gemcitabine); 122111-03-9 (gemcitabine hydrochloride).

ATC — L01BC05.

ATC Vet — QL01BC05.

UNII — U347PV74IL

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

Ph. Eur. 8: (Gemcitabine Hydrochloride). A white or almost white powder. Soluble in water; slightly soluble in methyl alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 2.0 to 3.0.

USP 36: (Gemcitabine Hydrochloride). A white to off-white solid. Soluble in water; practically insoluble in alcohol and in polar organic solvents; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers.

Incompatibility. Gemcitabine hydrochloride was reported to be physically incompatible with aciclovir sodium, amphotericin B, cefoperazone sodium, cefotaxime sodium, furosemide, ganciclovir sodium, imipenem with cilastatin sodium, irinotecan, methotrexate sodium, methylprednisolone sodium succinate, mezlocillin sodium, mitomycin, piperacillin sodium, piperacillin sodium with tazobactam, and prochlorperazine edisilate during simulated Y-site administration.[1]

1. Trissel LA, *et al.* Compatibility of gemcitabine hydrochloride with 107 selected drugs during simulated Y-site injection. *J Am Pharm Assoc* 1999; **39:** 514–18.

Uses and Administration

Gemcitabine is an analogue of cytarabine (p. 774.1) that is metabolised intracellularly to active diphosphate and triphosphate nucleosides, which inhibit DNA synthesis and induce apoptosis. It is mainly active against cells in S phase. It is given in the management of solid tumours including those of the bladder, breast, lung, ovary, and pancreas (see p. 700.2, p. 702.1, p. 710.2, p. 711.2, and p. 712.1, respectively).

Gemcitabine is given intravenously as the hydrochloride. Doses are calculated in terms of the base; gemcitabine hydrochloride 1.14 g is equivalent to about 1 g of gemcitabine. Doses are reconstituted in sodium chloride 0.9%. The concentration of the infusion solution should not exceed the equivalent of gemcitabine 40 mg/mL. Gemcitabine is given by infusion over 30 to 60 minutes; doses are subsequently adjusted according to response and toxicity.

In the treatment of **pancreatic cancer**, an initial course of gemcitabine 1 g/m² once weekly for up to 7 weeks may be given, followed after a one-week recovery period by a regimen of infusions once weekly for 3 consecutive weeks out of 4.

In **non-small cell lung cancer**, gemcitabine may be given as a single agent; 1 g/m² once weekly for 3 consecutive weeks out of 4 is recommended. Alternatively, it may be given before cisplatin. Two schedules have been used; gemcitabine 1.25 g/m² is given on days 1 and 8 of a 21-day cycle, or gemcitabine 1 g/m² is given on days 1, 8 and 15 of a 28-day cycle.

In the treatment of **bladder cancer**, gemcitabine is given before cisplatin. The recommended dose of gemcitabine is 1 g/m² on days 1, 8, and 15 of a 28-day cycle.

In **breast cancer**, gemcitabine is usually given after a taxane such as paclitaxel. A dose of gemcitabine 1.25 g/m² is given on days 1 and 8 of a 21-day cycle.

In **ovarian cancer**, gemcitabine is given before carboplatin. The recommended dose of gemcitabine is 1 g/m² on days 1 and 8 of a 21-day cycle.

1. Stadler WM. Gemcitabine doublets in advanced urothelial cancer. *Semin Oncol* 2002; **29** (suppl 3): 15–19.
2. Hussain M, *et al.* Novel gemcitabine-containing triplets in the management of urothelial cancer. *Semin Oncol* 2002; **29** (suppl 3): 20–4.
3. Hochster HS. Newer approaches to gemcitabine-based therapy of pancreatic cancer: fixed-dose-rate infusion and novel agents. *Int J Radiat Oncol Biol Phys* 2003; **56** (suppl): 24–30.
4. Yardley DA. Gemcitabine and taxanes as a new standard of care in breast cancer. *Clin Breast Cancer* 2004; **4** (suppl 3): S107–S112.
5. Natale R. A ten-year review of progress in the treatment of non-small-cell lung cancer with gemcitabine. *Lung Cancer* 2005; **50** (suppl): S2–S4.
6. Saha A, Rudd R. Gemcitabine and carboplatin: is this the best combination for non-small cell lung cancer? *Expert Rev Anticancer Ther* 2006; **6:** 165–73.
7. Kose MF, *et al.* Gemcitabine plus carboplatin in platinum-sensitive recurrent ovarian carcinoma. *Expert Rev Anticancer Ther* 2006; **6:** 437–43.
8. Wirk B, Perez E. Role of gemcitabine in breast cancer management: an update. *Semin Oncol* 2006; **33** (suppl 2): S6–S14.
9. Pfisterer J, *et al.* Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006; **24:** 4699–4707.
10. Kiba T, *et al.* Single-agent gemcitabine for biliary tract cancers: study outcomes and systematic review of the literature. *Oncology* 2006; **70:** 358–65.
11. Maki RG. Gemcitabine and docetaxel in metastatic sarcoma: past, present, and future. *Oncologist* 2007; **12:** 999–1006.
12. El Karak F, Flechon A. Gemcitabine in bladder cancer. *Expert Opin Pharmacother* 2007; **8:** 3251–6.
13. Serrano A, Gerson R. Chemotherapy with gemcitabine in advanced biliary tract carcinoma. *Rev Recent Clin Trials* 2008; **3:** 70–8.
14. Hilbig A, Oettle H. Gemcitabine in the treatment of metastatic pancreatic cancer. *Expert Rev Anticancer Ther* 2008; **8:** 511–23.
15. Dent S, *et al.* Gemcitabine in the management of metastatic breast cancer: a systematic review. *Breast Cancer Res Treat* 2008; **108:** 319–31.
16. Danesi R, *et al.* Pharmacogenomics of gemcitabine in non-small-cell lung cancer and other solid tumors. *Pharmacogenomics* 2009; **10:** 69–80.
17. Wong A, *et al.* Clinical pharmacology and pharmacogenetics of gemcitabine. *Drug Metab Rev* 2009; **41:** 77–88.
18. Rivera F, *et al.* Treatment of advanced pancreatic cancer: from gemcitabine single agent to combinations and targeted therapy. *Cancer Treat Rev* 2009; **35:** 335–9.

Administration. Gemcitabine is recommended as the standard of care in patients with advanced pancreatic cancer (p. 712.1). There is some suggestion that its efficacy may be improved if it is given at a fixed dose rate of 10 mg/m² per minute, rather than by conventional infusion.[1] However, while this regimen has been found to be well tolerated,[2] several studies have not shown an improvement in survival compared with the standard gemcitabine infusion[3] and some do not recommend it for routine use.[4]

1. Tempero M, *et al.* Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol* 2003; **21:** 3402–8.
2. Ko AH, *et al.* Phase II study of fixed dose rate gemcitabine with cisplatin for metastatic adenocarcinoma of the pancreas. *J Clin Oncol* 2006; **24:** 379–85.
3. Poplin E, *et al.* Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009; **27:** 3778–85.
4. Kulke MH, *et al.* Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. *J Clin Oncol* 2009; **27:** 5506–12.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The major dose-limiting adverse effect of gemcitabine is bone-marrow depression, although this is reported to be modest and rarely requires stopping therapy. Gastrointestinal disturbances occur, especially nausea and vomiting, but these are usually of mild to moderate severity. Rashes, often associated with pruritus, and flu-like symptoms are relatively common; severe desquamation and bullous skin eruptions, toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred rarely. Oedema, dyspnoea, myalgia, and alopecia are commonly reported. Pulmonary oedema has been reported infrequently; interstitial pneumonitis, pulmonary fibrosis, and acute respiratory distress syndrome have occurred. Therapy should be stopped if pulmonary toxicity occurs. There are rare cases of hypotension and anaphylactoid reactions. Haematuria,

proteinuria, transient liver enzyme elevations, and serious hepatotoxicity, including liver failure and death, have been reported. It should therefore be used with caution in patients with impaired renal or hepatic function. Haemolytic-uraemic syndrome and/or thrombocytopenic purpura have been reported and have led to irreversible renal failure; gemcitabine should be stopped at the first signs of microangiopathic haemolytic anaemia. Congestive heart failure, myocardial infarction, or arrhythmias may occur rarely. Ischaemic colitis with necrosis (including fatalities), peripheral vasculitis and gangrene, and cerebrovascular accident have also been reported.

Gemcitabine may produce somnolence: patients so affected should not drive or operate machinery. Severe toxicity, in the form of potentially life-threatening oesophagitis and pneumonitis has been seen in patients given radical radiotherapy to the thorax concurrently with gemcitabine.

Effects on the nervous system. A report of autonomic neuropathy associated with gemcitabine therapy.[1] Symptoms resolved 4 weeks after stopping therapy.

1. Dormann AJ, *et al.* Gemcitabine-associated autonomic neuropathy. *Lancet* 1998; 351: 644.

Effects on the skin. A patient who received gemcitabine a week after phototherapy developed a severe sunburn reaction in those areas exposed to UVB. The erythema resolved spontaneously, but recurred with each subsequent dose of gemcitabine, and became progressively more intense. A short course of high-dose prednisone was given with topical triamcinolone, and the patient was safely rechallenged with 2 further doses of gemcitabine.[1]

1. Badger J, *et al.* Photo therapy recall with gemcitabine following ultraviolet B treatment. *J Clin Oncol* 2005; 23: 7224–5.

Peripheral ischaemia. Pain, coldness, colour changes, and distal claudication in the feet have been reported in patients treated with gemcitabine and cisplatin.[1] Pain and colour changes in the fingertips have also been reported after gemcitabine monotherapy.[2]

1. Barceló R, *et al.* Distal ischemic changes related to combination chemotherapy with cisplatin and gemcitabine: description of four cases. *Ann Oncol* 2000; 11: 1191–4.
2. Yildiz R, *et al.* Digital ischemic changes after gemcitabine therapy in a patient with metastatic non-small-cell lung cancer. *Ann Pharmacother* 2007; 41: 901–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gemcitabine 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 29/09/11)

Interactions

Antineoplastics. In a study[1] of 14 patients with lung cancer, the use of *paclitaxel* before gemcitabine caused a decrease in the systemic clearance, volume of distribution, and interpatient pharmacokinetic variability of gemcitabine. This resulted in plasma concentrations of gemcitabine slightly higher than the desired range. However, there was no apparent relationship between pharmacokinetic changes and toxicity, and the clinical significance of this possible interaction is unclear.

A study investigating a modified chemotherapy regimen in which gemcitabine was substituted for etoposide was stopped because of unexpected pulmonary toxicity. This was considered to be due to the combination of gemcitabine and *bleomycin*, as the adverse effect was apparent in other studies using this combination.[2]

1. Shord SS, *et al.* Gemcitabine pharmacokinetics and interaction with paclitaxel in patients with advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2003; 51: 328–36.
2. Bredenfeld H, *et al.* Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's lymphoma study group. *J Clin Oncol* 2004; 22: 2424–9.

Pharmacokinetics

After intravenous doses gemcitabine is rapidly cleared from the blood and metabolised by cytidine deaminase in the liver, kidney, blood, and other tissues. Clearance is about 25% lower in women than in men. Almost all of the dose is excreted in urine as 2'-deoxy-2',2'-difluorouridine (dFdU), only about 1% being found in the faeces. Intracellular metabolism produces mono-, di-, and triphosphate metabolites, the latter two active. The half-life of gemcitabine ranges from 42 to 94 minutes depending on age and gender. The intracellular half-life of the triphosphate is stated to range from 0.7 to 12 hours.

References.
1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; 39: 5–26.
2. Shamseddine AI, *et al.* Comparative pharmacokinetics and metabolic pathway of gemcitabine during intravenous and intra-arterial delivery in unresectable pancreatic cancer patients. *Clin Pharmacokinet* 2005; 44: 957–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Abine; Antoril; Eriogem; Gebina; Gemofas; Gemtro; Gestredos; Gezt; Gramagen; Nabigem; Oncoplus; *Austral.*: Gemzar; *Austria*: Gemzar; *Belg.*: Gemzar; *Braz.*: Gemcit; Gemzar; *Canad.*: Gemzar; *Chile*: Gemzar; Genuten; *China*: Gemzar (健择); Yu Jie (誉捷); Ze Fei (泽菲); *Cz.*: Citegin; Gemalata; Gemcirena; Gemibane; Gemstad; Gemtex; Gemzar; Getmisi; Gitrabin; Lungera; Naruyd; *Denm.*: Gemabin†; Gemcit†; Gemcitelb†; Gemhal†; Gemind; Gemstada; Gemtiba†; Gemtifi†; Gemzar; Nallian†; *Fin.*: Gemzar; *Fr.*: Gemcirena†; Gemzar; *Ger.*: Axigem; Bendacitabin; Gemci-Cell; Gemcitan; Geniedac; Gemzar†; Ribozar; *Gr.*: Demozar; Gemcipen; Gemcirena; Gemnil; Gemzar†; Genvir; Medigem; Santabin; Tamcibin; *Hong Kong*: Gemzar; Gitrabin; *Hung.*: Dercin; Gemdex; Gemzar; Nallian; *India*: Abingem; Biogem; Celgem; Celzar; Cytogem; Gembin; Gemcite; Gemita; Gempower; Gemtaz; Lifogem; Oncogem; *Indon.*: Cytogem; Gemzar; *Irl.*: Gemabin†; Gemzar; *Israel*: Gemnil; Gemzar; Meditabine; *Ital.*: Gemzar; Jemta; *Malaysia*: Gemzar; *Mex.*: Gemzar; *Neth.*: Gemalata; Gemzar; Jemta; *Norw.*: Gemzar; *NZ*: Gemzar; *Philipp.*: Gemcit; Gemita; Gemtabine; Gemzar; Oncoril; Zefei; *Pol.*: Dercin; Gemciteva; Gemzar; Gitrabin; *Port.*: Gemcit; Gemzar; *Rus.*: Cytogem (Цитоген); Gemcitare (Гемцитар); Gemcitera (Гемцитера); Gemcitover (Гемцитовер); Gemzar (Гемзар); Ongecin (Онгецин); *S. Afr.*: Cytogem; Gemtaz; Gemzar; *Singapore*: Gemzar; *Spain*: Gemzar; *Swed.*: Gemzar; *Switz.*: Gemzar; *Thai.*: Gemcit; Gemita; Gemtaz; Gemzar; Gramagen; *Turk.*: Gemko; Gemzar; *UK*: Gemzar; *Ukr.*: Cytogem (Цитоген); *USA*: Gemzar; *Venez.*: Gemzar.

Pharmacopoeial Preparations
USP 36: Gemcitabine for Injection.

Gemtuzumab Ozogamicin *(USAN, rINNM)*

CDP-771; CMA-676; Gemtuzumab ozogamicina; Gemtuzumab Ozogamicine; Gemtuzumab Zogamicin; Gemtuzumabum Ozogamicinum; WAY-CMA-676; Гемтузумаб Озогамицин.

Immunoglobulin G4 (human-mouse monoclonal hP67.6 κ4-chain anti-human antigen CD 33), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer conjugate with ozogamicin.

CAS — 220578-59-6.
ATC — L01XC05.
ATC Vet — QL01XC05.
UNII — 8GZG754X6M.

Uses and Administration

Gemtuzumab ozogamicin is a recombinant humanised monoclonal antibody conjugated with calicheamicin, a cytotoxic antibiotic. The antibody binds specifically to the CD33 antigen, which is expressed on leukaemic myeloblasts but not normal haematopoietic stem cells. Gemtuzumab ozogamicin has been used for the second-line treatment of CD33-positive acute myeloid leukaemia (p. 693.1) in elderly patients who are unable to tolerate conventional chemotherapy. It is given in 100 mL of sodium chloride 0.9% via a low protein-binding in-line filter. A usual dose has been 9 mg/m² given by intravenous infusion over 2 hours, repeated once after 14 days. Lower doses have been investigated as part of combined induction or consolidation regimens.

References.
1. McGavin JK, Spencer CM. Gemtuzumab ozogamicin. *Drugs* 2001; 61: 1317–22.
2. Dowell JA, *et al.* Pharmacokinetics of gemtuzumab ozogamicin, an antibody-targeted chemotherapy agent for the treatment of patients with acute myeloid leukemia in first relapse. *J Clin Pharmacol* 2001; 41: 1206–14.
3. Sievers EL, *et al.* Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol* 2001; 19: 3244–54.
4. Sievers EL, Linenberger M. Mylotarg: antibody-targeted chemotherapy comes of age. *Curr Opin Oncol* 2001; 13: 522–7.
5. Larson RA, *et al.* Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). *Leukemia* 2002; 16: 1627–36.
6. Buckwalter M, *et al.* Pharmacokinetics of gemtuzumab ozogamicin as a single-agent treatment of pediatric patients with refractory or relapsed acute myeloid leukemia. *J Clin Pharmacol* 2004; 44: 873–80.
7. Lo-Coco F, *et al.* Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. *Blood* 2004; 104: 1995–9.
8. Fenton C, Perry CM. Gemtuzumab ozogamicin: a review of its use in acute myeloid leukaemia. *Drugs* 2005; 65: 2405–27.
9. Tsimberidou AM, *et al.* The role of gemtuzumab ozogamicin in acute leukaemia therapy. *Br J Haematol* 2006; 132: 398–409.
10. Stasi R, *et al.* Gemtuzumab ozogamicin in the treatment of acute myeloid leukemia. *Cancer Treat Rev* 2008; 34: 49–60.
11. Leukaemia Research Fund. AML14: Leukaemia Research Fund Acute Myeloid Leukaemia and High Risk MDS Trial 14. Available at: http://www.download.bham.ac.uk/bctu/aml14/trial%20documentation/amendment%20january%202004/Protocol%20Jan%202004.pdf (accessed 30/07/08)
12. Medical Research Council. AML15: Medical Research Council Working Parties on Leukaemia in Adults and Children Acute Myeloid Leukaemia Trial 15. Available at: http://www.download.bham.ac.uk/bctu/AML_15/Amendment%20Nov%202007/AML15%20protocol%20version%207%20Final%20200704201%20with%20no%20track%20changes.pdf (accessed 30/07/08)

Adverse Effects and Precautions

For general discussions see Antineoplastics, p. 726.1 and p. 732.2.

Myelosuppression is common with gemtuzumab ozogamicin, and thrombocytopenia may be prolonged. Infusion-related reactions characteristic of a cytokine release syndrome (including fever, chills, dyspnoea, and hypotension) and hypersensitivity may occur; prophylactic use of an antihistamine and paracetamol is recommended. Pulmonary sequelae may be fatal. Hepatotoxicity, including severe veno-occlusive disease, has also been reported. Electrolyte imbalances, especially hypokalaemia and hypomagnesaemia, and gastrointestinal disturbances may occur.

Blood and platelet counts, electrolytes, and liver function tests should be regularly monitored.

The drug was withdrawn from the market in the USA after reports of increased mortality in patients with acute myeloid leukaemia who were given gemtuzumab ozogamicin as part of a combination regimen.

Hypersensitivity. A 75-year-old man with acute myeloid leukaemia developed severe respiratory distress and died after being given gemtuzumab ozogamicin and platelets on the same day. He had previously had the drug and platelets on separate occasions with no untoward effects. It was suggested that this combination contributed to a fatal hypersensitivity reaction.[1]

1. Hanbali A, *et al.* Fatal hypersensitivity reaction to gemtuzumab ozogamicin associated with platelet transfusion. *Am J Health-Syst Pharm* 2007; 64: 1401–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mylotarg; *Gr.*: Mylotarg; *Israel*: Mylotarg; *Singapore*: Mylotarg†; *USA*: Mylotarg†; *Venez.*: Mylotarg.

Gimatecan *(rINN)*

CPT-184; Gimatécan; Gimatecán; Gimatecanum; LBQ-707; ST-1481; Гиматекан.

(4*S*)-11-[(*E*)-[(1,1-Dimethylethoxy)imino]methyl]-4-ethyl-4-hydroxy-1,12-dihydro-14*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione.

$C_{25}H_{25}N_3O_5$=447.5

CAS — 292618-32-7.
UNII — 7KKS9R192F.

Profile

Gimatecan is a camptothecin derivative that inhibits the enzyme topoisomerase I. Gimatecan is under investigation for the treatment of malignant glioma.

References.
1. Sessa C, *et al.* Concerted escalation of dose and dosing duration in a phase I study of the oral camptothecin gimatecan (ST1481) in patients with advanced solid tumors. *Ann Oncol* 2007; 18: 561–8.
2. Zhu AX, *et al.* Phase I and pharmacokinetic study of gimatecan given orally once a week for 3 of 4 weeks in patients with advanced solid tumors. *Clin Cancer Res* 2009; 15: 374–81.
3. Pecorelli S, *et al.* Phase II of oral gimatecan in patients with recurrent epithelial ovarian, fallopian tube or peritoneal cancer, previously treated with platinum and taxanes. *Ann Oncol* 2010; 21: 759–65.

Girentuximab *(USAN, rINN)*

cG-250; Girentuximabum; WX-G250; Гирентуксимаб.

CAS — 916138-87-9.
UNII — 539B57DFJF.

NOTE. The name Rencarex has been used as a trade mark for girentuximab. The name Redectane has been used as a trade mark for girentuximab labelled with iodine-124.

Profile

Girentuximab is a chimeric monoclonal antibody that binds specifically to the protein carbonic anhydrase IX (CA IX, MN, or G250 antigen) expressed on the cell surface in the majority of clear-cell renal cell carcinomas; the antigen is present in various other solid tumours. Girentuximab is under investigation for the treatment of clear-cell renal cell carcinoma.

Girentuximab labelled with iodine-124 (p. 2225.2) is being studied for the imaging of renal tumours.

Givinostat (rINN)

Givinostatum; Гивиностат.
(6-[(Diethylamino)methyl]naphthalen-2-yl)methyl [4-(hydroxycarbamoyl)phenyl]carbamate.
$C_{24}H_{27}N_3O_4$=421.5
CAS — 497833-27-9.
UNII — SP60F84FBH.

Profile

Givinostat is an orally active histone deacetylase inhibitor that is under investigation for the treatment of polycythaemia vera and juvenile idiopathic arthritis.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Vojinovic J, *et al.* Safety and efficacy of an oral histone deacetylase inhibitor in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 2011; 63: 1452–8.
2. Rambaldi A, *et al.* A pilot study of the histone-deacetylase inhibitor givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms. *Br J Haematol* 2010; 150: 446–55.

Glufosfamide (rINN)

D-19575; β-D-Glu-IPM; β-D-Glucosyl-ifosfamide Mustard; Glufosfamida; Glufosfamidum; Глуфосфамид.
β-D-Glucopyranose 1-[*N,N'*-bis(2-chloroethyl)phosphorodiamidate].
$C_{10}H_{21}Cl_2N_2O_7P$=383.2
CAS — 132682-98-5.
UNII — 1W5N8SZD9A.

Profile

Glufosfamide is a conjugate of glucose and the active part of the alkylating antineoplastic ifosfamide (p. 806.1). It is under investigation for the treatment of pancreatic cancer and other solid tumours.

References.

1. Chiorean EG, *et al.* A phase 1 dose-escalation trial of glufosfamide in combination with gemcitabine in solid tumors including pancreatic adenocarcinoma. *Cancer Chemother Pharmacol* 2008; 61: 1019–26.
2. Chiuleanu TE, *et al.* A randomised phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with gemcitabine. *Eur J Cancer* 2009; 45: 1589–96.

Hydroxycarbamide (BAN, rINN)

Hidroksikarbamid; Hidroksikarbamidas; Hidroxicarbamida; Hidroxikarbamid; Hydroksikarbamidi; Hydroksiüre; Hydroxikarbamid; Hydroxycarbamid; Hydroxycarbamidum; Hydroxymočovina; Hydroxyurea (USAN); Hydroxyurea; NSC-32065; SQ-1089; WR-83799; Гидроксикарбамид.
$NH_2CO.NHOH$=76.06
CAS — 127-07-1.
ATC — L01XX05.
ATC Vet — QL01XX05.
UNII — X6Q56QN5QC.

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

Ph. Eur. 8: (Hydroxycarbamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Hydroxyurea). A white to off-white powder. It is somewhat hygroscopic and decomposes in the presence of moisture. Freely soluble in water and in hot alcohol. Store in airtight containers in a dry atmosphere.

Stability. An oral solution of hydroxycarbamide 100 mg/mL was prepared[1] by first mixing the contents of 500-mg capsules (*Hydrea; BMS, USA*) in sterile water at room temperature to produce a concentration of 200 mg/mL. The mixture was vigorously stirred for several hours and then filtered to remove insoluble excipients. Flavoured syrup (*Syrpalta without color; Humco, USA*) was added to the filtered solution to produce a final concentration of 100 mg/mL.

The resulting solution was found to have lost 5% of its chemical content of hydroxycarbamide during the first 3-months of storage at room temperature in amber plastic bottles but there was no further loss up to 9 months later. The loss of its *in-vitro* inhibitory activity was less than 5% at 3 months, less than 10% at 6 months but activity was about 80% at 9 months. In contrast a solution that had been prepared by dissolving the contents of the capsules in heated water had an immediate loss of 40% of its chemical content and over 60% of its inhibitory activity.

1. Heeney MM, *et al.* Chemical and functional analysis of hydroxyurea oral solutions. *J Pediatr Hematol Oncol* 2004; 26: 179–84.

Uses and Administration

Hydroxycarbamide is an antineoplastic that may cause inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor. It is S-phase specific. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia, and may be used in the myeloproliferative disorders polycythaemia vera and primary (essential) thrombocythaemia. It has also been tried, often combined with radiotherapy, in some solid malignancies (see Malignant Neoplasms, p. 804.1). Hydroxycarbamide has also produced benefit in the haemoglobinopathies, particularly in sickle-cell disease (see below).

Hydroxycarbamide is given orally. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In the treatment of **chronic myeloid leukaemia** and **solid tumours**, hydroxycarbamide is given typically in a single dose of 20 to 30 mg/kg daily or in a single dose of 80 mg/kg every third day. Generally, the continuous regimen is used for chronic myeloid leukaemia, and the intermittent regimen for solid tumours. When used with radiotherapy, hydroxycarbamide is started 7 days before radiotherapy. If a beneficial effect is evident after 6 weeks, therapy may be continued indefinitely.

In **essential thrombocythaemia**, the initial dose of hydroxycarbamide is about 15 mg/kg daily; starting doses of 15 to 20 mg/kg daily are recommended for **polycythaemia vera**. Doses are subsequently adjusted according to platelet counts.

In **sickle-cell disease** initial doses of 15 mg/kg daily are suggested, increased if necessary by 2.5 to 5 mg/kg every 12 weeks according to response and blood counts; usual doses are 15 to 30 mg/kg daily with a maximum of 35 mg/kg daily. For doses in children, see below.

Blood counts and hepatic and renal function should be monitored during therapy; treatment may need to be interrupted if leucopenia or thrombocytopenia occur (see Adverse Effects, Treatment, and Precautions, p. 804.1).

Administration in children. In the UK hydroxycarbamide is licensed for use in children older than 2 years of age for the treatment of sickle-cell disease; doses are the same as for adults, see Uses and Administration, above. The *BNFC* advises that a slightly lower initial oral dose of 10 to 15 mg/kg daily may be used instead. For doses in renal impairment and for more information on hydroxycarbamide use in sickle-cell disease, see below.

For reference to the preparation and stability of an oral solution of hydroxycarbamide 100 mg/mL, see under Stability, above.

Administration in renal impairment. Results from a single-dose study in patients with sickle-cell disease indicated that systemic exposure to hydroxycarbamide correlates to renal function.[1] An initial oral dose of 7.5 mg/kg daily is recommended for adults and children over 2 years of age with sickle-cell disease and a creatinine clearance of less than 60 mL/minute. US product information also recommends this dose adjustment for adults with end-stage renal disease; on dialysis days the dose should be given after haemodialysis.

1. Yan J-H, *et al.* The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005; 45: 434–45.

Haemoglobinopathies. Hydroxycarbamide is considered a promising treatment for the haemoglobinopathies. It can stimulate fetal haemoglobin production, which in turn can reduce haemoglobin polymerisation and the numbers of deformed, dense, and damaged erythrocytes.[1] In adult patients with **sickle-cell disease** (p. 1123.2), a randomised controlled study produced evidence that initial oral doses of 15 mg/kg daily, adjusted according to response and tolerance to up to 35 mg/kg daily, reduced the rate of sickle-cell crisis compared with placebo.[2] An observational follow-up study[3] of this group found that patients taking hydroxycarbamide for frequent sickle-cell episodes appeared to have reduced mortality. A report in 2 adults has suggested that it might reverse splenic dysfunction.[4] A systematic review[5] has noted that despite the benefits, the paucity of long-term studies limits conclusions on the toxicity of treatment with hydroxycarbamide.

Despite some concerns about giving a potential carcinogen to children,[6] studies in paediatric populations have also reported evidence of benefit in terms of decreased hospitalisation[7,8] and sickle-cell crisis.[8,9] Although the evidence for the efficacy of hydroxycarbamide in children with sickle-cell disease is not as strong as that for adults[10] and is mostly based on observational studies, a systematic review[11] concluded that there was strong evidence of an increase in haemoglobin and decreased hospitalisations, moderate evidence of decreased painful crises, and weak evidence of decreased neurological events. There was insufficient evidence to draw conclusions on the effect of hydroxycarbamide on the frequency of transfusions or mortality. Hydroxycarbamide may be considered for children with sickle-cell disease and frequent complications such as painful crises, priapism, severe anaemia, or acute chest syndrome.[12] Hydroxycarbamide has also been suggested as an alternative to blood transfusions in children who have had a stroke.[8,13,14] Although a small study[15] has suggested benefit in paediatric patients in terms of splenic preservation, long-term prevention of organ damage remains to be established.[16,17]

It has been suggested that use of the drug with erythropoietin might enhance the production of fetal haemoglobin, but results from studies of the combination have been conflicting.[18,19]

There appear to have been few studies of hydroxycarbamide specifically in **thalassaemia** (p. 1124.1). Initial oral doses of 8.2 to 10.3 mg/kg daily, increased until toxicity occurred, did produce sustained increases in fetal haemoglobin in 3 patients, but did not result in a sustained increase in total haemoglobin.[20] Others have reported[21] that rises in fetal haemoglobin did not necessarily correlate with clinical improvement. Conversely, sustained responses have been seen in other studies.[22–25] Use with sodium phenylbutyrate has produced conflicting results.[26–28]

1. Halsey C, Roberts IAG. The role of hydroxyurea in sickle cell disease. *Br J Haematol* 2003; 120: 177–86.
2. Charache S, *et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; 332: 1317–22.
3. Steinberg MH, *et al.* Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003; 289: 1645–51. Correction. *ibid.*; 290: 756.
4. Claster S, Vichinsky E. First report of reversal of organ dysfunction in sickle cell anemia by the use of hydroxyurea: splenic regeneration. *Blood* 1996; 88: 1951–3.
5. Lanzkron S, *et al.* Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. *Ann Intern Med* 2008; 148: 939–55.
6. Zimmerman SA, *et al.* Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood* 2004; 103: 2039–45.
7. Scott JP, *et al.* Hydroxyurea therapy in children severely affected with sickle cell disease. *J Pediatr* 1996; 128: 820–8.
8. Gulbis B, *et al.* Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood* 2005; 105: 2685–90.
9. Jayabose S, *et al.* Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. *J Pediatr* 1996; 129: 559–65.
10. Brawley OW, *et al.* National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008; 148: 932–8.
11. Strouse JJ, *et al.* Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008; 122: 1332–42.
12. Mueller BU. When should hydroxyurea be used for children with sickle cell disease? *Pediatrics* 2008; 122: 1365–6.
13. Ware RE, *et al.* Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 1999; 94: 3022–6.
14. Ware RE, *et al.* Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004; 145: 346–52.
15. Wang WC, *et al.* A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001; 139: 790–6.
16. Powars DR. Hydroxyurea in very young children with sickle cell anemia is not a cure-all. *J Pediatr* 2001; 139: 763–4.
17. Kinney TR, *et al.* Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. *Blood* 1999; 94: 1550–4.
18. Goldberg MA, *et al.* Treatment of sickle cell anemia with hydroxyurea and erythropoietin. *N Engl J Med* 1990; 323: 366–72.
19. Rodgers GP, *et al.* Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle-cell disease. *N Engl J Med* 1993; 328: 73–80.
20. Hajjar FM, Pearson HA. Pharmacologic treatment of thalassemia intermedia with hydroxyurea. *J Pediatr* 1994; 125: 490–2.
21. de Paula EV, *et al.* Long-term hydroxyurea therapy in beta-thalassaemia patients. *Eur J Haematol* 2003; 70: 151–5.
22. Loukopoulos D, *et al.* Hydroxyurea therapy in thalassemia. *Ann N Y Acad Sci* 1998; 30: 120–8.
23. Rigano P, *et al.* Clinical and hematological responses to hydroxyurea in Sicilian patients with Hb S/β -thalassemia. *Hemoglobin* 2001; 25: 9–17.
24. Loukopoulos D, *et al.* Reduction of the clinical severity of sickle cell/β -thalassemia with hydroxyurea: the experience of a single center in Greece. *Blood Cells Mol Dis* 2000; 26: 453–66.
25. Bradai M, *et al.* Hydroxyurea can eliminate transfusion requirements in children with severe β -thalassemia. *Blood* 2003; 102: 1529–30.
26. Olivieri NF, *et al.* Treatment of thalassaemia major with phenylbutyrate and hydroxyurea. *Lancet* 1997; 350: 491–2.
27. Hoppe C, *et al.* Hydroxyurea and sodium phenylbutyrate therapy in thalassemia intermedia. *Am J Hematol* 1999; 62: 221–7.
28. Dover GJ. Hemoglobin switching protocols in thalassemia. *Ann N Y Acad Sci* 1998; 850: 80–6.

HIV infection and AIDS. Unlike most drugs used to treat HIV, which target viral enzymes, hydroxycarbamide inhibits ribonucleotide reductase, a host cellular enzyme that is less prone to mutation and subsequent development of resistance.[1] The drug acts synergistically with didanosine (p. 972.3). Of 25 HIV-positive patients given didanosine 200 mg twice daily with hydroxycarbamide 15 mg/kg daily in 2 divided doses, all showed a drop in viral load and an increase in CD4+ lymphocyte count.[2] Viraemia was not detectable in 13 of 24 patients evaluated at 6 months and 10 of 20 patients evaluated at 1 year. In 2 of these patients who subsequently received no antiviral treatments for 1 year there was no viral rebound, although some proviral DNA was detected.[3] In another study in 6 patients, didanosine 200 mg twice daily with hydroxycarbamide 250 mg

four times daily (suggested to be a better regimen because of the short half-life of the antineoplastic) produced a sharp decrease in viraemia, which was maintained for up to 72 weeks.[4] A rebound occurred in 1 patient on interrupting treatment but viral replication was again suppressed when treatment was restarted.

Combinations with didanosine and other HIV drugs have also been tried.[1] A controlled study[5] of hydroxycarbamide, didanosine, and stavudine indicated significantly enhanced activity when the antivirals were used with the antineoplastic rather than placebo. However, in a long-term follow-up[6] there was a high withdrawal rate amongst patients receiving this combination, due to virological failure and adverse effects such as peripheral neuropathy and fatigue. Another study[7] (ACTG 5025) was terminated due to the high risk of toxicity, including fatal pancreatitis, in patients receiving the hydroxycarbamide regimens. The authors noted that the use of a higher daily dosage of 1.2 g of hydroxycarbamide (rather than the usual 1 g daily) and increased exposure to didanosine (itself associated with pancreatitis) may have contributed to toxicity. An analysis of 2613 patients[8] determined that the use of hydroxycarbamide with didanosine, or didanosine and stavudine, resulted in a fourfold increase in the risk for development of pancreatitis, compared with didanosine alone. In a study of patients who had failed protease-inhibitor based regimens,[9] the addition of the antineoplastic to reverse transcriptase inhibitor-based therapy significantly improved virologic response. Despite an increased incidence of adverse events associated with its use, hydroxycarbamide was considered to be a valuable alternative in these patients. A small randomised study[10] of patients with chronic HIV infection given structured treatment interruptions with cycles of HAART, or HAART and hydroxycarbamide, found that use of the latter decreased viral load. There is some suggestion that a lower dose of hydroxycarbamide (300 mg twice daily) may have better antiretroviral activity, and fewer adverse effects, than higher doses.[11] For further discussion of the management of HIV infection and AIDS, see p. 957.2.

1. Gibbs MA, Sorensen SJ. Hydroxyurea in the treatment of HIV-1. *Ann Pharmacother* 2000; **34**: 89–93.
2. Vila J, *et al.* 1-year follow-up of the use of hydroxycarbamide and didanosine in HIV infection. *Lancet* 1996; **348**: 203–4.
3. Vila J, *et al.* Absence of viral rebound after treatment of HIV-infected patients with didanosine and hydroxycarbamide. *Lancet* 1997; **350**: 635–6.
4. Lori F, *et al.* Long-term suppression of HIV-1 by hydroxyurea and didanosine. *JAMA* 1997; **277**: 1437–8.
5. Rutschmann OT, *et al.* A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. *AIDS* 1998; **12**: F71–7.
6. Rutschmann OT, *et al.* Long-term hydroxyurea in combination with didanosine and stavudine for the treatment of HIV-1 infection. *AIDS* 2000; **14**: 2145–51.
7. Havlir DV, *et al.* Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS* 2001; **15**: 1379–88.
8. Moore RD, *et al.* Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS* 2001; **15**: 617–20.
9. Lafeuillade A, *et al.* The HYDILE trial: efficacy and tolerance of a quadruple combination of reverse transcriptase inhibitors versus the same regimen plus hydroxyurea or hydroxyurea and interleukin-2 in HIV-infected patients failing protease inhibitor-based combinations. *HIV Clin Trials* 2002; **3**: 263–71.
10. García P, *et al.* A cytostatic drug improves control of HIV-1 replication during structured treatment interruptions: a randomized study. *AIDS* 2003; **17**: 43–51.
11. Lisziewicz J, *et al.* Hydroxyurea in the treatment of HIV infection: clinical efficacy and safety concerns. *Drug Safety* 2003; **26**: 605–24.

Malignant neoplasms. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia (p. 694.2), and may be used in the myeloproliferative disorders polycythaemia vera (p. 695.2) and primary (essential) thrombocythaemia (p. 695.2). Hydroxycarbamide has been tried, often with radiotherapy, in some solid malignancies such as tumours of the cervix (p. 704.2), head and neck (p. 708.1), and ovary (p. 711.2).

Psoriasis. An immunosuppressant (usually methotrexate or ciclosporin) may be useful in patients with severe refractory psoriasis (p. 1688.1). Hydroxycarbamide has also been tried, although experience is limited.[1,2]

1. Layton AM, *et al.* Hydroxyurea in the management of therapy resistant psoriasis. *Br J Dermatol* 1989; **121**: 647–53.
2. Smith CH, *et al.* Use of hydroxyurea in psoriasis. *Clin Exp Dermatol* 1999; **24**: 2–6.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow suppression, including megaloblastic changes, is the main adverse effect of hydroxycarbamide. The erythema caused by irradiation may be exacerbated. Other adverse effects reported have included gastrointestinal disturbances, impairment of renal function, pulmonary oedema, dermatological reactions, alopecia, and neurological reactions such as headache, dizziness, drowsiness, disorientation, hallucinations, and convulsions. There are rare reports of acute pulmonary reactions consisting of pulmonary infiltrates or fibrosis, dyspnoea and fever. Symptoms resembling cutaneous vasculitis, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders treated with hydroxycarbamide, especially in those also given interferon. There are reports of hepatotoxicity and pancreatitis, some fatal, in patients with HIV infection, given hydroxycarbamide and antiretrovirals (see also HIV Infection and AIDS, p. 803.3); peripheral neuropathy has also occurred.

Pre-existing anaemia should be corrected before beginning therapy with hydroxycarbamide and the haemoglobin concentration, white cell and platelet counts, and hepatic and renal function should be determined repeatedly during treatment. Treatment should be interrupted if the white cell or platelet count fall below acceptable levels (see also Bone-marrow Depression, p. 730.3). If anaemia occurs when hydroxycarbamide is used as an antineoplastic, it may be corrected by transfusions of whole blood without stopping therapy. If anaemia (haemoglobin less than 4.5 g per 100 mL or reticulocyte count less than 80 000 cells/mm^3 when haemoglobin is less than 9 g per 100 mL) occurs when the drug is used for sickle-cell disease, therapy should be interrupted. Megaloblastic changes are usually self-limiting.

Hydroxycarbamide should be used with caution in patients with impaired renal function. Uric acid concentrations should be monitored, and a high fluid intake maintained during treatment. The elderly may be more sensitive to its adverse effects.

Breast feeding. In breast-milk samples from a woman given hydroxycarbamide 500 mg three times daily, the mean concentration of the drug was found to be about 6 mg/litre. It was estimated that, had the infant been breast-fed, it would have received about 3 to 4 mg daily. Although this amount appears to be low, women are advised not to breast feed while taking hydroxycarbamide.[1]

1. Sylvester RK, *et al.* Excretion of hydroxyurea into milk. *Cancer* 1987; **60**: 2177–8.

Carcinogenicity. Secondary leukaemias have occurred in patients receiving hydroxycarbamide for myeloproliferative disorders, although the extent to which this is due to the treatment or the underlying disorder is unknown.

Skin cancers have also been associated with its use. These are often multiple and include both squamous cell and basal cell carcinomas.

References.

1. Liozon E, *et al.* Is treatment with hydroxyurea leukemogenic in patients with essential thrombocythemia? An analysis of three new cases of leukaemic transformation and review of the literature. *Hematol Cell Ther* 1997; **39**: 11–18.
2. Pearson TC, *et al.* Leukemic transformation in polycythemia vera. *Blood* 1998; **92**: 1837–8.
3. De Simone C, *et al.* Multiple squamous cell carcinomas of the skin during long-term treatment with hydroxyurea. *Eur J Dermatol* 1998; **8**: 114–15.
4. Best PJM, Petitt RM. Multiple skin cancers associated with hydroxyurea therapy. *Mayo Clin Proc* 1998; **73**: 961–3.

Effects on the liver. Fever and hepatitis have been reported[1,2] in patients receiving hydroxycarbamide. Symptoms recurred when patients were rechallenged with the drug.

1. Heddle R, Calvert AF. Hydroxyurea induced hepatitis. *Med J Aust* 1980; **1**: 121.
2. Westerman DA, *et al.* Hydroxyurea-induced fever and hepatitis. *Aust N Z J Med* 1998; **28**: 657–9.

Effects on the skin and nails. Reports of skin reactions with hydroxycarbamide include hyperpigmentation of the skin,[1] and of nails (melanonychia).[2]

Hydroxycarbamide therapy has been associated with scaly erythematous skin lesions often resembling those of dermatomyositis.[1,3,4] Such lesions usually occur after several years of treatment and the course is usually benign. However, withdrawal of the drug is usually necessary for healing or improvement, in which case resolution may take several months.[1,4] Hydroxycarbamide can also cause painful leg ulcers, often on the malleoli, which may require stopping treatment.[1,5,6] Leg ulcers often coexist with dermatomyositis-like eruptions and may be caused by the same mechanism,[7] although mechanical injury may have a role in malleolar ulceration.[5] Licensed product information notes that vasculitic toxicities, including vasculitic ulceration and gangrene, have been associated with hydroxycarbamide use in patients with myeloproliferative disorders (particularly if also given interferon). However, histologically, perivascular lymphocytic infiltration without vasculitis has been reported in both early dermatomyositis-like lesions[1] and in leg ulcers.[5,8]

Skin cancers have also occurred, see Carcinogenicity above.

1. Vassallo C, *et al.* Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clin Exp Dermatol* 2001; **26**: 141–8.
2. Aste N, *et al.* Nail pigmentation caused by hydroxyurea: report o 9 cases. *J Am Acad Dermatol* 2002; **47**: 146–7.
3. Senet P, *et al.* Hydroxyurea-induced dermatomyositis-like erup ion. *Br J Dermatol* 1995; **133**: 455–9.
4. Daoud MS, *et al.* Hydroxyurea dermopathy: a unique lichenoid ruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol* 1997; **36**: 178–82.
5. Best PJ, *et al.* Hydroxyurea-induced leg ulceration in 14 patie nts. *Ann Intern Med* 1998; **128**: 29–32.
6. Chaine B, *et al.* Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. *Arch Dermatol* 2001; **137**: 467–70.
7. Suehiro M, *et al.* Hydroxyurea dermopathy with a dermatomyo sitis-like eruption and a large leg ulcer. *Br J Dermatol* 1998; **139**: 748–9.
8. Tarumoto T, *et al.* A case of bilateral heel ulcers associat d with hydroxyurea therapy for chronic myelogenous leukemia. *Jp n J Clin Oncol* 2000; **30**: 159–62.

Handling and disposal. *Urine* produced for up to 48 hours after a dose of hydroxycarbamide should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving c totoxic drugs. *Pharm J* 1985; **235**: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydroxycarb mide 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 28/09/11)

Interactions

For a general discussion of antineoplastic drug interac tions, see p. 733.3.

Pharmacokinetics

Hydroxycarbamide is readily absorbed from the gastrointestinal tract and distributed throughout the body. Peak plasma concentrations are reached within 2 hours. Up to 50% of a dose is metabolised by the liver; hydroxycarbamide is excreted in urine as metabolites and unchanged drug. Some is excreted as carbon dioxide via the lungs. About 80% of a dose is reported to be excreted in the urine within 12 hours. Hydroxycarbamide crosses the blood-brain barrier and the placenta, and is distributed into breast milk.

References.

1. Gwilt PR, Tracewell WG. Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clin Pharmacokinet* 1998; **34**: 347–58.
2. Gwilt PR, *et al.* Pharmacokinetics of hydroxyurea in plasma and cerebrospinal fluid of HIV-1-infected patients. *J Clin Pharmacol* 2003; **43**: 1003–7.
3. Yan J-H, *et al.* The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005; **45**: 434–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dacrodil†; Hidrolid; *Austral.*: Hydrea; *Austria*: Litalir; *Belg.*: Hydrea; *Braz.*: Hydrea; *Canad.*: Hydrea; *Chile*: Hydrea; *Cz.*: Litalir; Siklos; *Denm.*: Hydrea; *Fin.*: Hydrea; *Fr.*: Hydrea; Siklos; *Ger.*: Litalir; Siklos; Syrea; *Gr.*: Hydrea; Hydreasyn; Siklos; *Hong Kong*: Hydrea†; *Hung.*: Litalir; *India*: Cytodrox; Durea; Hondrea; Hydab; Hydran; Hydrea; Leukocel; Myelostat; Neodrea; Oxyrea; *Indon.*: Hydrea; *Irl.*: Hydrea; Siklos; *Ital.*: Onco-Carbide; *Mex.*: Hydrea; *Neth.*: Hydrea; Siklos; *Norw.*: Hydrea; *NZ*: Hydrea; *Philipp.*: Hydab; Hydrox; Krabinex; Litalir†; *Pol.*: Siklos; *Port.*: Hydrea†; Siklos; *Rus.*: Gidroxyurea (Гидроксиурея)†; Hydrea (Гидреа); *S.Afr.*: Hydrea; *Singapore*: Hydrine; *Spain*: Hydrea; Siklos; *Swed.*: Hydrea; *Switz.*: Litalir; *Thai.*: Hydrea; *Turk.*: Hydrea; *UK*: Hydrea; Siklos; *USA*: Droxia; Hydrea.

Pharmacopoeial Preparations

BP 2014: Hydroxycarbamide Capsules;
USP 36: Hydroxyurea Capsules.

Ibritumomab Tiuxetan *(BAN, USAN, rINN)*

Ibritumomab tiuxétan; Ibritumomab Tiuxétan; Ibritumomabum Tiuxetanum; IDEC-129; IDEC-Y2B8; Ибритумомаб Тиуксетан.

Immunoglobulin G1, anti(human CD20 (antigen))(mouse monoclonal IDEC-Y2B8 γ1-chain), disulfide with mouse monoclonal IDEC-Y2B8 κ-chain, dimer tiuxetan conjugate.

CAS — 206181-63-7.
UNII — 4Q52C550XK.

Uses and Administration

Ibritumomab is a murine monoclonal antibody to CD20 antigen, which is conjugated with tiuxetan to provide a chelation site for radioactive isotopes. Radiolabelled ibritumomab tiuxetan is used in the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (p. 696.3). Patients are pretreated with a low dose of rituximab (p. 852.1). In the USA this is followed by slow intravenous injection of ibritumomab tiuxetan chelated with indium-111 (p. 2224.3) for imaging to

confirm that biodistribution of tumour cells is acceptable, but in some other countries such imaging is considered to provide relatively little useful information, and is omitted. A second rituximab treatment is given 7 to 9 days after the first, followed by ibritumomab tiuxetan chelated with yttrium-90 (p. 2230.1) for radio-immunotherapy.

References.

1. Wiseman GA, *et al.* Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *Crit Rev Oncol Hematol* 2001; **39:** 181–94.
2. Wagner HN, *et al.* Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with ^{90}Y-labeled anti-CD20 monoclonal antibody. *J Nucl Med* 2002; **43:** 267–72.
3. Witzig TE, *et al.* Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 2453–63.
4. Witzig TE, *et al.* Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 3262–9.
5. Ansell SM, *et al.* Subsequent chemotherapy regimens are well tolerated after radioimmunotherapy with yttrium-90 ibritumomab tiuxetan for non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 3885–90.
6. Witzig TE. Yttrium-90-ibritumomab tiuxetan radioimmunotherapy: a new treatment approach for B-cell non-Hodgkin's lymphoma. *Drugs Today* 2004; **40:** 111–19.
7. Hagenbeek A, Lewington V. Report of a European consensus workshop to develop recommendations for the optimal use of ^{90}Y-ibritumomab tiuxetan (Zevalin) in lymphoma. *Ann Oncol* 2005; **16:** 786–92.
8. Meredith RF. Logistics of therapy with the ibritumomab tiuxetan regimen. *Int J Radiat Oncol Biol Phys* 2006; **66** (suppl): S35–S38.
9. Cheung MC, *et al.* Yttrium 90 ibritumomab tiuxetan in lymphoma. *Leuk Lymphoma* 2006; **47:** 967–77. Correction. *ibid.*: 1719–20.
10. Gisselbrecht C, *et al.* Current status and future perspectives for yttrium-90 (^{90}Y)-ibritumomab tiuxetan in stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2007; **40:** 1007–17.

Adverse Effects and Precautions

For general discussions, see Antineoplastics, p. 726.1 and p. 732.2.

Myelosuppression is common after doses of ibritumomab tiuxetan, and may be prolonged. Fatal intracranial haemorrhage has occurred. Infections and hypersensitivity reactions may also be severe. As ibritumomab tiuxetan is given with rituximab, severe infusion reactions due to the cytokine release syndrome may occur (see under Rituximab, p. 854.3). Severe cutaneous and mucocutaneous reactions, some fatal, have been reported and therapy should be stopped if they occur. Gastrointestinal disturbances are common. Other adverse effects include anorexia, asthenia, fever, cough, dyspnoea, dizziness, headache, insomnia, anxiety, arthralgia, myalgia, and peripheral oedema. Patients should be monitored for signs of extravasation in order to avoid radiation-associated tissue damage. If extravasation occurs, the infusion should be stopped immediately and restarted in another vein.

Complete blood and platelet counts should be monitored weekly, or more frequently if cytopenia is present, until haematological recovery. Ibritumomab tiuxetan should not be given to patients with extensive marrow involvement, impaired bone marrow reserve, or platelet or neutrophil counts below acceptable levels (see also Bone-marrow Depression, p. 730.3). Care should be taken during and after radiolabelling with indium-111 or yttrium-90 to minimise radiation exposure.

Effects on the skin. Severe cutaneous and mucocutaneous reactions have been reported after use of ibritumomab tiuxetan with rituximab, some of them with a fatal outcome.[1,2] Reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis. Onset was reported to vary from days to months. Treatment should be stopped if any patient has such a reaction.

1. Kooijmans-Coutinho M [Biogen Idec (USA)]. Important drug warning (issued October 2005). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicinalProducts/ucm164905.pdf (accessed 21/07/10)
2. Berlex, Canada. Association of severe mucocutaneous reactions with the ZEVALIN therapeutic regimen (issued 7th December 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zevalin_nth-aah_e.pdf (accessed 26/04/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zevamab; *Austria*: Zevalin; *Belg.*: Zevalin; *Canad.*: Zevalin; *Cz.*: Zevalin; *Fin.*: Zevalin; *Fr.*: Zevalin; *Ger.*: Zevalin; *Hong Kong*: Zevalin; *Hung.*: Zevalin; *Irl.*: Zevalin; *Israel*: Zevalin; *Ital.*: Zevalin; *Neth.*: Zevalin; *Norw.*: Zevalin; *NZ*: Zevalin†; *Pol.*: Zevalin; *Port.*: Zevalin; *S. Afr.*: Zevalin†; *Spain*: Zevalin; *Swed.*: Zevalin; *Switz.*: Zevalin; *Thai.*: Zevalin; *Turk.*: Zevalin; *UK*: Zevalin; *USA*: Zevalin.

Ibrutinib *(USAN, pINN)*

CRA-032765; Ibrutinibum; PCI-32765-00; PCI-32765; Ибрутиниб

1-[(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one.

$C_{25}H_{24}N_6O_2$=440.5

CAS — 936563-96-1.

Profile

Ibrutinib is an inhibitor of Bruton's tyrosine kinase that is used in the treatment of relapsed mantle cell lymphoma (p. 698.2). The usual dose is 560 mg orally once daily; capsules should be swallowed whole and not opened. If a daily dose is missed, the next day's dose should not be increased. If severe toxicity occurs, doses should be withheld until recovery to baseline or grade 1. For the first occurrence, treatment is restarted at the usual dose. Subsequently, the dose should be reduced to 420 mg daily after the second occurrence, and to 280 mg daily after the third occurrence. Ibrutinib should be stopped if the patient is unable to tolerate 280 mg daily. Treatment is continued until the patient no longer benefits, or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Ibrutinib is metabolised in the liver by the cytochrome P450 isoenzyme CYP3A family and use with strong or moderate inhibitors or strong inducers of these enzymes should be avoided. If use together is necessary, ibrutinib treatment may be interrupted for short-term therapy with a strong CYP3A inhibitor; the dose of ibrutinib should be reduced to 140 mg daily when used with a moderate CYP3A inhibitor.

The most commonly reported adverse effects include neutropenia, thrombocytopenia, anaemia, gastrointestinal disturbances, fatigue, musculoskeletal or abdominal pain, peripheral oedema, dyspnoea, rash, and decreased appetite. Haemorrhage, renal failure, and second primary malignancies have occurred.

Ibrutinib is also under investigation for chronic lymphocytic leukaemia.

References.

1. Burger JA, Buggy JJ. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765). *Leuk Lymphoma* 2013; **54:** 2385–91.
2. Chavez JC, *et al.* Ibrutinib: an evidence-based review of its potential in the treatment of advanced chronic lymphocytic leukemia. *Core Evid* 2013; **8:** 37–45.
3. Akinleye A, *et al.* Ibrutinib and novel BTK inhibitors in clinical development. *J Hematol Oncol* 2013; **6:** 59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Imbruvica.

Idarubicin Hydrochloride

(BANM, USAN, rINNM)

4-Demethoxydaunorubicin Hydrochloride; Hidrocloruro de idarubicina; Idarubicina, hidrocloruro de; Idarubicine, chlorhydrate d'; Idarubicinhydroklorid; Idarubicini Hydrochloridum; Idarubisiinihydrokloridi; Idarubisin Hidroklorür; IMI-30; NSC-256439 (idarubicin); Идарубицина Гидрохлорид.

(7*S*,9*S*)-9-Acetyl-7-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-7,8,9,10-tetrahydro-6,9,11-trihydroxynaphthacene-5,12-dione hydrochloride.

$C_{26}H_{27}NO_9$,HCl=534.0

CAS — 58957-92-9 (idarubicin); 57852-57-0 (idarubicin hydrochloride).

ATC — L01DB06.

ATC Vet — QL01DB06.

UNII — 5VV3MDU5IE.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Idarubicin Hydrochloride). A red-orange to red-brown powder. Slightly soluble in water; insoluble in acetone and in solvent ether; soluble in methyl alcohol. A 0.5% solution in water has a pH between 5.0 and 6.5. Store in airtight containers.

Incompatibility. Licensed product information states that precipitation occurs when idarubicin hydrochloride is mixed with heparin, and that it will degrade in alkaline solution.

Uses and Administration

Idarubicin like daunorubicin (p. 778.3), of which it is an analogue, is an anthracycline antibiotic and has antineoplastic actions similar to those of doxorubicin (p. 783.2). It is used as the hydrochloride, alone or with other drugs, for the induction of remission in patients with acute myeloid leukaemias (p. 693.1). It is also used as a second-line treatment in acute lymphoblastic leukaemia (p. 692.3), and advanced breast cancer (p. 702.1).

Idarubicin hydrochloride is given by *intravenous* injection into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 5 to 15 minutes. The suggested dose in adult acute myeloid leukaemia is 12 mg/m^2 daily for 3 days, with cytarabine. A similar dose, as a single agent, has been given in acute lymphoblastic leukaemia. An alternative dosage schedule in acute myeloid leukaemia is 8 mg/m^2 given daily for 5 days, either alone or in combination therapy. For suggested doses in children with acute lymphoblastic leukaemia see Administration in Children, below.

When the intravenous route cannot be used, idarubicin hydrochloride may be given orally. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* A suggested *oral* dose in adult acute myeloid leukaemia as a single agent is 30 mg/m^2 daily for 3 days; 15 to 30 mg/m^2 may be given daily for 3 days when used with other drugs.

In patients with breast cancer unresponsive to front-line chemotherapy not including anthracyclines, idarubicin hydrochloride has been given orally in doses of 45 mg/m^2, as a single dose or divided over 3 consecutive days; the treatment may be repeated every 3 or 4 weeks depending on the haematological recovery. A total cumulative oral dose of 400 mg/m^2 should not be exceeded.

Blood counts should be performed frequently in patients receiving idarubicin, and monitoring of cardiac, hepatic, and renal function is recommended. Doses should be reduced in patients with hepatic or renal impairment (see also below). In patients who receive a second course of idarubicin, intravenous dosage should be reduced by 25% if severe mucositis developed with the first course; therapy should be delayed until the patient has recovered from this toxicity.

The actions and uses of idarubicin have been reviewed.[1] A study in leukaemia cells *in vitro* suggested that idarubicin was more active than a conventional anthracycline, daunorubicin, against cells with the multidrug resistance (MDR) phenotype.[2] A collaborative overview of randomised studies for acute myeloid leukaemia found that idarubicin-based therapy achieved better remission rates and overall survival than daunorubicin-based regimens.[3] Its oral bioavailability has been suggested to offer an advantage in the management of malignancies in older patients.[4]

1. Cersosimo RJ. Idarubicin: an anthracycline antineoplastic agent. *Clin Pharm* 1992; **11:** 152–67.
2. Berman E, McBride M. Comparative cellular pharmacology of daunorubicin and idarubicin in human multidrug-resistant leukaemia cells. *Blood* 1992; **79:** 3267–73.
3. AML Collaborative Group. A systematic collaborative overview of randomised trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. *Br J Haematol* 1998; **103:** 100–9.
4. Crivellari D, *et al.* New oral drugs in older patients: a review of idarubicin in elderly patients. *Crit Rev Oncol Hematol* 2004; **49:** 153–63.

Administration in children. Idarubicin hydrochloride may be given as a second-line treatment to children with relapsed acute lymphoblastic leukaemia. The suggested intravenous dose for use as a single agent is 10 mg/m^2 daily for 3 days. Precautions and monitoring are as for adults, see Uses and Administration, above.

Administration in hepatic impairment. UK licensed product information for idarubicin hydrochloride recommends that a dose reduction be considered in patients with hepatic impairment. Although no specific doses are suggested, it is noted that a 50% reduction in dosage has been used with some other anthracyclines in patients whose bilirubin concentrations were between 12 and 20 micrograms/mL. Use of idarubicin is contra-indicated in patients with severe hepatic impairment.

US licensed product information states that in patients with moderate or severe hepatic impairment, the metabolism of idarubicin is expected to be reduced, leading to higher systemic drug concentrations, and that dose reduction should be considered. No specific doses are recommended; idarubicin should be withheld if bilirubin concentrations exceed 50 micrograms/mL.

Administration in renal impairment. Both UK and US licensed product information state renal impairment may affect the disposition of idarubicin and that, in many studies, treatment was contra-indicated if serum creatinine concentrations exceeded 20 micrograms/mL. US licensed product information suggests that dose reduction be considered in renal impairment, but gives no specific doses; UK licensed product information states that idarubicin should not be used in patients with severe renal impairment.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p. 784.1. Raised liver enzymes and bilirubin can occur with idarubicin. Severe enterocolitis with perforation has been reported rarely. A cumulative total dose limit has not yet been defined. UK licensed

product information states that total cumulative oral doses up to 400 mg/m² have a low probability of cardiotoxicity. Cardiomyopathy has been reported in some patients with cumulative intravenous doses of 150 to 290 mg/m². It has been suggested that idarubicin may be associated with less cardiotoxicity than doxorubicin. Idarubicin should be given with caution, and in reduced doses, to patients with renal or hepatic impairment.

Effects on the heart. Cardiotoxicity is a major factor in limiting the use of anthracyclines (see under Doxorubicin, p. 784.1). It has been suggested that idarubicin may be associated with less cardiotoxicity than doxorubicin. However, a 34-year-old woman with no risk factors for heart disease developed severe congestive heart failure after her first exposure to idarubicin, which was given as part of an induction regimen for acute myeloid leukaemia. The patient's left ventricular ejection fraction improved after 4 months, supporting the hypothesis that, while chronic anthracycline-induced cardiomyopathy is irreversible, subacute congestive heart failure after short-term anthracycline use may be partially or totally reversible.[1]

1. Yang S-G, *et al.* The development of congestive heart failure and ventricular tachycardia after first exposure to idarubicin in a patient with acute myeloid leukaemia. *Br J Clin Pharmacol* 2010; **69**: 209–11.

Effects on the skin and nails. For a report of transverse hyperpigmented bands of the nails in a patient who received idarubicin, see under Doxorubicin, p. 784.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies idarubicin 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 29/09/11)

Pharmacokinetics

On intravenous dosage idarubicin is rapidly distributed into body tissues and extensively tissue bound, with a volume of distribution which may be in excess of 2000 litres. It is extensively metabolised, both in the liver and extrahepatically; the principal metabolite, idarubicinol (13-dihydroidarubicin) has equal antineoplastic activity. Peak concentrations of idarubicin and idarubicinol in bone marrow and nucleated blood cells are 400 (idarubicin) and 200 (idarubicinol) times greater than those in plasma; cellular concentrations of drug and metabolite decline with apparent terminal half-lives of 15 and 72 hours respectively, whereas plasma half-lives are reported to be 20 to 22 hours and about 45 hours respectively. Idarubicin is excreted in bile, and to a lesser extent in urine, as unchanged drug and metabolites.

Idarubicin is also absorbed orally, reaching peak plasma concentrations within 4 hours. Estimates of its oral bioavailability vary from about 20 to 40%.

References.

1. Robert J. Clinical pharmacokinetics of idarubicin. *Clin Pharmacokinet* 1993; **24**: 275–88.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Epicina; Zavedos; *Austral.*: Zavedos; *Austria*: Zavedos; *Belg.*: Zavedos; *Braz.*: Evomid; Zavedos; *Canad.*: Idamycin; *Chile*: Zavedos; *China*: Ai Nuo Ning (艾诺宁); Zavedos (善唯达); *Cz.*: Zavedos; *Denm.*: Zavedos; *Fin.*: Zavedos; *Fr.*: Zavedos; *Ger.*: Zavedos; *Gr.*: Zavedos; *Hong Kong*: Zavedos; *Hung.*: Zavedos; *Irl.*: Zavedos; *Israel*: Zavedos; *Ital.*: Zavedos; *Malaysia*: Zavedos; *Mex.*: Idamycin; Idaralem†; *Neth.*: Zavedos; *Norw.*: Zavedos; *NZ*: Zavedos; *Philipp.*: Zavedos; *Pol.*: Zavedos; *Port.*: Zavedos; *Rus.*: Rubide (Рубида); Zavedos (Завелос); *S.Afr.*: Zavedos; *Singapore*: Zavedos; *Spain*: Zavedos; *Swed.*: Zavedos; *Switz.*: Zavedos; *Thai.*: Idaralem†; Zavedos; *Turk.*: Idamen; Zavedos; *UK*: Zavedos; *Ukr.*: Zavedos (Завелос); *USA*: Idamycin; *Venez.*: Zavedos.

Pharmacopoeial Preparations

USP 36: Idarubicin Hydrochloride for Injection.

Ifosfamide *(BAN, USAN, rINN)*

Ifosfamid; Ifosfamida; Ifosfamidas; Ifosfamidi; Ifosfamidum; Ifoszfamid; Iphosphamide; Isophosphamide; MJF-9325; NSC-109724; Z-4942; Ифосфамид.

3-(2-Chloroethyl)-2-(2-chloroethylamino)perhydro-1,3,2-oxazaphosphorinane 2-oxide.

$C_7H_{15}Cl_2N_2O_2P$=261.1

CAS — 3778-73-2.

ATC — L01AA06.

ATC Vet — QL01AA06.

UNII — UM20QQM95Y.

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

Ph. Eur. 8: (Ifosfamide). A white or almost white, hygroscopic, fine crystalline powder. Soluble in water; freely soluble in dichloromethane. Store in airtight containers.

USP 36: (Ifosfamide). A white, crystalline powder. M.p. about 40 degrees. Freely soluble in water; very soluble in alcohol, in methyl alcohol, in isopropyl alcohol, in dichloromethane, and in ethyl acetate; very slightly soluble in hexanes. A 10% solution in water has a pH of between 4.0 and 7.0. Store in airtight containers at a temperature not exceeding 25 degrees.

Incompatibility. Ifosfamide appears to be compatible when mixed in solution with mesna.[1,2] However, ifosfamide appears to be incompatible with benzyl alcohol used as a preservative in Water for Injections: solutions made up with water preserved in this way became turbid, with the formation of aqueous and oily phases, at concentrations of ifosfamide greater than 60 mg/mL.[3]

1. Shaw IC, Rose JWP. Infusion of ifosphamide plus mesna. *Lancet* 1984; **i**: 1353–4.
2. Rowland CG, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; **ii**: 468.
3. Bohme RJ, *et al.* Incompatibility of ifosfamide with benzyl-alcohol-preserved bacteriostatic water for injection. *Am J Hosp Pharm* 1988; **45**: 627–8.

Stability. Ifosfamide undergoes a reversible chemical rearrangement in aqueous solution, which is sensitive to changes in pH.[1] The ratio of these compounds to one another in biological fluids may have a bearing on the toxicity and efficacy of ifosfamide.

1. Küpfer A, *et al.* Intramolecular rearrangement of ifosfamide in aqueous solutions. *Lancet* 1990; **335**: 1461.

Uses and Administration

Ifosfamide is an alkylating agent with properties similar to those of cyclophosphamide (p. 771.1), of which it is a congener. It is used in the treatment of solid tumours including those of the cervix, lung, ovary, testis, and thymus, as well as in sarcoma and in the treatment of lymphomas. For further mention of these uses see the cross-references given below.

Ifosfamide is given intravenously, either by injection as a solution diluted to less than 4%, or by infusion. Licensed dosage regimens include a total dose of 8 to 12 g/m² divided over 3 to 5 days, with the course repeated at 2 to 4 week intervals; a total dose of 6 g/m² divided over 5 days, repeated every 3 weeks; and doses of 5 to 6 g/m², to a maximum of 10 g, given as a single 24-hour infusion, repeated at 3 to 4 week intervals. The interval between courses also depends on the blood count (see also Bone-marrow Depression, p. 730.3). Oral ifosfamide has also been studied but is associated with neurotoxicity (see Effects on the Nervous System, below).

Ifosfamide should be given with mesna (see Administration, below), and adequate hydration should be maintained, to avoid urological toxicity; fluid intake should not be less than 2 litres daily.

Administration. Mesna (p. 1557.2) can combine with urotoxic ifosfamide metabolites in the kidney to form stable and non-toxic compounds. It is therefore given prophylactically with ifosfamide. It has a shorter half-life than ifosfamide so repeated doses are needed to provide adequate protection of the bladder. A common schedule uses intravenous mesna at 60% of the ifosfamide dose, divided into 3 doses given with, or 15 minutes before, ifosfamide, then 4 and 8 hours after ifosfamide.[1] Mesna may also be given orally, but higher doses are required.

1. Siu LL, Moore MJ. Use of mesna to prevent ifosfamide-induced urotoxicity. *Support Care Cancer* 1998; **6**: 144–54.

Malignant neoplasms. Ifosfamide may be used as an alternative to cyclophosphamide in lymphomas such as Burkitt's lymphoma (p. 697.3). It is also used in a variety of solid neoplasms, including in palliative regimens for advanced cervical cancer (p. 704.2); in the treatment of lung cancer (p. 710.2); in ovarian cancer (p. 711.2) and second-line and salvage regimens for testicular cancer (p. 715.1); in thymoma (p. 715.3); in adjuvant therapy for bone sarcomas (p. 717.3) and rhabdomyosarcoma (see Soft-tissue Sarcoma, p. 718.2).

Adverse Effects, Treatment, and Precautions

As for Cyclophosphamide, p. 772.2. Toxic effects on the urinary tract may be more severe with ifosfamide and may involve the kidneys as well as the bladder. CNS adverse effects have been reported, especially confusion, drowsiness, depressive psychosis, hallucinations, and rarely, seizures.

Effects on the heart. Severe myocardial depression, with heart failure and ventricular arrhythmias, has been reported in patients given high-dose ifosfamide.[1] Symptoms were reversible with appropriate treatment in most cases although one patient died of cardiogenic shock.

1. Quezado ZMN, *et al.* High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med* 1993; **118**: 31–6.

Effects on the kidneys. In addition to its effects on the bladder ifosfamide may be associated with serious nephrotoxicity. A prospective study found that moderate and severe nephrotoxicity are common after ifosfamide treatment in children and adolescents, affecting 28% of patients.[1] Both proximal and distal tubular damage,[2,3] and to a lesser extent glomerular effects,[3] are seen, and the Fanconi syndrome (with development of hypophosphataemic rickets in several children),[3-7] and nephrogenic diabetes insipidus[2,7] may result. Progressive chronic renal failure after high-dose ifosfamide has been described.[8] Life-threatening hypokalaemia possibly due to a renal lesion has also occurred.[9] Results in *rats* suggest that generation of toxic metabolites within the kidney itself may be responsible, and that repairable renal damage occurs after the first dose, which is aggravated by repeated toxic insults.[10] This is in agreement with clinical results, since although renal damage has been seen after a single dose, perhaps representing an idiosyncratic reaction,[11,12] most cases have been in children receiving relatively high doses long-term. Renal damage appears to persist after withdrawal of ifosfamide in these patients and may be largely irreversible.[13] Toxicity may also progress over the months or years after treatment,[14] or late renal damage may develop after treatment has stopped.[15] Proximal tubular dysfunction was the most common form of damage in patients who had received ifosfamide at least 5 years previously for childhood malignancies,[14,15] and it has been suggested that reductions in the glomerular filtration rate are secondary to this, rather than a direct result of ifosfamide toxicity.[14] Although the risk of late toxicity was considered low, the damage was moderately severe even when the cumulative dose was small (60 g/m²).[15]

Possible risk factors for nephrotoxicity have included younger age (less than 5 years), high cumulative doses, use with cisplatin, or unilateral nephrectomy.[1,14,16] The cumulative dose appears to be the most important risk factor for the development and severity of toxicity.[1,16] The maximum safe dose of ifosfamide has not been established;[1,14,16] although *significant nephrotoxicity* is relatively infrequent below 84 g/m², doses above 119 g/m² are associated with a high risk of severe damage. Although some found no association between age at treatment and renal damage,[1] others noted that a younger age was associated with more severe nephrotoxicity,[14,16] and suggested that caution is needed when giving cumulative doses of 45 g/m² and above to children aged under 3 years[14] or 60 g/m² and above to those under 5 years.[16] Acetylcysteine has been investigated for its potential protective effect against nephrotoxicity.[17]

1. Skinner R, *et al.* Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. United Kingdom Children's Cancer Study Group. *Br J Cancer* 2000; **82**: 636–45.
2. Skinner R, *et al.* Nephrotoxicity after ifosfamide. *Arch Dis Child* 990; **65**: 732–8.
3. Burk CD, *et al.* Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms tumor. *J Pediatr* 1990; **117**: 331–5.
4. Skinner R, *et al.* Hypophosphataemic rickets after ifosfamide treatment in children. *BMJ* 1989; **298**: 1560–1.
5. Newbury-Ecob RA, Barbor PRH. Hypophosphataemic rickets after ifosfamide treatment. *BMJ* 1989; **299**: 258.
6. Newbury-Ecob RA, *et al.* Ifosfamide-induced Fanconi syndrome. *Lancet* 1989; **i**: 1328.
7. Skinner R, *et al.* Nephrotoxicity of ifosfamide in children. *Lancet* 1989; **ii**: 159.
8. Krämer A, *et al.* Progressive renal failure in two breast cancer patients after high-dose ifosfamide. *Lancet* 1994; **334**: 1569.
9. Husband DJ, Watkin SW. Fatal hypokalaemia associated with ifosfamide/mesna chemotherapy. *Lancet* 1988; **i**: 1116.
10. Graham MI, *et al.* A proposed mechanism for isophosphamide induced kidney toxicity. *Hum Toxicol* 1985; **4**: 545–6.
11. Heney D, *et al.* Acute ifosfamide-induced tubular toxicity. *Lancet* 1989; **ii**: 103–4.
12. Devalck C, *et al.* Acute ifosfamide-induced proximal tubular toxic reaction. *J Pediatr* 1991; **118**: 325–6.
13. Heney D, *et al.* Progressive renal toxicity due to ifosfamide. *Arch Dis Child* 1991; **66**: 966–70.
14. Loebstein R, *et al.* Risk factors for long-term outcome of ifosfamide-induced nephrotoxicity in children. *J Clin Pharmacol* 1999; **39**: 454–61.
15. Oberlin O, *et al.* Long-term evaluation of ifosfamide-related nephrotoxicity in children. *J Clin Oncol* 2009; **27**: 5350–5.
16. Loebstein R, Koren G. Ifosfamide-induced nephrotoxicity in children: critical review of predictive risk factors. *Pediatrics* 1998; **101**: 1167. Full version: http://pediatrics.aappublications.org/cgi/content/full/101/6/e8 (accessed 30/06/04)
17. Chen N, *et al.* Prevention of ifosfamide nephrotoxicity by N-acetylcysteine: clinical pharmacokinetic considerations. *Can J Clin Pharmacol* 2007; **14**: e246–e250.

Effects on the nervous system. Use of ifosfamide (with or without mesna for urothelial protection) may be associated with the development of severe encephalopathy, which develops in 10 to 40% of patients receiving high doses. Symptoms include confusion, stupor, seizures, hallucinations, blurred vision, and occasionally, coma; fatalities have been reported.[1] The effect has been suggested to be due to a metabolite, chloroacetaldehyde,[1] a hypothesis

supported by the increased incidence of encephalopathy after oral rather than intravenous doses.[2] Others suggest that the dechloroethylated metabolites may contribute, and in particular the *R*-enantiomer of 3-dechloroethyl-ifosfamide, which is a metabolite of *S*-ifosfamide.[3] There is some uncertainty about the contributory role of mesna, if any: encephalopathy has not been seen when mesna is given with cyclophosphamide,[4] and has been seen when ifosfamide is given alone,[2] but an exacerbatory role for mesna cannot be ruled out,[3] perhaps via its chelating properties.[4]

Proposed risk factors include renal and hepatic impairment, pelvic disease, brain metastases, electrolyte imbalances, and drug-drug interactions.[1] A retrospective review of 237 patients given ifosfamide, of whom 38 developed encephalopathy, found no evidence that age or ifosfamide dose influenced the development of the condition, and serum creatinine values were in the normal range in the affected group, although they were slightly higher than in those not affected; however, low serum albumin did seem to be associated with greater risk.[4] It has also been suggested that the drug be given by continuous infusion over several days where possible, since this route has by far the lowest incidence of encephalopathy (7%, versus 26% with intravenous bolus and 43% with oral doses).[7] Care may also be required when giving other antineoplastics to patients who have had encephalopathy after ifosfamide, since a case of encephalopathy with bleomycin (not normally associated with neurotoxicity) has been reported in such a patient.[8] In another case, ifosfamide neurotoxicity developed after the addition of aprepitant to a standard antiemetic regimen that included ondansetron and dexamethasone; induction of ifosfamide metabolism to neurotoxic metabolites may have accounted for the symptoms.[9] Hypoalbuminaemia has been identified as a risk factor in other case reports. A small cohort study identified hypoalbuminaemia, female sex, low total bilirubin, anaemia, and obesity as being associated with the development of ifosfamide-induced encephalopathy.[1]

Methylthioninium chloride has been tried to prevent or reverse signs of encephalopathy (see Glutaric Aciduria under Uses of Methylthioninium Chloride, p. 1559.2).

1. Sweiss KI, *et al.* Encephalopathy after high-dose ifosfamide: a retrospective cohort study and review of the literature. *Drug Safety* 2008; 31: 989–96.
2. Lewis LD, Meanwell CA. Ifosfamide pharmacokinetics and neurotoxicity. *Lancet* 1990; 335: 175–6.
3. Wainer IW, *et al.* Ifosfamide stereoselective dichloroethylation [sic] and neurotoxicity. *Lancet* 1994; 343: 982–3.
4. Osborne RJ, Slevin ML. Ifosfamide, mesna, and encephalopathy. *Lancet* 1985; I: 1398–9.
5. Pinkerton R, *et al.* Ifosfamide, mesna, and encephalopathy. *Lancet* 1985; I: 1399.
6. David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. *Am J Clin Oncol* 2005; 28: 277–80.
7. Cerny T, *et al.* Ifosfamide by continuous infusion to prevent encephalopathy. *Lancet* 1990; 335: 175.
8. Atherton P, *et al.* Drug-induced encephalopathy after previous ifosfamide treatment. *Lancet* 1988; II: 1084.
9. Jarkowski A. Possible contribution of aprepitant to ifosfamide-induced neurotoxicity. *Am J Health-Syst Pharm* 2008; 65: 2229–31.

Handling and disposal. A study[1] found that ifosfamide 8% solution penetrated all of 4 brands of latex glove and one PVC glove, although the diffusion rate was 4 or more times slower than through cadaver skin. Permeation was greater through the PVC glove than the latex gloves, partly due to its lesser thickness, although permeation was not dependent on thickness alone and varied between gloves of the same brand as well as between brands. They recommended that latex gloves of a suitable brand should be worn when handling ifosfamide, and changed at least every 2 hours. For reference to a method for the destruction of ifosfamide waste, see under Cyclophosphamide, p. 773.2.

1. Corlett SA, *et al.* Permeation of ifosfamide through gloves and cadaver skin. *Pharm J* 1991; 247: R39.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ifosfamide 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 28/09/11)

Interactions

As for Cyclophosphamide, p. 773.2. For a general outline of antineoplastic drug interactions, see p. 733.3. For reference to the effects of ifosfamide on oral anticoagulants, see under Warfarin Sodium, p. 1532.2. For a report of the enhancement of cisplatin-induced ototoxicity and nephrotoxicity, see under Cisplatin, p. 768.3.

Antibacterials. Oral *rifampicin* given twice daily for 6 days, starting 3 days before intravenous ifosfamide (as a 24-hour infusion), increased the clearance of ifosfamide by over 100%; however, exposure to metabolites of ifosfamide was relatively unchanged. The authors considered that rifampicin might decrease the therapeutic efficacy of ifosfamide.[1]

1. Kerbusch T, *et al.* Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; 70: 132–41.

Antifungals. *Ketoconazole* given orally for 4 days, starting 1 day before intravenous ifosfamide (given as a 24-hour infusion), decreased ifosfamide clearance. However, ifosfamide metabolism to active metabolites was decreased, and urinary excretion of ifosfamide was increased. Ketoconazole may decrease the therapeutic efficacy of ifosfamide.[1]

1. Kerbusch T, *et al.* Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; 70: 132–41.

Pharmacokinetics

Ifosfamide is normally given intravenously, although it is well absorbed from the gastrointestinal tract. The pharmacokinetics of ifosfamide are reported to exhibit considerable interindividual variation. It is a prodrug that is extensively metabolised, chiefly by cytochrome P450 isoenzymes such as CYP3A4 and CYP2B6 in the liver, to both active and inactive metabolites; there is some evidence that metabolism is saturated at very high doses. Although licensed product information states that a mean terminal elimination half-life is about 15 hours after a single high-dose intravenous bolus, most studies at lower doses appear to have recorded elimination half-lives of about 4 to 8 hours. After repeated doses (fractionated therapy) there is a decrease in the elimination half-life, apparently due to autoinduction of metabolism. Ifosfamide is distributed into the CSF. It is excreted largely in urine, as unchanged drug and metabolites.

General references.

1. Wagner T. Ifosfamide clinical pharmacokinetics. *Clin Pharmacokinet* 1994; 26: 439–56.
2. Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; 38: 291–304.
3. Kerbusch T, *et al.* Clinical pharmacokinetics and pharmacodynamics of ifosfamide and its metabolites. *Clin Pharmacokinet* 2001; 40: 41–62.

In a study[1] in 20 patients receiving intravenous ifosfamide over 3 or 5 days, the median elimination half-life of ifosfamide was 3.85 hours in patients under 60 years of age compared with 6.03 hours in those over age 60; this difference appeared to be due to an increased volume of distribution in the older age group. The autoinduction of metabolism typically seen with multiple doses of ifosfamide was not affected by age. The increased clearance seen over time during a 5-day cycle of ifosfamide treatment[2] was not sustained over the 21 days between cycles, but was reproducible and of similar magnitude in the subsequent cycle.

In another study[3] the half-life of the *S*-enantiomer of ifosfamide was found to be 5.98 hours after an intravenous bolus of the racemate, compared with 7.12 hours for the *R*-enantiomer.

1. Lind MJ, *et al.* The effect of age on the pharmacokinetics of ifosfamide. *Br J Clin Pharmacol* 1990; 30: 140–3.
2. Lewis LD. A study of 5 day fractionated ifosfamide pharmacokinetics in consecutive treatment cycles. *Br J Clin Pharmacol* 1996; 42: 179–86.
3. Corlett SA, *et al.* Pharmacokinetics of ifosfamide and its enantiomers following a single 1h intravenous infusion of the racemate in patients with small cell lung carcinoma. *Br J Clin Pharmacol* 1995; 39: 452–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cuantil; Fentul†; Ifocris; Ifosmixan; IFX; *Austral.*: Holoxan; *Austria*: Holoxan; *Belg.*: Holoxan; *Braz.*: Evolox; Holoxane; *Canad.*: Ifex; *Chile*: Holoxan; Holem; *China*: Holoxan (和乐生); Pi Fu Ping (匹服平); *Cz.*: Holoxan; *Denm.*: Holoxan; *Fin.*: Holoxan; *Fr.*: Holoxan; *Ger.*: Holoxan; IFO-cell; *Gr.*: Holoxan; *Hong Kong*: Holoxan; *Hung.*: Holoxan; *India*: Holoxan; Ifocip; Ifos; Ipamide; *Indon.*: Holoxan; *Irl.*: Mitoxana; *Israel*: Ifoxan†; *Ital.*: Holoxan; *Malaysia*: IFO-Cell; *Mex.*: Alquimid; Crifty; Fosfidex†; Ifadex; Ifolem; Ifomida; *Neth.*: Holoxan; *Norw.*: Holoxan; *NZ*: Holoxan; *Philipp.*: Holoxan; Iphox; *Pol.*: Holoxan; Macdafen; *Port.*: Holoxan; *Rus.*: Holoxan (Холоксан); *S.Afr.*: Holoxan; *Singapore*: Holoxan; *Spain*: Tronoxal; *Swed.*: Holoxan; *Switz.*: Holoxan; *Thai.*: Holoxan; IFO-cell†; Ifolem; *Turk.*: Haloxan; Holoxan; *USA*: Ifex.

Multi-ingredient Preparations. *India*: Holoxan Uromitexan; Ifex-M; Ifomid-M; Ifoxan with Mesna; Ipamide with Mesna†; Isoxan.

Pharmacopoeial Preparations
BP 2014: Ifosfamide Injection;
USP 36: Ifosfamide for Injection.

Imatinib Mesilate *(BANM, rINNM)*

CGP-57-148B; CGP-57148; Imatinib, Mésilate d'; Imatinib, mesilato de; Imatinib Mesylate (USAN); Imatinib Mesylate; Imatinibi Mesilas; Mesilato de imatinib; STI-571; Иматиниба Мезилат.

α-(4-Methyl-1-piperazinyl)-3′-[[4-(3-pyridyl)-2-pyrimidinyl]amino]-*p*-tolu-*p*-toluidide methanesulfonate.

$C_{29}H_{31}N_7O.CH_4O_3S$=589.7

CAS — 152459-95-5 (imatinib); 220127-57-1 (imatinib mesilate).

ATC — L01XE01.

UNII — 8A1O1M485B.

Uses and Administration

Imatinib is a tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukaemia (p. 694.2) and acute lymphoblastic leukaemia (p. 692.3). It also inhibits the tyrosine kinase for platelet-derived growth factor and stem cell factor, c-kit (CD117), which is overexpressed in gastrointestinal stromal tumours (see Soft-tissue Sarcoma, p. 718.2). Imatinib is also indicated for patients with myelodysplastic syndromes (p. 694.3), hypereosinophilic syndrome, aggressive systemic mastocytosis (p. 1226.3), and dermatofibrosarcoma protuberans. Imatinib is given orally as the mesilate but doses are expressed as the base. Imatinib mesilate 119.5 mg is equivalent to about 100 mg of imatinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In the treatment of **chronic myeloid leukaemia**, patients in chronic phase may be given the equivalent of 400 mg of the base daily, increased to 600 mg daily or 400 mg twice daily if required. Patients in blast crisis or accelerated phase are given 600 mg daily, increased to 400 mg twice daily if necessary.

In the treatment of patients with newly diagnosed **acute lymphoblastic leukaemia**, imatinib 600 mg daily may be given with induction, consolidation, or maintenance chemotherapy. The same dose may be given as monotherapy for patients with relapsed or refractory disease.

In the treatment of **gastrointestinal stromal tumours** (GIST), 400 mg daily is recommended. In patients with unresectable or metastatic disease that progresses at this dose, a dose increase up to 400 mg twice daily may be considered.

For patients with **myelodysplastic disease**, the recommended dose of imatinib is 400 mg daily. For **mastocytosis**, 400 mg daily is given, unless there is associated eosinophilia, in which case a starting dose of 100 mg daily is recommended, increased to 400 mg if response is inadequate. Similarly, the recommended dose for **hypereosinophilic syndrome** is 400 mg daily, although a subset of patients with FIP1L1-platelet-derived growth factor receptor-α fusion kinase should be started on 100 mg daily, increased to 400 mg if response is insufficient. Patients with **dermatofibrosarcoma protuberans** may be given 400 mg twice daily.

Doses should be taken with food, and accompanied by plenty of water, to minimise gastric irritation. Dose adjustments may be necessary if myelosuppression or hepatotoxicity occurs; blood counts and liver function should be regularly monitored (see Administration in Hepatic Impairment, p. 808.1). Doses are also adjusted in renal impairment, see p. 808.1.

Doses of imatinib should be increased by 50%, and clinical response should be carefully monitored, in patients given potent CYP3A4 inducers such as rifampicin or phenytoin. For children's doses, see Administration in Children, below.

Administration in children. In the UK, the licensed oral dose of imatinib for children with chronic myeloid leukaemia (CML) is 340 mg/m² daily, for those in chronic or advanced phase; a total dose of 800 mg should not be exceeded. The dose may be increased to 570 mg/m² daily (maximum total dose 800 mg) in children with disease progression, with unsatisfactory haematological response after at least 3 months of treatment, with no cytogenetic response after 12 months of treatment, or with loss of a previously achieved haematological or cytogenetic response.

In the USA, imatinib is given in a usual dose of 340 mg/m² daily in children with newly diagnosed CML or with chemotherapy in newly diagnosed acute lymphoblastic leukaemia; the dose should not exceed 600 mg.

Treatment can be given as a once-daily dose, or, in CML, split into morning and evening doses. There is no experience with the use of imatinib in children under 1 year of age.

Use in children has been reviewed.[1]

1. Barr RD. Imatinib mesylate in children and adolescents with cancer. *Pediatr Blood Cancer* 2010; 55: 18–25.

Administration in hepatic impairment. Imatinib is metabolised in the liver. Licensed product information in the UK recommends that patients with mild, moderate, or severe liver impairment should be given the minimum recommended oral dose of 400 mg daily. In the USA, patients with mild and moderate impairment should be given the recommended daily dose, but in those with severe hepatic impairment, a 25% decrease in dose is recommended. In both countries, degrees of hepatic impairment are defined as:

- mild: total bilirubin equal to 1.5 times the upper limit of normal (ULN); aspartate aminotransferase (AST/SGOT) greater than ULN. AST/SGOT can be normal or less than ULN if the total bilirubin is greater than ULN
- moderate: total bilirubin > 1.5 and up to 3 times the ULN
- severe: total bilirubin > 3 to 10 times the ULN

US licensed product information also states that if, during treatment, elevations in bilirubin > 3 times the ULN or liver transaminases > 5 times the ULN occur, imatinib should be withheld until bilirubin levels have returned to less than 1.5 times the ULN and transaminase levels to less than 2.5 times the ULN. Treatment may then be continued at a reduced daily dose. In adults the dose is reduced from 800 mg to 600 mg, from 600 mg to 400 mg, and from 400 mg to 300 mg. In children, the dose should be reduced from 340 mg/m^2 daily to 260 mg/m^2 daily, or from 260 mg/m^2 daily to 200 mg/m^2 daily.

Administration in renal impairment. UK licensed product information for imatinib states that patients with mild or moderate renal impairment, defined as creatinine clearance (CC) of 20 to 59 mL/minute, may be given an initial oral dose of 400 mg daily. Patients with severe renal impairment (CC less than 20 mL/minute) or on dialysis can also be started at this dose, although caution is recommended; the dose can be adjusted as needed.

In the USA, patients with mild renal impairment (CC 40 to 59 mL/minute) should not be given a dose greater than 600 mg. Patients with moderate renal impairment (CC 20 to 39 mL/minute) should have their initial dose halved; the dose can then be adjusted as needed, although a maximum dose of 400 mg is recommended. Caution is advised in those with severe impairment; doses of 100 mg daily have been used.

Hypereosinophilic syndrome. Imatinib has been reported to produce clinical responses in patients with the hypereosinophilic syndrome (HES).[1-4] Some reports suggest that imatinib also has activity in mast-cell disease, even in the absence of associated eosinophilia.[5] However, not all patients with HES respond to imatinib.[4] Many patients with the myelodysplastic variant of HES express a novel kinase derived from an abnormal fusion of platelet-derived growth factor receptor-α gene with a neighbouring gene, FIP1L1. Almost all patients with this FIP1L1-platelet-derived growth factor receptor-α fusion kinase will respond to imatinib, but a subset of patients with HES without known imatinib targets have also been reported to respond to the drug.[6,7]

1. Gleich GJ, *et al.* Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet* 2002; 359: 1577–8.
2. Cools J, *et al.* A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; 348: 1201–14.
3. Koury MJ, *et al.* Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib. *Am J Med* 2003; 115: 587–9.
4. Payne SM, Kovacs MJ. Imatinib mesylate treatment in two patients with idiopathic hypereosinophilic syndrome. *Ann Pharmacother* 2004; 38: 1215–18.
5. Pardanani A, *et al.* Imatinib for systemic mast-cell disease. *Lancet* 2003; 362: 535–7.
6. Müller AMS, *et al.* Imatinib mesylate as a novel treatment option for hypereosinophilic syndrome: two case reports and a comprehensive review of the literature. *Ann Hematol* 2006; 85: 1–16.
7. Antoniu SA. Imatinib mesylate for the treatment of hypereosinophilic syndromes. *Curr Opin Investig Drugs* 2006; 7: 980–4.

Malignant neoplasms. References.

1. Peggs K, Mackinnon S. Imatinib mesylate—the new gold standard for treatment of chronic myeloid leukemia. *N Engl J Med* 2003; 348: 1048–50.
2. Deininger MW, *et al.* Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol* 2003; 21: 1637–47.
3. Deininger M, *et al.* The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood* 2005; 105: 2640–53.
4. Kantarjian HM, *et al.* New insights into the pathophysiology of chronic myeloid leukemia and imatinib resistance. *Ann Intern Med* 2006; 145: 913–23.
5. Moen MD, *et al.* Imatinib: a review of its use in chronic myeloid leukaemia. *Drugs* 2007; 67: 299–320.
6. Siddiqui MAA, Scott LJ. Imatinib: a review of its use in the management of gastrointestinal stromal tumours. *Drugs* 2007; 67: 805–20.
7. Cross SA, Lyseng-Williamson KA. Imatinib: in relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukaemia. *Drugs* 2007; 67: 2645–54.
8. Jabbour E, *et al.* Suboptimal response to or failure of imatinib treatment for chronic myeloid leukemia: what is the optimal strategy? *Mayo Clin Proc* 2009; 84: 161–9.
9. Wolf D, Rumpold H. A benefit-risk assessment of imatinib in chronic myeloid leukaemia and gastrointestinal stromal tumours. *Drug Safety* 2009; 32: 1001–15.
10. Duffaud F, Le Cesne A. Imatinib in the treatment of solid tumours. *Target Oncol* 2009; 4: 45–56.
11. Adenis A, *et al.* Imatinib in gastrointestinal stromal tumor: does treatment duration matter? *Oncology* 2009; 77: 157–61.
12. Gronchi A, *et al.* The role of high-dose imatinib in the management of patients with gastrointestinal stromal tumor. *Cancer* 2010; 116: 1847–58.
13. Osborn M, Hughes T. Managing imatinib resistance in chronic myeloid leukaemia. *Curr Opin Hematol* 2010; 17: 97–103.
14. Sanford M, Scott LJ. Imatinib: as adjuvant therapy for gastrointestinal stromal tumour. *Drugs* 2010; 70: 1963–72.

Pulmonary hypertension. Imatinib has produced beneficial responses in patients with pulmonary arterial hypertension (p. 1278.2) and may have a role, particularly in patients who fail to respond to other therapies.[1-4]

1. Ghofrani HA, *et al.* Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 1412–13.
2. Patterson KC, *et al.* Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann Intern Med* 2006; 145: 152–3.
3. Souza R, *et al.* Long term imatinib treatment in pulmonary arterial hypertension. *Thorax* 2006; 61: 736.
4. Chhina MK, *et al.* Evaluation of imatinib mesylate in the treatment of pulmonary arterial hypertension. *Future Cardiol* 2010; 6: 19–35.

Adverse Effects and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects of imatinib mesilate include gastrointestinal disturbances, myelosuppression, superficial oedema, myalgia, arthralgia, muscle cramps, rashes, fatigue, and headache. Myelosuppression usually manifests as neutropenia, thrombocytopenia, anaemia, or febrile neutropenia; haemolytic anaemia has occurred rarely. Other common adverse effects include dizziness, taste disturbances, anorexia, paraesthesia, insomnia, eye disorders or visual disturbances, epistaxis, cough, dyspnoea, dry skin, pruritus, alopecia, night sweats, pyrexia, weakness, and rigors. Hepatotoxicity may occur; fatal cases of hepatic necrosis have been reported. Aseptic necrosis of bone, mainly in the femoral head, has been reported rarely. There are reports of serious and severe skin disorders, including erythema multiforme, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, exfoliative dermatitis, and bullous eruptions. Rhabdomyolysis has also occurred. Haemorrhages are common; gastrointestinal bleeding, however, is more frequent in those patients treated for stromal tumours. Ulceration can occur; gastrointestinal perforation, fatal in some cases, has been reported rarely.

Severe fluid retention commonly occurs, and may result in pleural and pericardial effusion, pulmonary oedema, and ascites. Some fatalities have been reported, and treatment may need to be stopped if there is unexpected, rapid weight gain. Elderly patients and those with a history of cardiac disease may be at increased risk. Isolated cases of left ventricular dysfunction have been reported; patients with cardiac disease or risk factors for cardiac failure should be monitored. Other reported cardiac disorders include congestive heart failure, palpitations, tachycardia, arrhythmias, angina pectoris, and myocardial infarction. There are reports, including fatalities, of cerebral oedema, increased intracranial pressure and papilloedema. Hypothyroidism has been reported in patients on levothyroxine replacement therapy; TSH concentrations should be monitored in these patients.

Imatinib mesilate should be taken with food and a large glass of water to minimise gastrointestinal irritation. Complete blood counts and liver function should be monitored regularly.

Effects on the heart. Ten patients receiving imatinib developed severe congestive heart failure without obvious cause; all patients had normal left ventricular function before imatinib was started. Mitochondrial abnormalities were found after myocardial biopsy on 2 of the patients. These findings were confirmed by studies on *mice* and *in vitro*. The authors suggested that patients be closely followed for clinical manifestations of left ventricular dysfunction.[1]

Subsequent evaluation by the manufacturer (*Novartis*) established that the frequency of reported cardiac events was less than 1%. However, they recommended that patients with known cardiac disease or risk factors for cardiac failure be monitored accordingly, that those developing clinical manifestations suggestive of congestive cardiac failure be thoroughly evaluated and treated, and that elderly patients or those with underlying heart disease be evaluated for baseline left ventricular ejection fraction.[2]

1. Kerkelä R, *et al.* Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006; 12: 908–16.
2. Novartis, Canada. Health Canada endorsed important safety information on Gleevec (imatinib mesylate): recent safety information regarding reports of significant left ventricular ejection fraction reduction and congestive heart failure with GLEEVEC (imatinib mesylate) (issued 21st September, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/gleevec_2_hpc-cps-eng.php (accessed 01/08/08)

Effects on the kidneys. Imatinib has been associated with the development of acute renal failure, requiring haemodialysis.[1-3]

1. Kitiyakara C, Atichartakarn V. Renal failure associated with a specific inhibitor of BCR-ABL tyrosine kinase, STI 571. *Nephrol Dial Transplan* 2002; 17: 685–7.
2. Pou M, *et al.* Acute renal failure secondary to imatinib mesylate treatment in chronic myeloid leukemia. *Leuk Lymphoma* 2003; 44: 1239–41.
3. Pottinger JR, *et al.* Acute renal failure secondary to imatinib mesylate treatment in prostate cancer. *Ann Pharmacother* 2005; 39: 2136–8.

Effects on the lungs. Interstitial pneumonitis has been reported with imatinib;[1-8] presenting symptoms include dry cough and dyspnoea. Doses of imatinib ranged from 100 mg to 600 mg daily. In most cases, the pneumonitis resolved after stopping imatinib and starting corticosteroid therapy. The mechanism was unclear, and may involve a hypersensitivity reaction. In an analysis of 27 cases of interstitial lung disease associated with imatinib therapy,[8] 30% of patients showed a hypersensitivity reaction radiological pattern. Pre-existing lung disease may be a risk factor.

1. Bergeron A, *et al.* Hypersensitivity pneumonitis related to imatinib mesylate. *J Clin Oncol* 2002; 20: 4271–2.
2. Rosado MF, *et al.* Imatinib mesylate-induced interstitial pneumonitis. *J Clin Oncol* 2003; 21: 3171–3.
3. Ma CX, *et al.* Imatinib mesylate-induced interstitial pneumonitis. *Mayo Clin Proc* 2003; 78: 1578–9.
4. Yokoyama T, *et al.* Interstitial pneumonia induced by imatinib mesylate: pathologic study demonstrates alveolar destruction and fibrosis with eosinophilic infiltration. *Leukemia* 2004; 18: 645–6.
5. Isshiki I, *et al.* Interstitial pneumonitis during imatinib therapy. *Br J Haematol* 2004; 125: 420.
6. Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol* 2005; 79: 80–1.
7. Lin J-T, *et al.* Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate. *Leuk Lymphoma* 2006; 47: 1693–5.
8. Ohnishi K, *et al.* Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. *Leukemia* 2006; 20: 1162–4.

Effects on reproductive potential. Oligospermia[1] and ovarian failure[2] have been reported after treatment with imatinib. Patients should be counselled before therapy about the risk of impaired fertility.

1. Seshadri T, *et al.* Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. *N Engl J Med* 2004; 351: 2134–5.
2. Christopoulos C, *et al.* Primary ovarian insufficiency associated with imatinib therapy. *N Engl J Med* 2008; 358: 1079–80.

Effects on the skin, hair, and nails. There are reports of acute generalised exanthematous pustulosis in patients given imatinib.[1,2] The authors noted that severe skin reactions had been reported in some other patients given the drug, and speculated that the effect might be dose-dependent and related to its pharmacological action. In subsequent reports[3-5] of cutaneous adverse effects, this dose-dependency has also been seen, with effects especially at doses of 600 mg daily and above. In a report of a livedoid pattern of rash in 3 patients taking imatinib, the authors noted that adverse skin reactions to imatinib tend to be strongly dose-dependent, are self-limiting, and do not usually affect the mucous membranes.[4] Epidermal necrolysis occurred in a patient who underwent stem cell transplantation after treatment with imatinib.[7] The authors suggested that prolonged inhibition of platelet-derived growth factor by imatinib may have impaired the repair of skin damage caused by the conditioning therapy. In a report of 19 patients with skin reactions, the authors suggested that the actions of imatinib on platelet-derived growth factor may have caused an increase in dermal interstitial fluid pressure, capable of inducing oedema and the subsequent erythema and desquamation that was seen. Rare reactions included psoriasis, hyaline cell syringoma, and malpighian epithelioma, all of which occurred after at least 1 year of therapy.[8] Follicular mucinosis[9] and panniculitis[10] have also been reported with use of imatinib, as has Stevens-Johnson syndrome.[11,12] Palmoplantar hyperkeratosis and nail dystrophy can occur,[13,14] as can lichenoid eruptions.[14] Repigmentation of grey hair has also been reported.[15]

Oral corticosteroids have been used to resolve most cases of skin eruptions.[8] In other instances, re-introduction of imatinib at low doses, gradually increased to full dosage, has been successfully tolerated.[8,12,16] In one patient, who developed exfoliative dermatitis with imatinib and had recurrent reactions despite decreased doses, a once-weekly dose of imatinib was associated with a less severe rash that eventually disappeared over a period of 4 months.[17]

1. Brouard M, Saurat J-H. Cutaneous reactions to STI571. *N Engl J Med* 2001; 345: 618–19.
2. Schwarz M, *et al.* Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. *Eur J Haematol* 2002; 69: 254–6.
3. Valeyrie L, *et al.* Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol* 2003; 48: 201–6.

4. Drummond A, *et al.* A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Glivec). *Br J Haematol* 2003; 120: 911–13.
5. Ugurel S, *et al.* Dose-dependent severe cutaneous reactions to imatinib. *Br J Cancer* 2003; 88: 1157–9.
6. Martínez-González MC, *et al.* Livedoid skin reaction probably due to imatinib therapy. *Ann Pharmacother* 2007; 41: 148–52.
7. Schaich M, *et al.* Severe epidermal necrolysis after treatment with imatinib and consecutive allogeneic hematopoietic stem cell transplantation. *Ann Hematol* 2003; 82: 303–4.
8. Breccia M, *et al.* Early and tardive skin adverse events in chronic myeloid leukaemia patients treated with imatinib. *Eur J Haematol* 2005; 74: 121–3.
9. Yanagi T, *et al.* Follicular mucinosis associated with imatinib (STI571). *Br J Dermatol* 2004; 151: 1276–8.
10. Ugurel S, *et al.* Panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib. *Br J Dermatol* 2003; 149: 678–9.
11. Hsiao L-T, *et al.* Stevens-Johnson syndrome after treatment with STI571: a case report. *Br J Haematol* 2002; 117: 620–2.
12. Rule SAJ, *et al.* Managing cutaneous reactions to imatinib therapy. *Blood* 2002; 100: 3434–5.
13. Deguchi N, *et al.* Imatinib mesylate causes palmoplantar hyperkeratosis and nail dystrophy in three patients with chronic myeloid leukaemia. *Br J Dermatol* 2006; 154: 1216–18.
14. Kuraishi N, *et al.* Lichenoid drug eruption with palmoplantar hyperkeratosis due to imatinib mesylate: a case report and a review of the literature. *Acta Derm Venereol* 2010; 90: 73–6.
15. Etienne G, *et al.* Imatinib mesylate and gray hair. *N Engl J Med* 2002; 347: 446.
16. Park MA, *et al.* Successful progressive challenge after a cutaneous reaction to imatinib mesylate (Gleevec): a case report and review of the literature. *Allergy Asthma Proc* 2004; 25: 345–7.
17. Tanvetyanon T, Nand S. Overcoming recurrent cutaneous reactions from imatinib using once-weekly dosing. *Ann Pharmacother* 2003; 37: 1818–20.

Effects on the spleen. There are isolated reports of splenic rupture in patients receiving imatinib mesilate.[1]

1. Elliott MA, *et al.* Adverse events after imatinib mesylate therapy. *N Engl J Med* 2002; 346: 712–13.

Gynaecomastia. Gynaecomastia was noted in 7 of 38 men assessed for hormone concentrations while enrolled in studies of imatinib; the authors attributed the disorder to reductions in testosterone concentrations due to imatinib.[1]

1. Gambacorti-Passerini C, *et al.* Gynaecomastia in men with chronic myeloid leukaemia after imatinib. *Lancet* 2003; 361: 1954–56.

Hypophosphataemia. Hypophosphataemia and associated changes in bone and mineral metabolism were reported in a study of patients receiving imatinib. Patients with normal serum-phosphate concentrations also had similar changes in bone turnover. Hypophosphataemia was apparently related to patient age and imatinib dose; it was also associated with decreased serum concentrations of calcium and vitamin D.[1] In a review of data, the manufacturers (*Novartis*) noted an incidence of 50% of patients in 2 studies; overall 1.5% had grade 4 hypophosphataemia. However, the reported incidence of hypophosphataemia as an adverse effect of imatinib was only 3%. They suggested that phosphate concentrations be monitored in patients taking imatinib until further elucidation of the effect of the drug on bone is available.[2] While some have questioned the association between treatment with imatinib and hypophosphataemia,[3] others have also reported hypophosphataemia during treatment with the drug.[4] The effect, however, appears to be reversible on stopping imatinib.

1. Berman E, *et al.* Altered bone and mineral metabolism in patients receiving imatinib mesylate. *N Engl J Med* 2006; 354: 2006–13.
2. Owen S, *et al.* Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; 355: 627.
3. Tournis S, Lyritis GP. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; 355: 627.
4. Joensuu H, Reichardt P. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; 355: 628. Correction. *ibid.*; 1627.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies imatinib 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 27/09/11)

Pregnancy. Two of 3 pregnancies in 2 patients taking imatinib were successful; the infants were both small for weight, but healthy and without congenital abnormalities. In the third case, a first trimester miscarriage occurred. Both women continued imatinib throughout their pregnancies.[1]

In another report,[2] 10 women became pregnant while being treated with imatinib for chronic myeloid leukaemia. Imatinib therapy was stopped upon discovery of the pregnancy; exposure to imatinib ranged from 4 to 9 weeks. Two patients had a spontaneous abortion shortly after stopping imatinib, and another patient elected to have a therapeutic abortion. Seven other pregnancies went to term, resulting in 8 babies. One infant had hypospadias which was surgically corrected without complications; all other infants were healthy. The partners of 8 male patients also conceived while the men were receiving imatinib, one of them twice. All male patients continued therapy with imatinib. One spontaneous abortion occurred. Of the 8 babies born, 1 was found to have a mild rotation of the small intestine requiring surgery shortly after birth. The authors considered it possible that the brief exposure to imatinib may have slightly increased the risk of spontaneous abortion. While concluding that normal pregnancies are possible during imatinib therapy, the authors of both reports emphasised that possible teratogenic effects cannot be ruled out, and that patients should still be advised to use appropriate and effective contraception.

A similar warning was issued in a review of outcome data from 125 pregnancies involving exposure to imatinib. The authors noted that 63 pregnancies had resulted in the live birth of normal infants; a further 35 women terminated the pregnancy (in 3 cases because fetal abnormalities were found), and 18 ended in spontaneous abortion.[3] However, there were 9 infants with congenital abnormalities, several of which were strikingly similar, a fact that was considered to be of some concern.

1. AlKindi S, *et al.* Imatinib in pregnancy. *Eur J Haematol* 2005; 74: 535–7.
2. Ault P, *et al.* Pregnancy among patients with chronic myeloid leukemia treated with imatinib. *J Clin Oncol* 2006; 24: 1204–8.
3. Pye SM, *et al.* The effects of imatinib on pregnancy outcome. *Blood* 2008; 111: 5505–8.

Syndrome of inappropriate ADH secretion. Hyponatraemia, leading to a syndrome of inappropriate ADH secretion (SIADH) has been reported after therapy with imatinib at a dose of 800 mg daily. Fluid restriction and dose reduction to 600 mg daily restored sodium concentrations to normal.[1]

1. Liapis K, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone associated with imatinib. *Ann Pharmacother* 2008; 42: 1882–6.

Tumour lysis syndrome. Tumour lysis syndrome has been reported with imatinib;[1,2] patients should be monitored closely. Allopurinol and adequate hydration have been suggested as prophylaxis in patients with a high tumour burden.[2]

1. Dann EJ, *et al.* Tumor lysis syndrome after STI571 in Philadelphia chromosome-positive acute lymphoblastic leukemia. *J Clin Oncol* 2002; 20: 354–5.
2. Chang H, Shih L-Y. Imatinib-induced tumor lysis syndrome: report of a case and review of the literature. *Chang Gung Med J* 2008; 31: 510–14.

Interactions

Imatinib mesilate is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals and macrolide antibacterials, may increase blood concentrations of imatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, St John's wort, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of imatinib; imatinib dosage may need to be increased in these patients (see Uses and Administration, p. 807.3).

In vitro studies have indicated that imatinib itself inhibits the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6, and may increase blood concentrations of drugs that are substrates of these enzymes.

The dose of levothyroxine may need to be increased before imatinib is given to patients with hypothyroidism (see Antineoplastics under Interactions of Levothyroxine, p. 2341.3).

Antifungals. In a small study in healthy subjects, *ketoconazole* significantly increased imatinib exposure; mean maximum plasma concentration and area under the concentration-time curve increased, and clearance of imatinib decreased. The half-life of imatinib appeared relatively unchanged. To avoid overexposure, single subtherapeutic doses of imatinib had been used (200 mg); the authors noted that clinical significance might arise with use of imatinib in daily doses of 800 mg or more.[1]

1. Dutreix C, *et al.* Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. *Cancer Chemother Pharmacol* 2004; 54: 290–4.

Calcium-channel blockers. For a report of a possible interaction between imatinib and *nifedipine*, see Antineoplastics under Interactions of Nifedipine, p. 1453.3.

St John's wort. Exposure to imatinib was significantly reduced when it was given after 2 weeks of treatment with St John's wort; area under the concentration-time curve was decreased, maximum plasma concentration and half-life of imatinib were reduced, and clearance increased.[1,2]

1. Frye RF, *et al.* Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther* 2004; 76: 323–9.
2. Smith PF, *et al.* The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 2004; 24: 1508–14.

Pharmacokinetics

Imatinib mesilate is well absorbed after oral doses and peak blood concentrations occur after 2 to 4 hours. The mean bioavailability is about 98%. Imatinib is reported to be about 95% bound to plasma proteins. Plasma elimination half-lives of imatinib and its major active metabolite, the *N*-demethylated piperazine derivative, are about 18 and 40 hours respectively. The major enzyme responsible for the metabolism of imatinib is cytochrome P450 isoenzyme CYP3A4; isoenzymes CYP1A2, CYP2D6, CYP2C9, and CYP2C19 also play a minor role. About 81% of a dose is eliminated within 7 days in the faeces (68%) and urine (13%). It is excreted mostly as metabolites, with only 25% as unchanged drug.

References.
1. Peng B, *et al.* Absolute bioavailability of imatinib (Glivec) orally versus intravenous infusion. *J Clin Pharmacol* 2004; 44: 158–62.
2. Peng B, *et al.* Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* 2005; 44: 879–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agacel; Glivec; Imatib; Mesinib; Tagonib; Timab; Zlatir; *Austral.*: Glivec; *Austria*: Glivec; *Belg.*: Glivec; *Braz.*: Glivec; *Canad.*: Gleevec; *Chile*: Glivec; *China*: Glivec (格列卫); *Cz.*: Glivec; *Denm.*: Glivec; *Fin.*: Glivec; *Fr.*: Glivec; *Ger.*: Glivec; *Gr.*: Glivec; *Hong Kong*: Glivec; *Hung.*: Glivec; *India*: Celonib; Glivec; Imalek; Imatib; Mesylonib; Mitinab; Zoleta†; *Indon.*: Glivec; *Irl.*: Glivec; *Israel*: Glivec; *Ital.*: Glivec; *Jpn*: Glivec; *Malaysia*: Glivec; *Mex.*: Glivec; *Neth.*: Glimatin; Glivec; Imakrebin; Tibaldix; *Norw.*: Glivec; *NZ*: Glivec; *Philipp.*: Glivec; *Pol.*: Glivec; *Port.*: Glivec; *Rus.*: Glivec (Гливек); *S.Afr.*: Gleevec; *Singapore*: Glivec; *Spain*: Glivec; *Swed.*: Glivec; *Switz.*: Glivec; *Thai.*: Glivec; *Turk.*: Glivec; *UK*: Glivec; *Ukr.*: Glivec (Гливек); *USA*: Gleevec; *Venez.*: Glivec.

Imexon *(rINN)*

BM-06002; Imexón; Imexonum; Имексон.
(5*R*,*S*)-4-Amino-1,3-diazabicyclo[3.1.0]hex-3-en-2-one.
$C_4H_5N_3O$=111.1
CAS — 59643-91-3.
UNII — 8F63U28T2V.

NOTE. The name Amplimexon has been used as a trade mark for imexon.

Profile

Imexon is a cyanoaziridine compound that appears to act as an antineoplastic in several ways, one of which is by causing mitochondrial disruption in the cancer cell, thus inducing apoptosis. It is under investigation for the treatment of malignant neoplasms, including ovarian cancer, pancreatic adenocarcinoma, multiple myeloma, and metastatic malignant melanoma.

Ingenol Mebutate *(USAN, rINN)*

Ingenol Mebutato; Ingenoli Mebutas; 3-Ingenyl Angelate; Mébutate d'Ingénol; PEP-005; Ингенол Мебутат.
(1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-5,5a-Dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1*H*-2,8a-methanocyclopenta[*a*]cyclopropa[*e*]cyclodecen-6-yl (2*Z*)-2-methylbut-2-enoate.
$C_{25}H_{34}O_6$=430.5
CAS — 75567-37-2.
ATC — D06BX02.
ATC Vet — QD06BX02.
UNII — 7686550JAH.

Uses and Administration

Ingenol mebutate is a protein kinase C activator isolated from the plant *Euphorbia peplus*. It is used in the topical treatment of actinic keratosis (see Basal Cell and Squamous Cell Carcinoma, p. 714.2). A gel containing 0.015% is applied once daily for 3 consecutive days to affected areas on the face and scalp. For areas on the trunk and extremities, a 0.05% gel is applied once daily for 2 days. Patients should wash their hands immediately after applying the gel, and treated areas should not be touched or washed for 6 hours.

Ingenol mebutate is also under investigation in the treatment of non-melanoma skin cancer.

References.
1. Anderson L, *et al.* Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. *J Am Acad Dermatol* 2009; 60: 934–43.
2. Siller G, *et al.* PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. *Australas J Dermatol* 2009; 50: 16–22.
3. Siller G, *et al.* PEP005 (ingenol mebutate) gel for the topical treatment of superficial basal cell carcinoma: results of a randomized phase IIa trial. *Australas J Dermatol* 2010; 51: 99–105.

Adverse Effects and Precautions

The topical application of ingenol mebutate typically causes local skin reactions including erythema, flaking, crusting,

swelling, blistering, and ulceration. These effects usually occur within 1 day of starting treatment, peak up to 1 week after finishing treatment, and resolve within 2 weeks for affected areas on the face and scalp and within 4 weeks for areas on the trunk and extremities. Reactions can sometimes be severe. Ingenol mebutate should not be used until the skin is healed from any previous drug or surgical treatment.

Severe eye pain, eyelid oedema, eyelid ptosis, and periorbital oedema have occurred after inadvertent ocular exposure to ingenol mebutate gel. Patients should wash their hands well after handling the gel, and avoid transferring the drug to the eye during and after application.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Picato; *UK*: Picato; *USA*: Picato.

Iniparib *(rINN)*

BSI-201; Iniparibum; Инипариб.

4-Iodo-3-nitrobenzamide.

$C_7H_5IN_2O_3$=292.0

CAS — 160003-66-7.

Profile

Iniparib is a poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor that is under investigation for the treatment of several malignant neoplasms including brain, breast, ovarian, uterine, and non-small cell lung cancer. Initial studies have had mixed results.

References.

1. O'Shaughnessy J, *et al.* Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med* 2011; 364: 205–14.
2. Liang H, Tan AR. Iniparib, a PARP1 inhibitor for the potential treatment of cancer, including triple-negative breast cancer. *IDrugs* 2010; 13: 646–56.

Inotuzumab Ozogamicin *(USAN, rINN)*

CMC-544; Inotuzumab ozogamicina; Inotuzumab Ozogamicine; Inotuzumabum Ozogamicinum; WAY-207294; Иноту-зумаб Озогамицин.

Immunoglobulin G4, anti-(human CD22 (antigen)) (human-mouse monoclonal G544 heavy chain), disulfide with human-mouse monoclonal G544 κ-chain, dimer, conjugate with ozogamicin.

CAS — 635715-01-4.

UNII — P93RUU11P7.

Profile

Inotuzumab ozogamicin is a recombinant humanised monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic. It is under investigation for the treatment of non-Hodgkin's lymphomas.

Interleukin-2

BG-8301 (teceleukin); Epidermal Thymocyte Activating Factor; ETAF; Factor de crecimiento de células T; IL-2; Interleucina 2; T-cell Growth Factor; TCGF; Интерлейкин-2.

Description. Interleukin-2 is a naturally-occurring 133-amino-acid glycoprotein with a molecular weight of about 15 000. It is available from natural sources or as a product of recombinant DNA technology (rIL-2).

In addition to aldesleukin (below) modified forms of interleukin-2 produced by recombinant DNA technology have included celmoleukin and teceleukin.

Aldesleukin *(BAN, USAN, rINN)*

Aldesleukiini; Aldesleukina; Aldesleukine; Aldesleukinum; Aldeslokin; Des-alanyl-1, Serine-125 Human Interleukin-2; Recombinant Interleukin-2; 125-L-Serine-2–133-interleukin 2 (human reduced); Альдеслейкин.

CAS — 110942-02-4.

ATC — L03AC01.

ATC Vet — QL03AC01.

UNII — M89N0Q7EQR.

Description. Aldesleukin (modified human recombinant interleukin-2) is produced by recombinant DNA technology using an *Escherichia coli* strain containing an analogue of the human interleukin-2 gene. It differs from native interleukin-2 in that it is not glycosylated, it has no N-terminal alanine, and it has serine substituted for cysteine at position 125.

Incompatibility. Aldesleukin 33 800 units/mL in glucose 5% lost significant biological activity when mixed with other drugs including ganciclovir sodium, lorazepam, pentamidine isetionate, prochlorperazine edisilate, and promethazine hydrochloride.[1] However, the incompatibility was not detectable by spectrophotometric methods and only lorazepam was visually incompatible, suggesting that these methods may be invalid for assessing the compatibility of proteins.

1. Alex S, *et al.* Compatibility and activity of aldesleukin (recombinant interleukin-2) in presence of selected drugs during simulated Y-site administration: evaluation of three methods. *Am J Health-Syst Pharm* 1995; 52: 2423–6.

Stability. Aldesleukin lost 75 to 100% of activity when reconstituted with glucose 5% or sodium chloride 0.9% in a plastic syringe and given over 24 hours with a syringe driver.[1,2] Loss of activity was not seen if aldesleukin was reconstituted with water alone[2] or with the addition of albumin.[1,2] It was suggested that loss of activity could be suspected because of lack of toxicity,[1,2] and that the lack of toxicity in some published studies could be due to this.[1,3] However, the authors of these studies indicated that they had reconstituted aldesleukin with albumin.[4,5] Reconstitution with low concentrations of albumin has been advocated to avoid bioavailability problems,[1,4,6] but is not recommended for currently licensed preparations. Vials of aldesleukin are reconstituted with water for injection.

However, UK licensed product information allows for further dilution of reconstituted aldesleukin with up to 500 mL of glucose 5%, containing human albumin 0.1%, when infused over a 24-hour period; the albumin should be added and mixed with the glucose before addition of the reconstituted aldesleukin.

For short intravenous infusion, the US licensed product information indicates that dilution in glucose 5% outside of a specified range (below 30 micrograms/mL and above 70 micrograms/mL) results in increased variability in drug delivery.

Reconstitution or dilution of aldesleukin preparations with sodium chloride 0.9% is not recommended because increased aggregation occurs.

1. Miles DW, *et al.* Reconstitution of interleukin 2 with albumin for infusion. *Lancet* 1990; 335: 1602–3.
2. Vlasveld LT, *et al.* Reconstitution of interleukin-2. *Lancet* 1990; 336: 446.
3. Miles DW, *et al.* Toxicity and reconstitution of recombinant interleukin-2 with albumin. *Lancet* 1991; 338: 1464.
4. Franks CR. Reconstitution of interleukin-2. *Lancet* 1990; 336: 445–6.
5. Hamblin T. Reconstitution of interleukin-2 with albumin for infusion. *Lancet* 1990; 336: 251.
6. Lamers CHJ, *et al.* Bioavailability of interleukin-2 after reconstitution with albumin. *Lancet* 1992; 340: 241.

Units

100 units of human interleukin-2 are contained in one ampoule of the first International Standard Preparation (1987). The activity of interleukin-2 has also been expressed in Nutley and Cetus units: 100 international units is reportedly equivalent to about 83.3 Nutley units and to about 16.7 Cetus units. US licensed product information states that 18 million international units of aldesleukin are equivalent to 1.1 mg of protein.

Uses and Administration

Interleukin-2 is a lymphokine which stimulates the proliferation of T-lymphocytes and thus amplifies immune response to an antigen; it also has actions on B-lymphocytes, and induces the production of interferon-γ and the activation of lymphokine-activated killer (LAK) cells and natural killer (NK) cells. Interleukin-2 is used in the immunotherapy of metastatic renal cell carcinoma in selected patients (see p. 708.3). It is also used in metastatic melanoma (p. 714.3), and has been tried in non-Hodgkin's lymphoma and acute myeloid leukaemia (see also below).

Interleukin-2 is usually given by intravenous infusion or subcutaneous injection of one of its recombinant forms, such as aldesleukin.

Many dosage regimens have been tried. In the UK, the recommended dose of aldesleukin for metastatic renal cell carcinoma is 18 million units given subcutaneously once daily for 5 days, followed by 2 days rest for the first week. For the next 3 weeks, 18 million units are then given on days 1 and 2 of each week, and 9 million units on days 3 to 5 of each week, followed by 2 days rest. This 4-week cycle may be repeated after an interval of 1 week. Doses may be delayed or reduced if the regimen is not tolerated.

Intravenous infusion of aldesleukin is now rarely used because of an association with capillary leak syndrome (see Adverse Effects and Treatment, p. 811.2). If it is used, 18 million units/m² per 24 hours is given as a continuous intravenous infusion for 5 days, followed by 2 to 6 days of rest. Then another 5 days of infusion is given, followed by 3 weeks of rest. This constitutes one induction cycle; a second cycle may be given after the 3-week rest period of the first cycle. After either subcutaneous or intravenous use, up to 4 maintenance cycles may be given, at 4-week intervals, to patients who respond or whose disease stabilises. In the USA, aldesleukin is licensed for use by intravenous infusion for metastatic renal cell carcinoma or metastatic melanoma. The recommended dose is an infusion of 600 000 units/kg over 15 minutes, every 8 hours for up to 14 doses. This 5-day cycle is repeated after 9 days. Further courses may be given at intervals of at least 7 weeks in patients who respond. Doses should be withheld for toxicity.

Interleukin-2 given by inhalation is being investigated in the treatment of renal cell carcinoma.

Interleukin-2 has also been studied in adaptive immunotherapy with LAK cells or tumour-infiltrating lymphocytes (TIL), which are harvested from the patient, activated *ex vivo*, and then re-infused.

Interleukin-2 is also being tried in patients with HIV infection and AIDS in an attempt to restore immune response (see below) and has been given in some other infections or immune diseases.

Other interleukins are under investigation (see also Interleukin-1, p. 2533.3). Conjugates of interleukin-2 with macrogol (PEG-IL2; pegaldesleukin) have also been investigated and liposome-encapsulated interleukin-2 has also been investigated for the treatment of renal, brain and CNS tumours.

A mixture of naturally occurring cytokines, including interleukins, interferons, chemokines, and colony-stimulating factors (Multikine) is under investigation for neoadjuvant therapy in patients with squamous cell carcinoma of the head and neck.

Reviews.

1. Noble S, Goa K. Aldesleukin (recombinant interleukin-2): a review of its pharmacological properties, clinical efficacy and tolerability in patients with metastatic melanoma. *BioDrugs* 1997; 7: 394–422.
2. Atkins MB, *et al.* High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999; 17: 2105–16.
3. Malaguarnera M, *et al.* Use of interleukin-2 in advanced renal carcinoma: meta-analysis and review of the literature. *Eur J Clin Pharmacol* 2001; 57: 267–73.
4. Atkins MB, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part I: IL-2-based clinical trials. *Med Oncol* 2001; 18: 197–207.
5. Gaffen SL, Liu KD. Overview of interleukin-2 function, production and clinical applications. *Cytokine* 2004; 28: 109–23.
6. Eklund JW, Kuzel TM. A review of recent findings involving interleukin-2-based cancer therapy. *Curr Opin Oncol* 2004; 16: 542–6.
7. Eklund JW, Kuzel TM. Interleukin-2 in the treatment of renal cell carcinoma and malignant melanoma. *Cancer Treat Res* 2005; 126: 263–87.
8. Porta C. Maintenance biotherapy with interleukin-2 and interferon for metastatic renal cell cancer. *Expert Rev Anticancer Ther* 2006; 6: 141–52.
9. McDermott DF. Update on the application of interleukin-2 in the treatment of renal cell carcinoma. *Clin Cancer Res* 2007; 13: 716s–720s.
10. Petrella T, *et al.* Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. *Cancer Treat Rev* 2007; 33: 484–96.

Administration. A review[1] of the administration of interleukin-2.

1. Shaker MA, Younes HM. Interleukin-2: evaluation of routes of administration and current delivery systems in cancer therapy. *J Pharm Sci* 2009; 98: 2268–98.

Acute myeloid leukaemia. Interleukin-2 is given with histamine hydrochloride (p. 2525.2) to patients with acute myeloid leukaemia in first remission after consolidation therapy.[1,2] The role of histamine hydrochloride is to protect lymphocytes, especially NK and T cells, which are responsible for immune-mediated destruction of residual leukaemic cells.

Interleukin-2 is given by subcutaneous injection in a dose of 16 400 units/kg twice daily with a minimum of 6 hours between each dose. These doses of interleukin-2 are followed after 1 to 3 minutes by histamine hydrochloride in a dose of 500 micrograms by subcutaneous injection over 5 to 15 minutes (injection rate not to exceed 100 micrograms/min). The maximum injection time of 15 minutes for histamine hydrochloride may be necessary to reduce severe histamine-induced adverse effects (see p. 2525.3). Patients should rest for 20 minutes after the histamine dose. Histamine hydrochloride should not be injected at the same time as interleukin-2 nor into the same anatomical region. The regimen is given over a treatment cycle of 3 weeks and repeated for a total of 10 treatment cycles; the first 3 cycles are followed by a treatment-free interval of 3 weeks, increased to 6 weeks after subsequent cycles. Doses of either drug may be modified if adverse effects are severe.

1. Thorén FB, *et al.* Histamine dihydrochloride and low-dose interleukin-2 as post-consolidation immunotherapy in acute myeloid leukemia. *Expert Opin Biol Ther* 2009; 9: 1217–23.
2. Romero AI, *et al.* Post-consolidation immunotherapy with histamine dihydrochloride and interleukin-2 in AML. *Scand J Immunol* 2009; 70: 194–205.

HIV infection and AIDS. The immunodeficiency of HIV infection and AIDS (p. 957.2) has been associated with a defect in interleukin-2 production. Interleukin-2 stimulates the proliferation of lymphocytes and activates natural killer cells and studies have therefore examined the potential benefits of adding interleukin-2 to the treatment of patients with HIV infection.[1,2] After earlier pilot studies,

trials of antiretroviral therapy plus interleukin-2 have shown it to produce a much greater increase in CD4 cell counts than antiretroviral therapy alone,[3-7] even where therapy included HAART. However, it is not clear that this results in any additional clinical benefit. A pooled analysis[8] of earlier results showed a non-significant trend towards improved clinical outcome but the ESPRIT and SILCAAT studies[9] could not show any clinical benefit in terms of survival or risk of opportunistic disease from adding subcutaneous interleukin-2 to antiretroviral regimens, despite sustained increases in CD4 cell counts over a median of 7 years or more.

Although teceleukin has been tried[3] most studies of interleukin-2 therapy in HIV have used aldesleukin. Doses and routes have varied: in general doses seem to have ranged from 6 to 18 million units daily by intravenous infusion, or 3 to 30 million units daily subcutaneously, given in most cases for a 5-day cycle every 8 weeks. Subcutaneous dosage appears to be as effective as intravenous,[4,10] is more convenient,[4] and may be less toxic.[11] There is evidence that 5-day dose cycles of 3, 4.5 or 7.5 million units twice daily by subcutaneous injection are effective,[5,6,10,12-14] whereas cycles with a lower dose of 1.5 million units twice daily are not.[5,12,14] A meta-analysis[15] of 3 studies found that subcutaneous doses of 7.5 million units twice daily for 5 days every 8 weeks resulted in greater increases in CD4 cell counts after 3 cycles of therapy than doses of 4.5 million units or 1.5 million units. However, others have reported benefit from a dose as low as 3 million units daily when used with HAART in patients with advanced disease.[16] Continuous low-dose daily therapy appears to accelerate the normalisation of T-cell and natural killer cell concentrations over the course of several months.[11]

Adverse effects are common, particularly at higher doses and with intravenous infusion rather than subcutaneous use.[7,11] However, concerns about a potential stimulant effect on viral replication with a consequent increase in viral load do not seem to have been borne out.[4-7,10] Some studies have reported reduced viral loads in interleukin-treated patients,[4,17] including decreases in hepatitis C viral load in those HIV patients co-infected with hepatitis C.[10,18]

The macrogol conjugate of interleukin-2, PEG-IL2, has also been investigated in this context, but results have been disappointing, since it appears markedly less effective than aldesleukin in stimulating CD4 counts.[4,19]

1. Pau AK, Tavel JA. Therapeutic use of interleukin-2 in HIV-infected patients. *Curr Opin Pharmacol* 2002; **2**: 433–9.
2. Temesgen Z. Interleukin-2 for the treatment of human immunodeficiency virus infection. *Drugs Today* 2006; **42**: 791–801.
3. Bartlett JA, *et al.* Coadministration of zidovudine and interleukin-2 increases absolute CD4 cells in subjects with Walter Reed stage 2 human immunodeficiency virus infection: results of ACTG protocol 042. *J Infect Dis* 1998; **178**: 1170–3.
4. Levy Y, *et al.* Comparison of subcutaneous and intravenous interleukin-2 in asymptomatic HIV-1 infection: a randomised controlled trial. *Lancet* 1999; **353**: 1923–9.
5. Losso MH, *et al.* A randomized, controlled, phase II trial comparing escalating doses of subcutaneous interleukin-2 plus antiretrovirals versus antiretrovirals alone in human immunodeficiency virus-infected patients with CD4+ cell counts ⩾350/mm³. *J Infect Dis* 2000; **181**: 1614–21. Correction. *ibid.*; 2122.
6. Davey RT, *et al.* Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: a randomized controlled trial. *JAMA* 2000; **284**: 183–9.
7. Pisticelli SC, *et al.* A risk-benefit assessment of interleukin-2 as an adjunct to antiviral therapy in HIV infection. *Drug Safety* 2000; **22**: 19–31.
8. Emery S, *et al.* Pooled analysis of 3 randomized, controlled trials of interleukin-2 therapy in adult human immunodeficiency virus type 1 disease. *J Infect Dis* 2000; **182**: 428–34.
9. Abrams D, *et al.* INSIGHT-ESPRIT Study Group. SILCAAT Scientific Committee. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med* 2009; **361**: 1548–59.
10. Tambussi G, *et al.* Efficacy of low-dose intermittent subcutaneous interleukin (IL)–2 in antiviral drug–experienced human immunodeficiency virus–infected persons with detectable virus load: a controlled study of 3 IL-2 regimens with antiviral drug therapy. *J Infect Dis* 2001; **183**: 1476–84.
11. Smith KA. Low-dose daily interleukin-2 immunotherapy: accelerating immune restoration and expanding HIV-specific T-cell immunity without toxicity. *AIDS* 2001; **15** (suppl 2): S28–S35.
12. Davey RT, *et al.* A randomized trial of high-versus low-dose subcutaneous interleukin-2 outpatient therapy for early human immunodeficiency virus type 1 infection. *J Infect Dis* 1999; **179**: 849–58.
13. David D, *et al.* Rapid effect of interleukin-2 therapy in human immunodeficiency virus-infected patients whose CD4 cell counts increase only slightly in response to combined antiretroviral treatment. *J Infect Dis* 2001; **183**: 730–5.
14. Ruxrungtham K, *et al.* A randomized, controlled 24-week study of intermittent subcutaneous interleukin-2 in HIV-1 infected patients in Thailand. *AIDS* 2000; **14**: 2509–13.
15. Arduino RC, *et al.* CD4 cell response to 3 doses of subcutaneous interleukin 2: meta-analysis of 3 Vanguard studies. *Clin Infect Dis* 2004; **39**: 115–22.
16. Arnó A, *et al.* Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with ⩽250/microlitre CD4 T cells and undetectable plasma virus load. *J Infect Dis* 1999; **180**: 56–60.
17. Lafeuillade A, *et al.* Pilot study of a combination of highly active antiretroviral therapy and cytokines to induce HIV-1 remission. *J Acquir Immune Defic Syndr* 2001; **26**: 44–55.
18. Schlaak JF, *et al.* Sustained suppression of HCV replication and inflammatory activity after interleukin-2 therapy in patients with HIV/hepatitis C virus coinfection. *J Acquir Immune Defic Syndr* 2002; **29**: 145–8.
19. Carr A, *et al.* Outpatient continuous intravenous interleukin-2 or subcutaneous, polyethylene glycol-modified interleukin-2 in human immunodeficiency virus-infected patients: a randomized, controlled, multicenter study. *J Infect Dis* 1998; **178**: 992–9.

Postherpetic neuralgia. A 46-year-old HIV patient with chronic, treatment-resistant postherpetic neuralgia (p. 10.3) received 1 cycle of subcutaneous interleukin-2 (7.5 million units twice daily for 5 consecutive days) within the context of a clinical HIV study. He reported immediate resolution of his postherpetic neuralgia, and no recurrence of pain occurred during 3 years of follow-up.[1]

1. Rotty J, *et al.* Interleukin-2: a potential treatment option for postherpetic neuralgia? *Clin Infect Dis* 2006; **43**: e109–e110.

Adverse Effects and Treatment

Toxicity is related to dose and route and is often severe; fatalities have been recorded. Decreased vascular resistance and increased capillary permeability (the 'capillary leak syndrome') is common in patients given aldesleukin, and results in hypotension, reduced organ perfusion, and oedema. The incidence and severity of this syndrome is lower after subcutaneous than intravenous dosage. Fluid replacement may be necessary to treat the resultant hypovolaemia and dopamine or other pressor agents may be needed to help maintain organ perfusion. Capillary leak syndrome may also be associated with cardiac effects including tachycardia, angina, myocardial infarction; respiratory effects such as dyspnoea, pulmonary oedema, and respiratory failure; renal abnormalities including uraemia and oliguria or anuria; mental status changes including irritability, depression, confusion, and drowsiness. Therapy should be stopped if patients develop severe lethargy or somnolence, as continuing may result in coma. Raised liver enzymes, gastrointestinal disturbances, fever and flu-like symptoms (malaise, rigors, chills, arthralgia, and myalgia), rashes, pruritus, anaemia, leucopenia, and thrombocytopenia, are also relatively common. Paracetamol (but not NSAIDs, see Effects on the Kidneys, below) may be used prophylactically for fever. Pethidine may be used to control rigors. Antiemetics and antidiarrhoeals may also be required. Antihistamines may benefit some patients with pruritic rash. Injection site reactions are common after subcutaneous doses; necrosis has occurred. Aldesleukin therapy is associated with impaired neutrophil function, and an increased risk of bacterial infections (see below), including sepsis and bacterial endocarditis; this has been reported mainly after intravenous use, and antibacterial prophylaxis may be necessary.

References.

1. Sundin DJ, Wolin MJ. Toxicity management in patients receiving low-dose aldesleukin therapy. *Ann Pharmacother* 1998; **32**: 1344–52.
2. Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. *J Immunother* 2001; **24**: 287–93.
3. Dutcher J, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part II: management of IL-2 toxicity and studies with other cytokines. *Med Oncol* 2001; **18**: 209–19.
4. Schwartz RN, *et al.* Managing toxicities of high-dose interleukin-2. *Oncology (Huntingt)* 2002; **16** (suppl 13): 11–20.

Bacterial infections. The incidence of sepsis and bacteraemia is increased in patients receiving interleukin-2 via intravenous catheters,[1,2] and possibly subcutaneously,[3] although others have not found this to be the case.[4,5] The increased incidence of nonopportunistic bacterial infection may be a particular problem in patients with AIDS who are treated with interleukin-2.[6] The mechanism is uncertain, but may be related to impairment of neutrophil function by the cytokine.[7]

1. Snydman DR, *et al.* Nosocomial sepsis associated with interleukin-2. *Ann Intern Med* 1990; **112**: 102–7.
2. Shiloni E, *et al.* Interleukin-2 therapy, central venous catheters, and nosocomial sepsis. *Ann Intern Med* 1990; **112**: 882–3.
3. Jones AL, *et al.* Infectious complications of subcutaneous interleukin-2 and interferon-alpha. *Lancet* 1992; **339**: 181–2.
4. Buter J, *et al.* Infection after subcutaneous interleukin-2. *Lancet* 1992; **339**: 552.
5. Schomburg AG, *et al.* Cytokines and infection in cancer patients. *Lancet* 1992; **339**: 1061.
6. Murphy PM, *et al.* Marked disparity in incidence of bacterial infections in patients with the acquired immunodeficiency syndrome receiving interleukin-2 or interferon-γ. *Ann Intern Med* 1988; **108**: 36–41.
7. Klempner MS, *et al.* An acquired chemotactic defect in neutrophils from patients receiving interleukin-2 immunotherapy. *N Engl J Med* 1990; **322**: 959–65.

Effects on the cardiovascular system. Interleukin-2 treatment can cause cardiotoxicity such as arrhythmias and acute myocardial infarction. High-dose therapy (600 000 units/kg intravenously every 8 hours) has been associated with myocarditis, which appears to be reversible; haemodynamic instability that can lead to an acute coronary syndrome has also been described. Careful screening of patients for cardiopulmonary disease is recommended.[1]

1. Elsner RM, *et al.* Case report and brief review: IL-2-induced myocarditis. *Cancer Invest* 2004; **22**: 401–4.

Effects on endocrine function. It has been suggested that patients with adrenal metastases may be particularly susceptible to adrenal haemorrhage and consequent failure during interleukin therapy.[1] Results also suggested that lack of endogenous steroid production may increase the risk of early severe interleukin-2 toxicity.[1]

Effects on thyroid function have also been reported, with the development of hypothyroidism[2-4] and goitre.[3]

1. VandeMolen LA, *et al.* Adrenal insufficiency and interleukin-2 therapy. *Ann Intern Med* 1989; **111**: 185.
2. Atkins MB, *et al.* Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N Engl J Med* 1988; **318**: 1557–63.
3. van Ilessum PA, *et al.* Hypothyroidism and goitre during interleukin-2 therapy without LAK cells. *Lancet* 1989; **i**: 224.
4. Sauter NP, *et al.* Transient thyrotoxicosis and persistent hypothyroidism due to acute autoimmune thyroiditis after interleukin-2 and interferon-α therapy for metastatic carcinoma: a case report. *Am J Med* 1992; **92**: 441–4.

Effects on the kidneys. Intravenous aldesleukin therapy was associated with varying degrees of acute renal dysfunction in almost all of 99 adult patients.[1] The clinical syndrome of hypotension, oliguria, fluid retention, and associated azotaemia with intense tubular avidity for filtered sodium all support prerenal acute renal failure as the cause of renal dysfunction. However, renal function values returned to baseline levels within 7 days in 62% of patients and in 95% by 30 days. Patients with elevated pretreatment serum-creatinine values, particularly those aged over 60 years, and those who had previously undergone a nephrectomy, were at risk of more severe and prolonged changes in renal function, and might be particularly vulnerable to the use of indometacin for associated fever and chills, which could potentiate renal impairment through its effects on intrarenal prostaglandin production. Similar effects were noted in a study[2] of 15 children given continuous infusion of aldesleukin. A further study[3] of the renal haemodynamic effects of aldesleukin infusion found it to have a specific renal vasoconstrictor effect; changes in renal prostaglandin synthesis contributed to the decreased renal blood flow.

1. Belldegrun A, *et al.* Effects of interleukin-2 on renal function in patients receiving immunotherapy for advanced cancer. *Ann Intern Med* 1987; **106**: 817–22.
2. Cochat P, *et al.* Renal effects of continuous infusion of recombinant interleukin-2 in children. *Pediatr Nephrol* 1991; **5**: 33–7.
3. Geertsen PF, *et al.* Renal haemodynamics, sodium and water reabsorption during continuous intravenous infusion of recombinant interleukin-2. *Clin Sci* 1998; **95**: 73–81.

Effects on the skin. Pseudosystemic sclerosis has been reported after use of aldesleukin; a reduction in skin thickening was seen after aldesleukin therapy was stopped and corticosteroids started.[1]

1. Marie I, *et al.* Pseudosystemic sclerosis as a complication of recombinant human interleukin 2 (aldesleukin) therapy. *Br J Dermatol* 2007; **156**: 182–3.

Precautions

Aldesleukin should be given with great care, if at all, to patients with pre-existing cardiac or pulmonary disease, and those with severe renal or hepatic impairment. It should be avoided in patients with CNS metastases or seizure disorders.

Risk factors for toxicity and poor response include restricted physical activity (Eastern Cooperative Oncology Group performance status of 1 or greater), 2 or more metastatic sites, and a period of less than 24 months between diagnosis of primary tumour and consideration for aldesleukin therapy. UK licensed product information states that aldesleukin should not be used to treat metastatic renal cell carcinoma in patients with all three of these risk factors.

Aldesleukin may worsen auto-immune diseases, and should be used with caution in patients with these conditions. Bacterial infections should be adequately treated before beginning therapy. Aldesleukin may increase effusions from serosal surfaces, and these should generally be treated before starting aldesleukin therapy.

Vital signs, blood counts, renal and hepatic function, serum electrolytes, and pulmonary and cardiac function should be monitored before starting treatment and then regularly during therapy.

Activity. For mention of the loss of activity when aldesleukin was given by continuous infusion without albumin, see Stability p. 810.2.

Inflammatory bowel disease. Two patients with a history of Crohn's disease had a recurrence of the condition when given aldesleukin. It was suggested that interleukin-2 should be contra-indicated in such patients.[1]

1. Sparano JA, *et al.* Symptomatic exacerbation of Crohn disease after treatment with high-dose interleukin-2. *Ann Intern Med* 1993; **118**: 617–18.

Psoriasis. Exacerbations of psoriasis developed in 3 patients during therapy with aldesleukin alone or with lymphokine-activated killer cells. The psoriatic symptoms remitted with topical therapy.[1]

1. Lee RE, *et al.* Interleukin 2 and psoriasis. *Arch Dermatol* 1988; **124**: 1811–15.

Interactions

Corticosteroids (which reduce some of the adverse effects of interleukin-2) may also reduce its antineoplastic properties: use together should generally be avoided. The use of iodinated contrast media after aldesleukin therapy may result in symptoms resembling the immediate adverse effects of aldesleukin. Although most events were reported to occur within 2 to 4 weeks of the last dose of aldesleukin, some occurred several months afterward.

Antivirals. For the effect of interleukin-2 on plasma concentrations of *indinavir*, see p. 987.3.

NSAIDs. NSAIDs are effective in preventing or reducing fever and myalgia caused by interleukin-2. However, there is concern that they could exacerbate renal toxicity (see also Effects on the Kidneys, p. 811.3). Use of *indometacin* in patients receiving interleukin-2 led to more severe weight gain, oliguria, and azotaemia in 1 study.[1] However, *ibuprofen* was used successfully to reduce interleukin-2 toxicity in another study.[2]

1. Sosman JA, *et al.* Repetitive weekly cycles of interleukin-2 II: clinical and immunologic effects of dose, schedule, and addition of indomethacin. *J Natl Cancer Inst* 1988; **80**: 1451–61.
2. Eberlein TJ, *et al.* Ibuprofen causes reduced toxic effects of interleukin 2 administration in patients with metastatic cancer. *Arch Surg* 1989; **124**: 542–7.

Pharmacokinetics

After intravenous bolus, the serum distribution and elimination half-lives of aldesleukin are 13 and 85 minutes, respectively. After subcutaneous doses, the absorption half-life is 45 minutes and the elimination half-life is 5.3 hours, while bioavailability ranges between 35 and 47%.

Aldesleukin is metabolised to amino acids by the kidneys.

References.

1. Anderson PM, Sorenson MA. Effects of route and formulation on clinical pharmacokinetics of interleukin-2. *Clin Pharmacokinet* 1994; **27**: 19–31.
2. Piscitelli SC, *et al.* Pharmacokinetics and pharmacodynamics of subcutaneous interleukin-2 in HIV-infected patients. *Pharmacotherapy* 1996; **16**: 754–9.
3. Kirchner GI, *et al.* Pharmacokinetics of recombinant human interleukin-2 in advanced renal cell carcinoma patients following subcutaneous application. *Br J Clin Pharmacol* 1998; **46**: 5–10.
4. Kamikawa S, *et al.* Pharmacokinetic study of interleukin-2 following intravenous injection in hemodialysis patients with renal cell carcinoma. *Ther Apher Dial* 2008; **12**: 67–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ilcass; Ilgen; Proleukin†; ***Austria***: Proleukin; ***Belg.***: Proleukin; ***Braz.***: Proleukin; ***Canad.***: Proleukin; ***China***: An Jie Suo (安捷素); Bai Jie Yi (百杰依); De Lu Sheng (德路生); Inleusin (英路因); Jin Lu Kang (金路康 ???); Ju He Li (巨和粒); Luo Jin (洛金); Ou Nai Te (欧耐特); Quan Qi (泉奇); Sai Di En (赛迪恩); Te Er Kang (特尔康); Xin De Lu Sheng (新德路生); Xin Ji Er (欣吉尔); Xin Luo Er (辛洛尔); Yin Te Kang (因特康); Ying Te Kang Xin (英特康欣); Yuan Ce Xin (远策欣); Yue Kang Xian (悦康仙); ***Cz.***: Proleukin; ***Denm.***: Proleukin; ***Fin.***: Proleukin; ***Fr.***: Proleukin; ***Ger.***: Proleukin; ***Gr.***: Proleukin; ***Hong Kong***: Proleukin†; ***Hung.***: Proleukin; ***Irl.***: Proleukin; ***Israel***: Proleukin; ***Ital.***: Proleukin; ***Jpn***: Celeuk; Imunace; ***Mex.***: Proleukin; ***Neth.***: Proleukin; ***NZ***: Proleukin; ***Pol.***: Proleukin†; ***Port.***: Proleukin; ***Rus.***: Proleukin (Пролейкин); Roncoleukin (Ронколейкин); ***S.Afr.***: Chiron IL-2; ***Singapore***: Proleukin; ***Spain***: Proleukin; ***Switz.***: Proleukin; ***Turk.***: Proleukin; ***UK***: Proleukin; ***Ukr.***: Bioleukin (Биолейкин); ***USA***: Proleukin.

Ipilimumab *(USAN, rINN)*

BMS-734016; Ipilimumabum; MDX-010; MDX-CTLA-4; Ипилимумаб.

Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulfide with human κ-chain, dimer.

CAS — 477202-00-9.

UNII — 6T8C155666.

Uses and Administration

Ipilimumab is a recombinant, human monoclonal antibody to the cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), which is a cell surface receptor involved in the downregulation of T-cell activation. Ipilimumab is used for the treatment of unresectable or metastatic melanoma (p. 714.3). The recommended intravenous dose is 3 mg/kg every 3 weeks, to a total of 4 doses; the dose is diluted in sodium chloride 0.9% or glucose 5% to a final concentration ranging from 1 to 2 mg/mL, and the infusion given over 90 minutes, via a low-protein-binding in-line filter.

Ipilimumab may be withheld or permanently stopped if immune-mediated reactions occur, see Adverse Effects, Treatment, and Precautions, below.

Ipilimumab is also under investigation for the treatment of prostate cancer and various other solid tumours.

References.

1. Weber J, *et al.* A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clin Cancer Res* 2009; **15**: 5591–8.
2. Wolchok JD, *et al.* Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol* 2010; **11**: 155–64.
3. Ku GY, *et al.* Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. *Cancer* 2010; **116**: 1767–75.
4. Hodi FS, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363**: 711–23. Correction. *ibid.*; 1290.
5. Robert C, *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; **364**: 2517–26.
6. Cameron F, *et al.* Ipilimumab: first global approval. *Drugs* 2011; **71**: 1093–1104.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of ipilimumab are fatigue, diarrhoea, pruritus, rash, and colitis. Severe, life-threatening, or fatal immune-mediated reactions, involving any organ, can occur. Enterocolitis (including intestinal perforation), hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy (including hypopituitarism and adrenal insufficiency) have been reported most commonly. Rare effects considered to be immune-mediated include pneumonitis, meningitis, nephritis, eosinophilia, and pericarditis. Myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, erythema multiforme, psoriasis, pancreatitis, arthritis, and auto-immune thyroiditis have also been reported.

Ipilimumab should be stopped permanently if any severe immune-mediated reactions occur, and the patient treated with high-dose systemic corticosteroids. Ipilimumab therapy should be withheld in those with moderate reactions; the patient may require corticosteroids and symptomatic treatment. Therapy may be resumed after complete or partial resolution of the reaction in patients who are taking prednisone at less than 7.5 mg daily (or equivalent); ipilimumab is restarted at the recommended dose, until all 4 doses are given, or until 16 weeks have elapsed from the first dose, whichever occurs earlier. If moderate disease persists, or the corticosteroid dose cannot be reduced to prednisone 7.5 mg daily (or equivalent), ipilimumab should be stopped permanently. Corticosteroid eye drops can be used to treat patients who develop uveitis, iritis, or episcleritis; ipilimumab should be stopped permanently if immune-mediated ocular disease occurs that is unresponsive to local immunosuppressive therapy. Patients should be monitored for any signs and symptoms of immune-mediated reactions. Liver function tests and thyroid function tests should be assessed at baseline and before each dose.

References.

1. Beck KE, *et al.* Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; **24**: 2283–9.
2. Weber J. Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist* 2007; **12**: 864–72.
3. Weber J. Ipilimumab: controversies in its development, utility and autoimmune adverse events. *Cancer Immunol Immunother* 2009; **58**: 823–30.

Pharmacokinetics

Ipilimumab steady-state concentrations occur by the third dose. Clearance was found to increase with increasing bodyweight. The mean terminal half-life is 14.7 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Yervoy; ***Belg.***: Yervoy; ***Canad.***: Yervoy; ***Denm.***: Yervoy; ***Fr.***: Yervoy; ***Ger.***: Yervoy; ***Irl.***: Yervoy; ***Israel***: Yervoy; ***Neth.***: Yervoy; ***Norw.***: Yervoy; ***Spain***: Yervoy; ***Swed.***: Yervoy; ***Switz.***: Yervoy; ***UK***: Yervoy; ***USA***: Yervoy.

Irinotecan Hydrochloride

(BANM, USAN, rINNM)

Camptothecin 11 (irinotecan); CPT-11 (irinotecan); DQ-2805; Hidrocloruro de irinotecán; Irinotécan, Chlorhydrate d'; Irinotecán, hidrocloruro de; Irinotecani Hydrochloridum; Irinotekaanihydrokloridi; Irinotekan Hidroklorür; Irinotekan-hydroklorid; U-101440E; Иринотекана Гидрохлорид.

(+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4′-bipiperidine]-1′-carboxylate hydrochloride trihydrate; (*S*)-4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6′,7′]indolizino[1,2-*b*]quinolin-9-yl [1,4′-dipiperidine]-1′-carboxylate hydrochloride trihydrate.

$C_{33}H_{38}N_4O_6HCl,3H_2O$=677.2

CAS — 97682-44-5 (irinotecan); 136572-09-3 (irinotecan hydrochloride trihydrate).

ATC — L01XX19.

ATC Vet — QL01XX19.

UNII — 042LAQ1IIS.

Pharmacopoeias. In *US.*

USP 36: (Irinotecan Hydrochloride). Pale yellow to yellow, crystalline powder. Sparingly soluble in water and in organic solvents. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Irinotecan is a semisynthetic derivative of the alkaloid camptothecin, obtained from the shrub *Camptotheca acuminata*. The camptothecin derivatives are inhibitors of the enzyme topoisomerase I and thus interfere with the coiling and uncoiling of DNA during replication and prevent nucleic acid synthesis. This action is specific for S phase.

Irinotecan is used in the treatment of advanced colorectal cancer (p. 706.3). It may be used with fluorouracil and folinic acid (with or without bevacizumab), or with capecitabine (with or without bevacizumab), as first-line therapy, and is also given as monotherapy in patients whose disease has recurred or progressed after initial fluorouracil-based therapy. It is further indicated for use with cetuximab (p. 762.3) in the treatment of EGFR-expressing, *KRAS* wild-type, metastatic colorectal cancer, either first-line or after the failure of other regimens containing irinotecan. It has been tried in the management of other solid tumours including those of the lung (p. 710.2).

It is given as the hydrochloride, by intravenous infusion in at least 250 mL of glucose 5%, or sodium chloride 0.9%. In the treatment of refractory colorectal malignancies one suggested single-agent dose regimen is irinotecan hydrochloride 125 mg/m² infused over 90 minutes once a week for 4 weeks, followed by a 2-week rest period. Additional courses may be given if required, with doses modified according to toxicity. Another regimen requires an initial dose of 350 mg/m² over 30 to 90 minutes repeated every 3 weeks and adjusted according to toxicity (for dosage in hepatic impairment, see p. 813.1).

For the suggestion that initial doses should be modified to reduce toxicity in those with certain genotypes, see Genetic Factors, p. 813.3.

Irinotecan may also be given as part of a regimen with fluorouracil and folinic acid in the first-line treatment of metastatic colorectal cancer. Many regimens exist. The irinotecan hydrochloride component of the course may be given at a dose of 180 mg/m² over 30 to 90 minutes every 2 weeks. Alternatively, 125 mg/m² may be given weekly usually on days 1, 8, 15, and 22 of a 42-day cycle. (For reference to toxicity from such regimens see under Interactions, p. 814.1.)

Treatment cycles may be continued indefinitely as long as patients continue to benefit.

In the treatment of EGFR-expressing metastatic colorectal cancer, in patients who have failed previous treatment, irinotecan is given usually at the same dose as was used in the last cycles of the previous irinotecan-containing regimen; irinotecan should not be given for at least 1 hour after the end of the cetuximab infusion. When used first-line with cetuximab, the dose of irinotecan will depend on the specific regimen used.

A formulation of irinotecan with hyaluronic acid is being developed for colorectal cancer. A stable nanoliposomal formulation, MM-398, is under investigation for the treatment of pancreatic cancer. Also under investigation is a pegylated formulation of irinotecan (NKTR-102) for various malignancies including ovarian cancer, and irinotecan-eluting beads, for injection directly into the brain in the treatment of glioma, or for chemoembolisation in colorectal cancer.

References.

1. Douillard JY, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355**: 1041–7. Correction. *ibid.*; 1372.
2. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343**: 905–14.
3. Rothenberg ML. Irinotecan (CPT-11): recent developments and future directions—colorectal cancer and beyond. *Oncologist* 2001; **6**: 66–80.
4. Saltz LB, *et al.* Irinotecan plus fluorouracil/leucovorin for metastatic colorectal cancer: a new survival standard. *Oncologist* 2001; **6**: 81–91.
5. Cunningham D, *et al.* Optimizing the use of irinotecan in colorectal cancer. *Oncologist* 2001; **6** (suppl 4): 17–23.
6. Vanhoefer U, *et al.* Irinotecan in the treatment of colorectal cancer: clinical overview. *J Clin Oncol* 2001; **19**: 1501–18.
7. Douillard JY, *et al.* Update on European adjuvant trials with irinotecan for colorectal cancer. *Oncology (Huntingt)* 2002; **16** (suppl 3): 13–15.
8. Ulukan H, Swaan PW. Camptothecins: a review of their chemotherapeutic potential. *Drugs* 2002; **62**: 2039–57.
9. Pizzolato JF, Saltz LB. The camptothecins. *Lancet* 2003; **361**: 2235–42.
10. Gilmelius B. Benefit-risk assessment of irinotecan in advanced colorectal cancer. *Drug Safety* 2005; **28**: 417–33.

11. Fuchs C, *et al.* Irinotecan in the treatment of colorectal cancer. *Cancer Treat Rev* 2006; 32: 491–503.
12. Sato T, *et al.* Treatment of advanced or recurrent colorectal cancer with irinotecan in Japan and elsewhere. *Expert Opin Pharmacother* 2008; 9: 1223–8.
13. Van Cutsem E, *et al.* Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; 360: 1408–17.
14. Hebbar M, *et al.* Current place of high-dose irinotecan chemotherapy in patients with metastatic colorectal cancer. *J Cancer Res Clin Oncol* 2009; 135: 749–52.
15. Van Cutsem E, *et al.* Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol* 2009; 27: 3117–25.
16. Weekes J, *et al.* Irinotecan therapy and molecular targets in colorectal cancer: a systemic [sic] review. *World J Gastroenterol* 2009; 15: 3597–602.
17. Zhuang L, *et al.* Meta-analysis of chemotherapy with irinotecan or oxaliplatin-involved regimen for untreated metastatic advanced colorectal cancer. *Oncol Res* 2010; 18: 437–44.
18. Oostendorp LJ, *et al.* Systematic review of benefits and risks of second-line irinotecan monotherapy for advanced colorectal cancer. *Anticancer Drugs* 2010; 21: 749–58.

Administration. The intravenous formulation of irinotecan (*Camptosar, Pfizer, USA*) has been given orally to children with refractory solid tumours.[1] The dose (typically 15 mg/m²) was drawn up in a plastic oral syringe on the day of dosing, although the reconstituted solution has been reported to be stable for 21 days at 4 degrees in these syringes. The dose was mixed with cranberry-grape juice immediately before use.

When this single oral dose of irinotecan was given with oral *gefitinib*, median irinotecan bioavailability was significantly higher, and systemic exposure to irinotecan and its metabolite SN-38 was greater, than that seen in patients not given gefitinib.[1]

1. Furman WL, *et al.* Tyrosine kinase inhibitor enhances the bioavailability of oral irinotecan in pediatric patients with refractory solid tumors. *J Clin Oncol* 2009; 27: 4599–4604.

Administration in the elderly. UK licensed product information states that elderly patients treated with irinotecan require more intensive monitoring, and that the dose should be chosen with care. US licensed product information reports that exposure to the active metabolite SN-38 is increased by about 11% in patients aged 65 years and older compared with younger patients. No change in the initial dose is recommended for elderly patients given weekly irinotecan, but in those given the 3-weekly schedule, a lower initial dose is recommended in patients 70 years and older based on clinical toxicity with this schedule (although the pharmacokinetics of this schedule have not been studied in a geriatric population). A review[1] found that delayed diarrhoea was increased in elderly patients, although response rates appear unaffected by age. While there were no data to support a specific dose modification, it was recommended that those older than 70 years, those with previous pelvic irradiation, or those with poor performance status, be treated with reduced initial doses.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in hepatic impairment. In patients with hyperbilirubinaemia, the clearance of irinotecan is decreased, exposure to the active metabolite SN-38 is increased, and the risk of haematological toxicity is increased. US licensed product information recommends a reduction in the initial dose of irinotecan for those patients with increased bilirubin concentrations. However, doses in patients with bilirubin greater than 2 mg per 100 mL cannot be determined due to insufficient data.

In the UK, licensed product information recommends the following dosage reduction for monotherapy regimens in which irinotecan hydrochloride is normally given at 350 mg/m² every 3 weeks (see Uses and Administration, p. 812.3):

- in patients with bilirubin up to 1.5 times the upper limit of normal range (ULN): no dosage reduction is considered necessary and irinotecan hydrochloride 350 mg/m² is recommended;
- in patients with bilirubin ranging from 1.5 to 3 times the ULN: irinotecan hydrochloride 200 mg/m² may be given;
- in patients with bilirubin over 3 times the ULN: the use of irinotecan is not recommended.

Administration in renal impairment. UK and US licensed product information state that irinotecan is not recommended or should be used with caution in patients with renal impairment due to a lack of data; creatinine clearance was reported[1] to be inversely related to the risk of severe neutropenia in one study. US licensed product information states that irinotecan is not recommended for use in dialysis. However, there is a report of its use in a colorectal cancer patient on long-term haemodialysis;[2] the initial intravenous dose used was irinotecan 50 mg/m² weekly for 3 weeks, repeated after a rest period of 1 week. This dose was well tolerated, and irinotecan was increased to 80 mg/m² after 2 cycles. Pharmacokinetic study showed a lower apparent clearance and a higher maximum concentration of the active metabolite SN-38, compared with patients with normal renal function. The authors concluded that an initial dose of 80 mg/m² (about ⅔ of the standard dose) given weekly for 3 weeks followed by a rest period of 1 week might be feasible in patients with end-stage renal failure.

1. de Jong FA, *et al.* Renal function as a predictor of irinotecan-induced neutropenia. *Clin Pharmacol Ther* 2008; 84: 254–62.
2. Czock D, *et al.* Irinotecan in cancer patients with end-stage renal failure. *Ann Pharmacother* 2009; 43: 363–9.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. Neutropenia and diarrhoea may be dose-limiting in patients given irinotecan. The nadir of the white cell count usually occurs about 8 days after a dose, with recovery by about day 22. Leucopenia and anaemia also occur and, less commonly, thrombocytopenia. Complete blood counts should be monitored weekly during treatment. Those who are homozygous for the uridine diphosphate glucuronosyltransferase allele UGT1A1*28 are at increased risk of neutropenia (see Genetic Factors, below). Radiotherapy also increases the risk of myelosuppression. Treatment should be withheld until neutropenia recovers to at least grade 1, and further doses reduced for severe haematological toxicity.

Nausea, vomiting, and diarrhoea are common with irinotecan, and can be severe. Acute diarrhoea, occurring within 24 hours of a dose, may be part of a transient cholinergic syndrome which can also include sweating, hypersalivation, abdominal cramps, lachrymation, miosis, conjunctivitis, vasodilatation, hypotension, chills, and dizziness. These symptoms can be controlled with atropine. However, a more severe, prolonged diarrhoea may occur, beginning more than 24 hours after a dose, and can be life-threatening; prompt management with high-dose loperamide and fluid replacement is required (see Effects on the Gastrointestinal Tract, below), and irinotecan treatment should be interrupted and any further doses reduced. Elderly patients, women, those who have had abdominal or pelvic radiotherapy, those with pre-existing hyperleucocytosis, and those with poor performance status are at increased risk of diarrhoea. There is also an increased risk of infection and haematological toxicity in patients with severe diarrhoea. A prophylactic antibacterial should be given if there is diarrhoea and severe neutropenia (neutrophil count < 500 cells/mm³) or fever. Dehydration can occur and in severe cases has led to acute renal failure, hypotension, and cardio-circulatory failure. Other gastrointestinal disturbances include toxic megacolon, colitis including typhlitis, ischaemia, and ulceration, leading to haemorrhage, obstruction, and perforation. Pseudomembraneous colitis has also been reported. Irinotecan should not be given to patients with inflammatory bowel disease or bowel obstruction.

Other adverse effects include hiccups, weakness, reversible alopecia, skin reactions, pancreatitis, and increases in liver enzymes, bilirubin, creatinine, amylase, and lipase. Liver function tests should be carried out at baseline and before each cycle. Hypertension has occurred rarely during or after infusion. There are rare reports of hypersensitivity reactions including anaphylaxis, mild injection site reactions, transient speech disorders (dysarthria), muscular contraction or cramps, and paraesthesia. Interstitial lung disease with pulmonary infiltrates is uncommon during irinotecan treatment, but can be fatal; patients with risk factors should be closely monitored. If symptoms such as dyspnoea, cough, and fever occur, irinotecan and any other chemotherapy should be withheld, and stopped permanently if interstitial lung disease is diagnosed.

Thromboembolic events have occurred, including myocardial ischaemia and infarction, cerebral infarction, pulmonary embolism, arterial thrombosis, angina, and vascular disorders.

Severe toxicity resulting in an increased number of deaths has been reported when irinotecan was given with fluorouracil and folinic acid (see under Interactions, p. 814.1).

Effects on the gastrointestinal tract. *Acute* diarrhoea occurring as part of a cholinergic syndrome with irinotecan is rarely severe. The syndrome is usually treated or prevented with atropine, but pretreatment with hyoscine butylbromide has also been tried.[1,2] In contrast, *delayed* diarrhoea can be dose-limiting or even fatal in some patients. Standard treatment involves fluid and electrolyte replacement and a high-dose loperamide regimen consisting of 4 mg loperamide immediately after the first loose stool, then 2 mg every 2 hours until 12 hours after the last liquid stool. During the night, the patient may take 4 mg every 4 hours. The high-dose therapy should not be given for more than 48 hours and should never be given prophylactically. Specific recommendations[3] state that if the diarrhoea persists for more than 24 hours despite loperamide therapy, patients should also take an oral fluoroquinolone for 7 days. If the diarrhoea persists for more than 48 hours, patients should be hospitalised for parenteral hydration. Other treatments have been tried, including acetorphan, activated charcoal, budesonide, glutamine, and octreotide.[2,4-9] A regimen of thalidomide with irinotecan has been reported to have a striking lack of gastrointestinal adverse effects such as diarrhoea and nausea.[2,10] However, a pharmacokinetic study found no decrease in gastrointestinal toxicity when these 2 drugs were given together, see Thalidomide, under Interactions, p. 814.2.

Diarrhoea may be caused by direct intestinal damage due to SN-38, the active metabolite of irinotecan; reduction of intestinal SN-38 concentrations using the poorly absorbed aminoglycoside neomycin as prophylaxis was reported to ameliorate diarrhoea in 6 of 7 patients who had this adverse effect.[11]

1. Zampa G, Magnolfi E. Premedication for irinotecan. *J Clin Oncol* 2000; 18: 237.
2. Yang X, *et al.* Novel agents that potentially inhibit irinotecan-induced diarrhea. *Curr Med Chem* 2005; 12: 1343–58.
3. Rothenberg ML, *et al.* Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001; 19: 3801–7.
4. Saliba F, *et al.* Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment. *J Clin Oncol* 1998; 16: 2745–51.
5. Lenfers BHM, *et al.* Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment. *Ann Oncol* 1999; 10: 1251–3.
6. Savarese D, *et al.* Glutamine for irinotecan diarrhea. *J Clin Oncol* 2000; 18: 450–1.
7. Ychou M, *et al.* Randomized comparison of prophylactic antidiarrheal treatment versus no prophylactic antidiarrheal treatment in patients receiving CPT-11 (irinotecan) for advanced 5-FU-resistant colorectal cancer: an open-label multicenter phase II study. *Am J Clin Oncol* 2000; 23: 143–8.
8. Pro B, *et al.* Therapeutic response to octreotide in patients with refractory CPT-11 induced diarrhea. *Invest New Drugs* 2001; 19: 341–3.
9. Michael M, *et al.* Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. *J Clin Oncol* 2004; 22: 4410–17.
10. Govindarajan R, *et al.* Effect of thalidomide on gastrointestinal toxic effects of irinotecan. *Lancet* 2000; 356: 566–7.
11. Kehrer DFS, *et al.* Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. *Clin Cancer Res* 2001; 7: 1136–41.

Genetic factors. Irinotecan is hydrolysed to SN-38, an active metabolite, which is inactivated by glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes.[1] Genetic variation in the UGT family may affect irinotecan pharmacodynamics. Although UGT1A1*28 polymorphism appears to be only one of several identified causes of altered SN-38 pharmacokinetics,[1,2] it has been strongly associated with the development of severe neutropenia, and genotyping has been proposed as a method of identifying patients at risk of severe toxicity from irinotecan.[3,4] However, genotyping does not predict for all toxicities, and a significant association between the UGT1A1*28 homozygous genotype and diarrhoea has not been proven. Furthermore, a normal UGT1A1 genotype does not ensure lack of toxicity, although the risk is less; the possibility of underdosing in those with the normal genotype may need to be considered.[5] Despite these limitations, it has been suggested that every patient receiving irinotecan for the first time be tested for UGT1A1 genotype.[5]

Licensed product information in the USA states that reduced initial doses should be considered for patients known to be homozygous for the UGT1A1*28 allele; however, the most appropriate dose reduction in the homozygous population is unknown. Some have suggested an initial 20% dose reduction, with escalation to full dosage in subsequent courses in the event of little or no toxicity.[5] A prospective study[6] found that the UGT1A1*28 genotype (homozygous or heterozygous) was significantly associated with haematological toxicity, but only during the first cycle of irinotecan-containing chemotherapy. This called into question the need for a dose reduction in irinotecan for patients with this genotype, particularly since homozygous patients showed a trend to improve clinical response. A study in paediatric patients[7] found that, for low-dose, protracted schedules of irinotecan (doses ranged from 15 to 75 mg/m² daily, given either intravenously or orally, for 5 days, for 2 consecutive weeks), UGT1A1 genotyping was not a useful prognostic indicator of severe toxicity. A similar lack of influence of UGT1A1 genotype was seen in adults given a low-dose regimen for metastatic colon cancer.[8] A meta-analysis[9] found that the risk of haematological toxicity was similar for all genotypes at lower doses of irinotecan. The authors suggested that at low doses of irinotecan, decisions about treating individual patients could be made according to standard clinical practice, whereas genotype-based decisions were advisable at higher doses. Many studies on so-called 'irinogenetics' have been conducted.[10,11] One such study[11] examined 42 common genetic variants, as well as some non-genetic variables. UGT1A1*93 was found to be a strong predictor for neutropenia, and drug

transporter polymorphisms may also have a significant impact on irinotecan pharmacokinetics and pharmacodynamics. Non-genetic factors were also found to be significant; females were more prone to neutropenia, for example, and total bilirubin may also be a factor.[11] Since smoking and other medications can also influence irinotecan disposition, it has been asked whether the drug-elimination phenotype needs to be ascertained, rather than genotype alone, and whether too many genes are involved in drug elimination for genotyping to be of practical clinical use. However, further studies might elucidate a drug elimination genotype with relevance for other drugs, not only irinotecan.[12]

1. Paoluzzi L, *et al.* Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. *J Clin Pharmacol* 2004; **44**: 854–60.
2. Ramchandani RP, *et al.* The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. *J Clin Pharmacol* 2007; **47**: 78–86.
3. Innocenti F, *et al.* Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; **22**: 1382–8.
4. Hahn KK, *et al.* Pharmacogenetics and irinotecan therapy. *Am J Health-Syst Pharm* 2006; **63**: 2211–17.
5. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. *J Clin Oncol* 2006; **24**: 4534–8.
6. Toffoli G, *et al.* The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24**: 3061–8.
7. Stewart CF, *et al.* UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol* 2007; **25**: 2594–2600.
8. Schulz C, *et al.* UGT1A1 gene polymorphism: impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. *World J Gastroenterol* 2009; **15**: 5058–66.
9. Hoskins JM, *et al.* UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. *J Natl Cancer Inst* 2007; **99**: 1290–5.
10. Hoskins JM, *et al.* Irinotecan pharmacogenetics: influence of pharmacodynamic genes. *Clin Cancer Res* 2008; **14**: 1788–96.
11. Innocenti F, *et al.* Comprehensive pharmacogenetic analysis of irinotecan neutropenia and pharmacokinetics. *J Clin Oncol* 2009; **27**: 2604–14.
12. Mathijssen RHJ, Gurney H. Irinogenetics: how many stars are there in the sky? *J Clin Oncol* 2009; **27**: 2578–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies irinotecan 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 26/08/11)

Interactions

Irinotecan is partly metabolised by cytochrome P450 CYP3A isoenzymes. Inducers of this system such as carbamazepine, phenobarbital, or phenytoin reduce exposure to irinotecan and its active metabolite SN-38; use with St John's Wort is contra-indicated. Conversely, inhibitors of this system such as ketoconazole increase exposure to irinotecan and SN-38; use with ketoconazole is contra-indicated.

Antidepressants. In a small, crossover study[1] of cancer patients, use of *St John's wort* during irinotecan therapy was found to decrease plasma concentrations of SN-38, the active metabolite of irinotecan. Myelosuppression was also reduced with this combination. The interaction is thought to be due to the induction of the cytochrome P450 isoenzyme CYP3A4 by St John's wort.

1. Mathijssen RHJ, *et al.* Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002; **94**: 1247–9.

Antineoplastics. Although previously reported to be effective, and not associated with excessive toxicity,[1] a regimen of irinotecan with bolus *fluorouracil* and folinic acid was found to be associated with an excess of early deaths in 2 further studies, which were consequently terminated.[2] Deaths were associated with a variety of events including dehydration (due to diarrhoea, nausea, and vomiting), neutropenia, and sepsis. It has been suggested that use of irinotecan with fluorouracil by continuous infusion might be better tolerated,[3,4] and a small study[5] found that the sequence may be important. Irinotecan followed by an infusion of fluorouracil over 48 hours, was associated with less dose-limiting toxicity, and higher maximum tolerated doses, than fluorouracil infusion followed by irinotecan.

Sorafenib may increase systemic exposure to irinotecan.

Gefitinib has been used to increase the bioavailability of *oral* irinotecan, see under Administration, p. 813.1.

1. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343**: 905–14.
2. Sargent DJ, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345**: 144–5.
3. Ledermann JA, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345**: 145–6.
4. Van Cutsem E, *et al.* Toxicity of irinotecan in patients with colorectal cancer. *N Engl J Med* 2001; **345**: 1351–2.
5. Falcone A, *et al.* Sequence effect of irinotecan and fluorouracil treatment on pharmacokinetics and toxicity in chemotherapy-naive metastatic colorectal cancer patients. *J Clin Oncol* 2001; **19**: 3456–62.

Smoking. A study found that tobacco smoking significantly affected the pharmacokinetics and toxicity of irinotecan.[1] Clearance of irinotecan was faster in smokers, and systemic exposure to the active metabolite SN-38 (see Pharmacokinetics, below) was almost 40% lower in smokers. This effect probably contributed to the significantly lower haematological toxicity seen in smokers; no significant difference in diarrhoea was seen between smokers and non-smokers. Smoking may induce cytochrome P450 isoenzymes, or possibly affect carboxylesterase activity. The study did not determine an effect of smoking on the outcome of treatment with irinotecan. However, smokers may need a higher dose of irinotecan relative to non-smokers, since the lower exposure to irinotecan and SN-38 may indicate a potential risk of treatment failure.

1. van der Bol JM, *et al.* Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. *J Clin Oncol* 2007; **25**: 2719–26.

Thalidomide. A pharmacokinetic study found that the metabolism of irinotecan to SN-38 was significantly decreased by thalidomide. Despite reports of reduced gastrointestinal toxicity when these 2 drugs were given together (see Effects on the Gastrointestinal System, p. 813.2), 3 out of 19 patients enrolled in the study had severe delayed diarrhoea after being given irinotecan with thalidomide.[1]

1. Allegrini G, *et al.* Irinotecan in combination with thalidomide in patients with advanced solid tumors: a clinical study with pharmacodynamic and pharmacokinetic evaluation. *Cancer Chemother Pharmacol* 2006; **58**: 585–93.

Pharmacokinetics

Irinotecan exhibits biphasic or triphasic pharmacokinetics, with a terminal half-life of about 14 hours. After intravenous doses it is hydrolysed by carboxylesterase in body tissues to active SN-38 (7-ethyl-10-hydroxycamptothecin), which has a biphasic elimination profile with a terminal half-life of about 14 hours. Plasma protein binding for irinotecan and SN-38 is about 65% and 95%, respectively. SN-38 is mainly eliminated by glucuronidation, predominantly by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Irinotecan is also partly metabolised by cytochrome P450 isoenzymes CYP3A4 and perhaps CYP3A5. More than 50% of an intravenous dose of irinotecan is excreted as unchanged drug, with about 30% in the faeces via the bile and about 20% in the urine.

References.
1. Chabot GG. Clinical pharmacokinetics of irinotecan. *Clin Pharmacokinet* 1997; **33**: 245–59.
2. Rivory LP. Metabolism of CPT-11: impact on activity. *Ann N Y Acad Sci* 2000; **922**: 205–15.
3. Mathijssen RH, *et al.* Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clin Cancer Res* 2001; **7**: 2182–94.
4. Ma MK, McLeod HL. Lessons learned from the irinotecan metabolic pathway. *Curr Med Chem* 2003; **10**: 41–9.
5. Smith NF, *et al.* Pharmacogenetics of irinotecan metabolism and transport: an update. *Toxicol In Vitro* 2006; **20**: 163–75.
6. Di Paolo A, *et al.* Clinical pharmacokinetics of irinotecan-based chemotherapy in colorectal cancer patients. *Curr Clin Pharmacol* 2006; **1**: 311–23.
7. Fujita K, Sparreboom A. Pharmacogenetics of irinotecan disposition and toxicity: a review. *Curr Clin Pharmacol* 2010; **5**: 209–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Biotecan; Camptosar; Efixano; Irenax; Irinogen; Itoxaril; Kebirtecan; Pipetecan; Satigene; Sibudan; Trinotecan; Winol; ***Austral.***: Camptosar; ***Austria***: Campto; ***Belg.***: Campto; Irinosin; ***Braz.***: Biotecan; Camptosar; Irenax; Irinolibbs; Irnocam; Ironotel; Proto-Itecan; Tecnotecan; ***Canad.***: Camptosar; ***Chile***: Camptosar; Linatecan; ***China***: Ai Li (艾力); Campto (开普拓); ***Cz.***: Campto; Canri; Irinoxin; Riemid; ***Denm.***: Campto; Irinosor†; ***Fin.***: Campto; ***Fr.***: Campto; ***Ger.***: Axinotecan; Campto; Irinomedac; Irinotesin; Riboirino; ***Gr.***: Biotecan; Campto; Irinocan; Iritec; Mizantrone; Santacil; Vintecan; ***Hong Kong***: Campto; Irinotesin; ***Hung.***: Campto; Tekazol; ***India***: Irinotel; Irnocam; ***Indon.***: Campto; Irnocam; ***Irl.***: Campto; ***Israel***: Campto; Irinomed; ***Ital.***: Campto; ***Jpn***: Campto; Topotecin; ***Malaysia***: Campto; Irnocam; ***Mex.***: Camptolem†; Camptosar; Daritex A; Iraplax; Itoxaril; Tetican; ***Neth.***: Campto; Cetomedica; Iricam; Iritec; Jovadolin; Narimed; Xavetta; ***Norw.***: Campto; ***NZ***: Camptosar; Irinoccord; ***Philipp.***: Campto; Irican; ***Pol.***: Campto; Irinotesin; ***Port.***: Campto; Faultenocan; Irkan; ***Rus.***: Camptera (Камптера); Campto (Кампто); Camptotecan (Камптотекан); Iriten (Иритен); Irnocam (Ирнокам); ***S.Afr.***: Campto; Irinotas; ***Singapore***: Campto; Irinotesin; ***Spain***: Campto; ***Swed.***: Campto†; ***Switz.***: Campto; ***Thai.***: Campto; Irenax†; Irino†; Irinoll; Irinotel; Irinotesin; ***Turk.***: Campto; Irinocam; Tekamen; ***UK***: Campto; ***Ukr.***: Campto (Кампто); Irnocam (Ірнокам); ***USA***: Camptosar; ***Venez.***: Camptosar; Elinatecan.

Pharmacopoeial Preparations

USP 36: Irinotecan Hydrochloride Injection.

Ixabepilone *(USAN, rINN)*

Azaepothilone B; BMS-247550-01; Ixabepilona; Ixabépilone; Ixabepilonum; Иксабепильон.

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-2-(2-methylthiazol-4-yl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione.

$C_{27}H_{42}N_2O_5S$=506.7

CAS — 219989-84-1.

ATC — L01DC04.

ATC Vet — QL01DC04.

UNII — K27005NP0A.

Uses and Administration

Ixabepilone is an analogue of the epothilone compound patupilone (p. 843.3) that is used for the treatment of patients with metastatic or locally advanced breast cancer. It is given as monotherapy in those whose tumours are resistant or refractory to anthracyclines, taxanes, and capecitabine. Ixabepilone is also used with capecitabine in those whose tumours are resistant to anthracycline and taxanes, or in those with cancer resistant to taxanes, and for whom further anthracycline therapy is contra-indicated.

The recommended dose of ixabepilone is 40 mg/m² (to a maximum of 88 mg) given by intravenous infusion over 3 hours every 3 weeks. Ixabepilone is diluted with a suitable infusion fluid (pH 6 to 9), such as lactated Ringer's solution, to a final concentration of 200 to 600 micrograms/mL before infusion.

Doses are adjusted for toxicity. If moderate or severe neuropathy, or any severe toxicity (other than neuropathy) occurs, the dose should be decreased by 20%. If severe neuropathy lasts 7 days or more, or any disabling toxicity occurs, therapy should be stopped. If the neutrophil count falls below 500 cells/mm³ for 7 days or more, if platelets fall below 25 000 cells/mm³ (or below 50 000 cells/mm³ with bleeding), or if febrile neutropenia occurs, the dose should be decreased by 20%. If toxicities recur, an additional 20% dose reduction should be made. Patients should not begin a new cycle of treatment unless the neutrophil count is at least 1500 cells/mm³, the platelet count is at least 100 000 cells/mm³, and non-haematological toxicities have improved to grade 1 (mild) or resolved.

Doses are also adjusted in hepatic impairment (see Administration in Hepatic Impairment, below).

Use of strong inhibitors of CYP3A4 should be avoided with ixabepilone. If no alternative is available, a dose reduction of ixabepilone to 20 mg/m² should be considered. Once the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of ixabepilone is increased back to the original dose.

Use of strong CYP3A4 inducers should also be avoided with ixabepilone, but if they must be used, the dose of ixabepilone may be gradually increased up to 60 mg/m² if increased doses should be given as an intravenous infusion over 4 hours. Once the inducer is stopped, ixabepilone should be reduced to the original dose.

References.
1. Gianni L. Ixabepilone and the narrow path to developing new cytotoxic drugs. *J Clin Oncol* 2007; **25**: 3389–91.
2. Pormier MN. Ixabepilone, first in a new class of antineoplastic agents: the natural epothilones and their analogues. *Clin Breast Cancer* 2007; **7**: 757–63.
3. Thomas ES, *et al.* Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2007; **25**: 5210–17.
4. Moen MD. Ixabepilone: in locally advanced or metastatic breast cancer. *Drugs* 2009; **69**: 1471–81.

Administration in hepatic impairment. Ixabepilone and capecitabine *combination therapy* is contra-indicated in patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2.5 times the upper limit of normal (ULN), or in those with bilirubin greater than the ULN. Patients with values equal to or below these figures may be given the standard dose of ixabepilone.

In *monotherapy*, the following doses of ixabepilone may be given:

- mild; AST and ALT up to 2.5 times the ULN, and normal bilirubin: 40 mg/m² *or* AST or ALT equal to or less than 10 times the ULN and bilirubin equal to or less than 1.5 times the ULN: 32 mg/m²
- moderate; AST and ALT equal to or less than 10 times the ULN and bilirubin greater than 1.5 times the ULN, but equal to or less than 3 times the ULN: patients should be started at 20 mg/m², and the dosage in subsequent cycles escalated up to, but not exceeding, 30 mg/m² if tolerated
- severe; AST or ALT greater than 10 times the ULN or bilirubin greater than 3 times the ULN: not recommended

Data are limited for patients with a baseline AST or ALT greater than 5 times the ULN.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Peripheral neuropathy is common with ixabepilone, but is generally reversible. Dose reduction, or delaying or stopping treatment may be necessary (see Uses and Administration, p. 814.3). Dose-dependent myelosuppression can occur, manifested mainly as neutropenia; febrile neutropenia and fatalities have been reported. Frequent blood counts are recommended. Ixabepilone is formulated in polyoxyl castor oil and should be avoided in patients hypersensitive to this substance; patients should be premedicated with a histamine H_1-and histamine H_2-antagonist about 1 hour before infusion. Therapy should be stopped if a hypersensitivity reaction occurs, and symptomatic treatment given. Subsequent cycles may be given with additional corticosteroid therapy, and extension of the infusion time should be considered.

Cardiac adverse effects such as hypotension, myocardial ischaemia, myocardial infarction, arrhythmias, ventricular dysfunction, and cardiomyopathy have been reported. Caution is advised in patients with a history of cardiac disease and therapy may need to be stopped if cardiac effects occur. Effects on the respiratory system include dyspnoea, cough, pneumonitis, pulmonary oedema, and respiratory failure. Increases in hepatic enzymes, jaundice, and acute hepatic failure have occurred, as has renal failure.

Other adverse effects include gastrointestinal disturbances, anorexia, myalgia, arthralgia, fatigue, alopecia, insomnia, headache, taste disorders, dizziness, increased lachrymation, hot flushes, nail disorders, skin disorders including rashes, erythema multiforme, palmar-plantar erythrodysesthesia syndrome, pruritus, and skin exfoliation or hyperpigmentation, renal calculi, electrolyte disturbances, coagulopathy, cognitive disorders, syncope, thrombotic or haemorrhagic events, and vasculitis.

Interactions

Ixabepilone undergoes extensive metabolism by cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, can increase exposure to ixabepilone. Conversely, CYP3A4 inducers can reduce exposure to ixabepilone. Use of ixabepilone with strong inhibitors or inducers of CYP3A4 should be avoided. If strong inhibitors are used, dose adjustments may be required (see Uses and Administration, p. 814.3). Grapefruit juice may also increase plasma concentrations of ixabepilone and should be avoided. St John's wort may decrease plasma concentrations of ixabepilone unpredictably and should also be avoided.

Pharmacokinetics

Ixabepilone is extensively distributed. Plasma protein binding is about 67 to 77%. It is extensively metabolised in the liver, mainly by oxidation via cytochrome P450 isoenzyme CYP3A4. It is eliminated mainly as metabolites; about 86% of a dose is eliminated within 7 days, 65% in faeces, and 21% in the urine. The terminal elimination half-life is reported to be about 52 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ixempra; *Chile*: Ixempra; *Fr.*: Ixempra†; *Israel*: Ixempra; *NZ*: Ixempra; *Singapore*: Ixempra; *Switz.*: Ixempra; *Thai.*: Ixempra; *USA*: Ixempra.

Lapatinib Tosilate *(rINNM)*

GW-572016F; Lapatinib Ditosylate (USAN); Lapatinib, Tosilate de; Lapatinibi Tosilas; Tosilato de lapatinib; Лапатиниба Тозилат.

N-[3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl]-6-[5-([[2-(methylsulfonyl)ethyl]amino}methyl)furan-2-yl]quinazolin-4-amine bis(4-methylbenzenesulfonate) monohydrate.

$C_{29}H_{26}ClFN_4O_4S.2C_7H_8O_3S.H_2O$=943.5

CAS — 231277-92-2 (lapatinib); 388082-78-8 (lapatinib tosilate).

UNII — G873GX646R.

Uses and Administration

Lapatinib tosilate is a dual tyrosine kinase inhibitor directed against two members of the human epidermal growth factor receptor family, namely epidermal growth factor receptor (EGFR; ErbB1) and human epidermal receptor type 2 (HER2; ErbB2). Lapatinib is used in the treatment of breast cancer (p. 702.1) that overexpresses HER2, either with capecitabine (p. 757.3) in patients with advanced or metastatic disease who have had previous therapy including an anthracycline, a taxane, and trastuzumab, or, in some countries, with an aromatase inhibitor in postmenopausal women with hormone-receptor positive metastatic disease.

Doses of lapatinib tosilate are expressed in terms of the base; lapatinib tosilate 405 mg is equivalent to about 250 mg of lapatinib. It is given orally, at least one hour before or one hour after food. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

When given with capecitabine, the recommended dose of lapatinib is 1.25 g once daily on days 1 to 21 of a 21-day cycle. Capecitabine is given at a dose of 2 g/m² daily (given orally in 2 doses about 12 hours apart, with food or within 30 minutes after food) on days 1 to 14 of the cycle. Treatment may be continued until disease progression or unacceptable toxicity occurs. If a daily dose is missed, the next day's dose should not be doubled.

When given with an aromatase inhibitor, the recommended dose of lapatinib is 1.5 g given orally once daily.

Dosage should be reduced in patients with severe hepatic impairment (see Administration in Hepatic Impairment, below). Treatment with lapatinib should be stopped in patients who develop a decreased left ventricular ejection fraction (LVEF); however, patients may be restarted at a reduced dose of lapatinib after a minimum of 2 weeks if the LVEF recovers to normal and if the patient is asymptomatic. When given with capecitabine, lapatinib is restarted at 1 g daily, or when given with an aromatase inhibitor, lapatinib 1.25 g daily is used. Lapatinib may need to be stopped or treatment interrupted if other severe toxicities develop. Patients can be restarted at the recommended dose when the toxicity improves. However, if toxicity recurs, lapatinib should be restarted at a lower dose; when given with capecitabine, lapatinib is restarted at 1 g daily, or when given with an aromatase inhibitor, lapatinib 1.25 g daily is used.

If use with potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, US licensed product information recommends dose adjustments of lapatinib based on pharmacokinetic studies. Lapatinib should be given at a dose of 500 mg daily when given with a potent CYP3A4 inhibitor; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the lapatinib dose is increased to the usual recommended dose. When given with a potent inducer of this isoenzyme, the dose of lapatinib should be increased gradually, based on tolerability. When given with capecitabine, lapatinib is titrated from 1.25 g daily up to 4.5 g daily; when given with the aromatase inhibitor letrozole, lapatinib is titrated from 1.5 g daily up to 5.5 g daily. If the inducer is stopped, the dose of lapatinib should be reduced to the usual recommended dose.

Lapatinib is also under investigation for the treatment of gastric cancer and head and neck squamous cell carcinoma.

References.

1. Nelson MH, Dolder CR. Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors. *Ann Pharmacother* 2006; **40**: 261–9.
2. Moy B, Goss PE. Lapatinib: current status and future directions in breast cancer. *Oncologist* 2006; **11**: 1047–57.
3. Geyer CE, *et al.* Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; **355**: 2733–43.
4. Montemurro F, *et al.* Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity. *Expert Opin Biol Ther* 2007; **7**: 257–68.
5. Ito Y, *et al.* Does lapatinib, a small-molecule tyrosine kinase inhibitor, constitute a breakthrough in the treatment of breast cancer? *Breast Cancer* 2007; **14**: 156–62.
6. Dhillon S, Wagstaff AJ. Lapatinib. *Drugs* 2007; **67**: 2101–8.
7. Paul B, *et al.* Lapatinib: a dual tyrosine kinase inhibitor for metastatic breast cancer. *Am J Health-Syst Pharm* 2008; **65**: 1703–10.
8. Frampton JE. Lapatinib: a review of its use in the treatment of HER2-overexpressing, trastuzumab-refractory, advanced or metastatic breast cancer. *Drugs* 2009; **69**: 2125–48.

Administration in hepatic impairment. US licensed product information states that systemic exposure to lapatinib after a single 100-mg oral dose increased by about 14% and 63% in subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, respectively, when compared with healthy control subjects. Caution is advised when lapatinib is given to patients with severe hepatic impairment. Oral doses should be reduced; when given with capecitabine, lapatinib is reduced to 750 mg daily, or when given with letrozole, a dose of lapatinib 1 g daily is used. However, licensed product information warns that there are no clinical data with this dose adjustment in patients with severe hepatic impairment.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of lapatinib tosilate are gastrointestinal disturbances, dermatological reactions such as palmar-plantar erythrodysesthesia and rash, and fatigue. Diarrhoea may be severe and dose-limiting. Decreases in left ventricular ejection fraction (LVEF) have been reported with lapatinib, usually within the first 12 weeks of treatment. LVEF should be evaluated in all patients before therapy is started, and periodically evaluated during treatment. Prolongation of the QT interval has also been reported, and lapatinib should be given with caution to those patients with relevant risk factors such as hypokalaemia or hypomagnesaemia, congenital QT prolongation, use of antiarrhythmics, or cumulative high-dose anthracycline therapy. Other reported adverse effects include stomatitis, mucosal inflammation, pain in extremities, back pain, dyspnoea, insomnia, epistaxis, alopecia, nail disorders such as paronychia, and hypersensitivity reactions including anaphylaxis. Lapatinib has been associated with interstitial lung disease and pneumonitis, and treatment should be stopped if severe pulmonary symptoms develop. Hepatotoxicity has occurred and may be severe; deaths have been reported. Liver function should be monitored before, and every 4 to 6 weeks during, treatment. If severe hepatotoxicity develops during treatment, lapatinib should be permanently stopped. Lapatinib should be given with caution to those with pre-existing severe hepatic impairment; doses may need to be reduced.

Effects on the heart. A pooled analysis[1] of data from 44 studies, involving 3689 subjects given lapatinib, found that asymptomatic changes in ventricular ejection fraction occurred in 53 cases and symptomatic events in 7 cases; there were no cardiac deaths attributed to the drug. Of the symptomatic cases 5 were receiving monotherapy and 2 were also taking letrozole or paclitaxel. Symptoms, which included dyspnoea, heart failure, or palpitations, lasted for 2 and 6 weeks respectively in 2 patients who recovered fully, and one of these patients subsequently restarted lapatinib treatment. Of the remaining 5, 2 died due to disease progression (including one in whom lapatinib was not withdrawn as in the other cases), 2 had partial recovery (one of whom later restarted lapatinib), and one remained symptomatic. The frequency of cardiac events was similar in control patients who did not take lapatinib, and there was no evidence of cumulative cardiotoxicity with the drug, nor did previous anthracycline or trastuzumab treatment seem to increase the risk of a reaction in this relatively small group of patients. Despite these results, which suggested a reassuringly low level of cardiotoxicity, the authors considered that cardiac monitoring every 3 months during lapatinib treatment should still be recommended until more data were available.

1. Perez EA, *et al.* Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc* 2008; **83**: 679–86.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lapatinib 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 27/09/11)

Interactions

Lapatinib tosilate undergoes extensive metabolism by cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, can increase exposure to lapatinib. Conversely, CYP3A4 inducers, such as carbamazepine, can reduce exposure to lapatinib. Use of lapatinib with strong inhibitors or inducers of CYP3A4 should be avoided; if they are to be given together, dose adjustments may be required (see Uses and Administration, above). Grapefruit juice may also increase plasma concentrations of lapatinib and should be avoided. *In vitro* studies indicate that lapatinib itself inhibits CYP3A4 and CYP2C8; it should be used cautiously with substrates of these isoenzymes that have a narrow therapeutic index.

Lapatinib is a substrate of P-glycoprotein and P-glycoprotein inhibitors can increase plasma concentrations of lapatinib. Lapatinib itself also inhibits human P-glycoprotein and may in turn increase plasma concentrations of drugs that are substrates of P-glycoprotein.

References.

1. Smith DA, *et al.* Effects of ketoconazole and carbamazepine on lapatinib pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2009; **67**: 421–6.

Pharmacokinetics

Absorption after an oral dose of lapatinib tosilate is variable and incomplete. Peak plasma concentrations occur after about 4 hours. Systemic exposure to lapatinib is increased when it is given with food. It is highly protein bound. Lapatinib undergoes extensive metabolism, mainly by cytochrome P450 isoenzymes CYP3A4 and CYP3A5; CYP2C19 and CYP2C8 account for some minor metabolism. The terminal half-life after a single dose has been reported to be about 14 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours. About 27% and 14% of an oral dose is recovered in the faeces, as parent

lapatinib and metabolites, respectively; renal excretion is negligible.

References.
1. Koch KM, *et al.* Effects of food on the relative bioavailability of lapatinib in cancer patients. *J Clin Oncol* 2009; 27: 1191–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Tykerb; *Austria*: Tyverb; *Belg.*: Tyverb; *Braz.*: Tykerb; *Canad.*: Tykerb; *Chile*: Tykerb; *Cz.*: Tyverb; *Denm.*: Tyverb; *Fr.*: Tyverb; *Ger.*: Tyverb; *Gr.*: Tyverb; *Hong Kong*: Tykerb; *Hung.*: Tyverb; *Indon.*: Tykerb; *Irl.*: Tyverb; *Israel*: Tykerb; *Ital.*: Tyverb; *Jpn*: Tykerb; *Malaysia*: Tykerb; *Mex.*: Tykerb; *Neth.*: Tyverb; *Norw.*: Tyverb; *NZ*: Tykerb; *Philipp.*: Tykerb; *Pol.*: Tyverb; *Port.*: Tyverb; *Rus.*: Tyverb (Тайверб); *Singapore*: Tykerb; *Spain*: Tyverb; *Swed.*: Tyverb; *Switz.*: Tyverb; *Thai.*: Tykerb; *Turk.*: Tykerb; *UK*: Tyverb; *Ukr.*: Tyverb (Тайверб); *USA*: Tykerb.

Laromustine *(USAN, rINN)*

Laromustina; Laromustinum; 101-M; VNP-40101M; Ларомустин.

2′-(2-Chloroethyl)-*N*-methyl-1′,2′-bis(methylsulfonyl)carbamohydrazide.

$C_6H_{14}ClN_3O_5S_2$=307.8

CAS — 173424-77-6.

UNII — 14J2G0U3NQ.

NOTE. The name Cloretazine has been used as a trade mark for laromustine; it should not be confused with chlorethazine, which is a synonym for chlormethine (p. 765.1).

Profile

Laromustine is an alkylating agent that is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndromes, and brain cancer.

References.
1. Pigneux A. Laromustine, a sulfonyl hydrolyzing alkylating prodrug for cancer therapy. *IDrugs* 2009; 12: 39–53.
2. Giles F, *et al.* Phase 3 randomized, placebo-controlled, double-blind study of high-dose continuous infusion cytarabine alone or with laromustine (VNP40101M) in patients with acute myeloid leukemia in first relapse. *Blood* 2009; 114: 4027–33.
3. Schiller GJ, *et al.* Single-agent laromustine, a novel alkylating agent, has significant activity in older patients with previously untreated poor-risk acute myeloid leukemia. *J Clin Oncol* 2010; 28: 815–21.
4. Vey N, Giles F. Laromustine (cloretazine). *Expert Opin Pharmacother* 2010; 11: 657–67.

Lenalidomide *(BAN, USAN, rINN)*

CC-5013; CDC-501; CDC-5013; ENMD-0997; IMiD-3; Lenalidomid; Lenalidomida; Lénalidomide; Lenalidomidum; Леналидомид.

3-(4-Amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione.

$C_{13}H_{13}N_3O_3$=259.3

CAS — 191732-72-6.

ATC — L04AX04.

ATC Vet — QL04AX04.

UNII — F0P408N6V4.

NOTE. IMiD-3 has also been used as a synonym for pomalidomide (p. 847.3).

Uses and Administration

Lenalidomide is an analogue of thalidomide (p. 867.3) that has immunomodulatory and antiangiogenic properties. It is used for the treatment of transfusion-dependent anaemia due to myelodysplastic syndromes (p. 694.3) associated with certain abnormalities of chromosome 5 (deletion 5q abnormalities), and is given with dexamethasone for multiple myeloma (p. 699.2) in patients who have received at least one prior therapy. Lenalidomide is also used for relapsed or refractory mantle cell lymphoma (p. 698.2).

Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

For transfusion-dependent anaemia due to myelodysplastic syndromes the recommended initial oral dose is 10 mg daily; UK licensed product information recommends that this is given for 21 days of a 28-day cycle, whereas in the USA it is given continuously.

For multiple myeloma or mantle cell lymphoma the recommended initial oral dose of lenalidomide is 25 mg daily, given for 21 days of a 28-day cycle. In multiple myeloma it is given with oral dexamethasone at a dose of 40 mg daily on days 1 to 4, days 9 to 12, and days 17 to 20 of each 28-day cycle, for the first 4 cycles, and then 40 mg daily on days 1 to 4 of each 28-day cycle thereafter.

Lenalidomide is associated with significant neutropenia and thrombocytopenia, and dosage is adjusted according to haematological toxicity. Doses are also adjusted for some other severe toxicities and for renal impairment (see Administration in Renal Impairment, below).

References.
1. Anderson KC. Lenalidomide and thalidomide: mechanisms of action—similarities and differences. *Semin Hematol* 2005; 42 (suppl 4): S3–S8.
2. Zeldis JB, *et al.* Lenalidomide in multiple myeloma: current role and future directions. *Expert Opin Pharmacother* 2010; 11: 829–42.
3. Komrokji RS, List AF. Lenalidomide for treatment of myelodysplastic syndromes: current status and future directions. *Hematol Oncol Clin North Am* 2010; 24: 377–88.
4. Scott LJ, Lyseng-Williamson KA. Lenalidomide: a review of its use in the treatment of relapsed or refractory multiple myeloma. *Drugs* 2011; 71: 625–49.
5. Komrokji RS, List AF. Lenalidomide for treatment of myelodysplastic syndromes. *Curr Pharm Des* 2012; 18: 3198–203.
6. Syed YY, Scott LJ. Lenalidomide: a review of its use in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndrome associated with 5q chromosome deletion. *Drugs* 2013; 73: 1183–96.

Administration in renal impairment. Lenalidomide is eliminated mainly via the kidneys as unchanged drug. Clearance decreases as renal function decreases, prolonging the half-life and increasing exposure to the drug. A study recommended that dose adjustments be made for patients with creatinine clearance (CC) less than 50 mL/minute; a 40% reduction to 60% of the starting dose was recommended for these patients. For those with CC less than 30 mL/minute, the reduced dose should be given at extended dosing intervals. About 30% of circulating lenalidomide was removed by a 4-hour session of haemodialysis.[1]

Licensed product information also recommends that doses are adjusted according to the degree of renal impairment; moderate impairment is defined as CC from 30 to less than 50 mL/minute in UK product information or from 30 to less than 60 mL/minute in US literature, severe as CC less than 30 mL/minute, and end-stage renal disease as CC less than 30 mL/minute and requiring dialysis. In patients with **multiple myeloma** or **mantle cell lymphoma**, initial oral doses are adjusted as follows:

- moderate renal impairment: 10 mg once daily. In multiple myeloma this dose may be increased to 15 mg once daily after 2 cycles if the patient is not responding to treatment, but is tolerating lenalidomide
- severe renal impairment: 7.5 mg once daily or 15 mg every other day. In multiple myeloma this dose may be increased to 10 mg daily if tolerated
- end-stage renal disease: 5 mg once daily; on dialysis days the dose should be given after haemodialysis

In **myelodysplastic syndromes**, initial oral doses are adjusted as follows:

- moderate impairment: 5 mg once daily
- severe impairment and end-stage renal disease: 2.5 mg once daily; on dialysis days the dose should be given after haemodialysis

1. Chen N, *et al.* Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J Clin Pharmacol* 2007; 47: 1466–75.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Because of potential teratogenicity lenalidomide use is restricted in women of child-bearing potential and similar precautions to thalidomide are required, see p. 869.2.

Lenalidomide is associated with significant neutropenia and thrombocytopenia. Anaemia is also common and other haematological toxicities can occur. Dose reduction or delaying or stopping therapy may be needed; supportive therapy such as growth factors may be necessary. Full blood counts should be monitored at baseline, weekly for the first 8 weeks of therapy, and monthly thereafter. In multiple myeloma patients given lenalidomide with dexamethasone, US product information recommends monitoring full blood counts every 2 weeks for the first 12 weeks, and then monthly thereafter. There is also an increased risk of thrombotic events with lenalidomide, particularly deep-vein thrombosis and pulmonary embolism in multiple myeloma patients; prophylactic therapy may be considered. Haemorrhagic disorders have also occurred. Cardiac disorders including hypotension or hypertension, arrhythmias, myocardial infarction, and heart failure have also been reported.

Renal failure has been reported during lenalidomide treatment. Caution is advised in patients with renal impairment as lenalidomide is excreted via the kidneys; dose adjustments may be required, see above. Hepatotoxicity has also been reported; liver function should be monitored.

Peripheral neuropathy, insomnia, headache, hypoaesthesia, dizziness, and changes to mental status such as depression, hallucinations, mood swings, dysgeusia, and tremor have occurred.

Endocrine disorders that may occur include hirsutism and hypothyroidism; thyroid function should be monitored. Erectile dysfunction has occurred.

Tumour flare reactions and tumour lysis syndrome (p. 730.2) may be seen, and those with a high tumour burden should be monitored closely and appropriate precautions taken, see p. 732.2. An increased rate of second primary malignancies has been noted in some multiple myeloma patients including those taking lenalidomide plus dexamethasone (mainly skin cancers and solid tumours, those taking lenalidomide plus melphalan (acute myeloid leukaemia, myelodysplastic syndromes, and solid tumours, or those taking lenalidomide after high-dose melphalan and stem cell transplantation (B-cell malignancies including Hodgkin's disease).

Lenalidomide has been associated with hypersensitivity reactions including angioedema and severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. If these are suspected, or if a severe, exfoliative, or bullous rash develops, lenalidomide treatment should be permanently stopped. For other forms of skin reaction, lenalidomide should be withheld or stopped depending on the severity. Cross sensitivity may occur in patients with previous hypersensitivity to thalidomide, and such patients should be monitored closely; patients who have previously had a severe skin reaction with thalidomide should not be treated with lenalidomide.

Other adverse effects include gastrointestinal disturbances, pruritus, fatigue, dyspnoea, respiratory distress cough, interstitial pneumonitis, skin hyperpigmentation dry skin, hyperhidrosis, cerebrovascular accident, pancreatitis, infections such as pneumonia and herpes, alopecia peripheral oedema, pyrexia, electrolyte disturbances, and vertigo. Eye disorders include blurred vision, irritation cataracts, and loss of vision. Musculoskeletal effects include muscle cramps, myopathy, myalgia, arthralgia, and musculoskeletal pain.

Elderly patients may be more susceptible to adverse effects.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lenalidomide 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 28/09/11)

Tumour flare. Tumour flare characterised by painful lymphadenopathy, and sometimes accompanied by musculoskeletal pain and fever, has been reported in patients receiving lenalidomide for relapsed or refractory chronic lymphocytic leukaemia (CLL)[1-3] or for refractory Hodgkin's disease.[4] A lower incidence was noted in CLL patients given a low-dose continuous oral regimen (10 mg once daily for 28 days, increased as tolerated by 5 mg every 28 days to a maximum of 25 mg daily) compared with those given 25 mg once daily orally for 21 days of a 28-day cycle.[1,2] Although serious consequences have been reported in some cases, including one fatality,[3] most cases were not severe and responded to treatment with corticosteroids or NSAIDs;[1,2,4] a reduction in lenalidomide dose has also allowed continued treatment.[4] Lenalidomide-induced B-cell activation has been suggested as contributing to the reaction.[3]

1. Chanan-Khan A, *et al.* Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. *J Clin Oncol* 2006; 24: 5343–9.
2. Ferrajoli A, *et al.* Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. *Blood* 2008; 111: 5291–7.
3. Andritsos LA, *et al.* Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia. *J Clin Oncol* 2008; 26: 2519–25.
4. Corazzelli G, *et al.* Tumor flare reactions and response to lenalidomide in patients with refractory classic Hodgkin lymphoma. *Am J Hematol* 2010; 85: 87–90.

Interactions

Lenalidomide may increase peak plasma concentrations of digoxin. Epoetins or other drugs that increase the risk of thrombosis should be used with caution in patients taking lenalidomide.

Pharmacokinetics

Lenalidomide is rapidly absorbed with peak plasma concentrations occurring between about 0.6 and 1.5 hours after an oral dose. Giving lenalidomide with food does not alter the extent of absorption. Binding to plasma proteins is about 30%. About 80% of a dose is eliminated unchanged through the kidneys. The mean half-life is 3 hours in healthy subjects and 3 to 5 hours in patients with multiple myeloma, myelodysplastic syndromes, or mantle cell lymphoma. Clearance decreases proportionally with renal function. Lenalidomide is distributed into the semen in

small amounts, less than 0.01% of the dose, and semen concentrations are undetectable 3 days after stopping treatment (male patients should use barrier methods of contraception, see Adverse Effects and Precautions, under Thalidomide, p. 869.2).

References.
1. Chen N, *et al.* Distribution of lenalidomide into semen of healthy men after multiple oral doses. *J Clin Pharmacol* 2010; **50**: 767–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ladevina; ***Austral.***: Revlimid; ***Austria***: Revlimid; ***Belg.***: Revlimid; ***Canad.***: Revlimid; ***Chile***: Revlimid; ***Cz.***: Revlimid; ***Denm.***: Revlimid; ***Fr.***: Revlimid; ***Ger.***: Revlimid; ***Gr.***: Revlimid; ***Hong Kong***: Revlimid; ***India***: Lenangio; Lenid; Mydolen; ***Irl.***: Revlimid; ***Israel***: Revlimid; ***Ital.***: Revlimid; ***Malaysia***: Revlimid; ***Neth.***: Revlimid; ***Norw.***: Revlimid; ***NZ***: Revlimid; ***Philipp.***: Revlimid; ***Pol.***: Revlimid; ***Port.***: Revlimid; ***Rus.***: Revlimid (Ревлимид); ***Singapore***: Revlimid; ***Spain***: Revlimid; ***Swed.***: Revlimid; ***Switz.***: Revlimid; ***Thai.***: Revlimid; ***UK***: Revlimid; ***USA***: Revlimid.

Lenvatinib *(USAN, rINN)*

ER-203492-00; Lenvatinibum; Ленватиниб.
N-[4-[(6-Carbamoyl-7-methoxyquinolin-4-yl)oxy]-2-chlorophenyl]-*N'*-cyclopropylurea.
$C_{21}H_{19}ClN_4O_4$=426.9
CAS — 417716-92-8.
UNII — EE083865G2.

Lenvatinib Mesilate *(rINNM)*

E-7080; Lenvatinib, Mesilate de; Lenvatinib Mesylate (USAN); Lenvatinibi Mesilas; Mesilato de lenvatinib; Ленватиниба Мезилат.
N-[4-[(6-Carbamoyl-7-methoxyquinolin-4-yl)oxy]-2-chlorophenyl]-*N'*-cyclopropylurea monomethanesulfonate.
$C_{21}H_{19}ClN_4O_4CH_4O_3S$=523.0
CAS — 857890-39-2.
UNII — 3J78384F61.

Profile

Lenvatinib is an oral tyrosine kinase inhibitor that targets the vascular endothelial growth receptor VEGFR2, and several other kinases involved in angiogenesis and tumour proliferation. Lenvatinib is under investigation for the treatment of various solid tumours, including thyroid cancer, melanoma, glioma, and endometrial cancer.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

Lestaurtinib *(USAN, rINN)*

A-154475.0; CEP-701; KT-5555; Lestaurtinibum; SP-924; Лестауртиниб.
(9*S*,10*S*,12*R*)-10-Hydroxy-10-(hydroxymethyl)-9-methyl-2,3,9,10,11,12-hexahydro-1*H*-9,12-epoxydiindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one.
$C_{26}H_{21}N_3O_4$=439.5
CAS — 111358-88-4.
UNII — DO989GC5D1.

Profile

Lestaurtinib is a tyrosine kinase inhibitor directed against the FLT3 receptor, that is under investigation for the treatment of acute myeloid leukaemia.

Letrozole *(BAN, USAN, rINN)* ⊗

CGS-20267; Letrotsoli; Letrozol; Létrozole; Letrozolum; Летрозол.
4,4'-(1*H*-1,2,4-Triazol-1-ylmethylene)dibenzonitrile.
$C_{17}H_{11}N_5$=285.3
CAS — 112809-51-5.
ATC — L02BG04.
ATC Vet — QL02BG04.
UNII — 7LKK855W8I.

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

Ph. Eur. 8: (Letrozole). A white or yellowish, crystalline powder. Practically insoluble in water; sparingly soluble in methyl alcohol; freely soluble in dichloromethane.

USP 36: (Letrozole). A white to yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.

Uses and Administration

Letrozole is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p. 742.2). It is used in the treatment of advanced or locally advanced breast cancer (p. 702.1) in postmenopausal women. It may be given as neoadjuvant (pre-operative) therapy to those with localised hormone-receptor positive disease, to allow subsequent breast-conserving surgery. Letrozole is also used for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer; treatment is generally given for 5 years or until tumour relapse occurs, although optimal duration of therapy is unknown. In postmenopausal women given 5 years of adjuvant tamoxifen for early breast cancer, letrozole may be used as extended adjuvant therapy; treatment should continue for 5 years or until tumour relapse occurs, although optimal duration of therapy is unknown. The usual oral dose is 2.5 mg daily.

References.
1. Nabholtz JM, *et al.* Comparative review of anastrozole, letrozole and exemestane in the management of early breast cancer. *Expert Opin Pharmacother* 2009; **10**: 1435–47.
2. Keating GM. Letrozole: a review of its use in the treatment of postmenopausal women with hormone-responsive early breast cancer. *Drugs* 2009; **69**: 1681–1705.
3. Dellapasqua S, Colleoni M. Letrozole. *Expert Opin Drug Metab Toxicol* 2010; **6**: 251–9.
4. Geisler J. Differences between the non-steroidal aromatase inhibitors anastrozole and letrozole—of clinical importance? *Br J Cancer* 2011; **104**: 1059–66.

Administration in hepatic impairment. Licensed product information in the UK and USA states that no dosage adjustment of letrozole is required for patients with mild to moderate hepatic impairment (Child-Pugh category A and B). While letrozole is contra-indicated in the UK in severe hepatic impairment (Child-Pugh category C), in the USA, it is recommended that the dose of letrozole be reduced by 50% in those patients with cirrhosis and severe hepatic impairment; the recommended oral dose for these patients is 2.5 mg given every other day.

Endometriosis. Aromatase inhibitors have been investigated for the treatment of endometriosis, see under Uses of Anastrozole, p. 742.2.

Infertility. Letrozole has been investigated[1-5] as an adjunct to assisted reproduction technologies in the management of infertility (p. 2253.1). A systematic review and meta-analysis[6] concluded that there was insufficient evidence to judge the benefits of letrozole and other aromatase inhibitors in ovulation induction, although use appeared to be associated with a higher number of mono-ovulatory cycles. A recommended regimen for intra-uterine insemination was letrozole 2.5 mg daily from day 3 to day 7 of the cycle, followed by follicle-stimulating hormone from day 8; this might be an attractive alternative to the use of gonadotrophins because of the reduced risk of ovarian hyperstimulation syndrome and multiple gestation.

Aromatase inhibitors such as anastrozole and letrozole have been used for infertility associated with polycystic ovary syndrome;[7] although there is not enough evidence to recommend them routinely for ovulation induction, they may be considered in women who have not responded to clomifene, or where other treatments are not suitable. Letrozole has also been tried successfully[8] in a male patient with azoospermia.

However, concerns about unlicensed use have been raised by the Canadian manufacturer (*Novartis, Canad.*) because of the potential for maternal and fetal toxicity, and fetal malformations:[9] licensed product information contra-indicates the use of letrozole in premenopausal women, and there have been reports of congenital anomalies in the infants of women treated with letrozole for infertility.

1. Healey S, *et al.* Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. *Fertil Steril* 2003; **80**: 1325–9.
2. Al-Fozan H, *et al.* A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. *Fertil Steril* 2004; **82**: 1561–3.
3. García-Velasco JA, *et al.* The aromatase inhibitor letrozole increases the concentration of intraovarian androgens and improves in vitro fertilization outcome in low responder patients: a pilot study. *Fertil Steril* 2005; **84**: 82–7.
4. Al-Fadhli R, *et al.* A randomized trial of superovulation with two different doses of letrozole. *Fertil Steril* 2006; **85**: 161–4.
5. Pritts EA. Letrozole for ovulation induction and controlled ovarian hyperstimulation. *Curr Opin Obstet Gynecol* 2010; **22**: 289–94.
6. Requena A, *et al.* Reproductive Endocrinology Interest Group of Spanish Society of Fertility. Use of letrozole in assisted reproduction: a systematic review and meta-analysis. *Hum Reprod Update* 2008; **14**: 571–82.
7. Eckmann KR, Kockler DR. Aromatase inhibitors for ovulation and pregnancy in polycystic ovary syndrome. *Ann Pharmacother* 2009; **43**: 1338–46.
8. Patry G, *et al.* Use of the aromatase inhibitor letrozole to treat male infertility. *Fertil Steril* 2009; **92**: 829.e1–829.e2.
9. Novartis, Canada. Health Canada endorsed important safety information: contraindication of Femara (letrozole) in premenopausal women (issued 17th November, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/femara_hpc-cps-eng.pdf (accessed 31/07/08)

Precocious puberty. A pilot study assessing the use of letrozole in the treatment of 9 girls with precocious puberty (p. 2254.1) due to the McCune-Albright syndrome concluded that it could be an effective initial therapy and might offer an alternative for those who fail to respond to tamoxifen. Possible adverse effects included ovarian enlargement and cyst formation, and further studies were considered necessary.[1]

For a report of the effective use of letrozole with bicalutamide in the treatment of familial male precocious puberty (testotoxicosis), see Precocious Puberty, under Bicalutamide, p. 749.2.

1. Feuillan P, *et al.* Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome: a pilot study. *J Clin Endocrinol Metab* 2007; **92**: 2100–6.

Adverse Effects, Treatment, and Precautions

As for Anastrozole, p. 742.3.

Breast feeding. Licensed product information states that it is unknown whether letrozole is distributed into human milk; in the UK its use during breast feeding is contra-indicated while in the USA a decision to use may be made based on clinical judgement.

Effects on blood lipids. For a comparison of the effects of anastrozole, letrozole, and exemestane on blood lipids see under Exemestane, p. 792.3.

Effects on the musculoskeletal system. Postmenopausal women with primary breast cancer were reported to have significant decreases in bone mineral density at the hip and lumbar spine after 24 months of letrozole therapy.[1]

See also Effects on the Musculoskeletal System, under Anastrozole, p. 743.1.

1. Perez EA, *et al.* Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. *J Clin Oncol* 2006; **24**: 3629–35.

Effects on the skin. Toxic epidermal necrolysis, attributed to letrozole, has been reported in a patient with breast cancer who was also receiving dexamethasone and omeprazole.[1] She had been switched from tamoxifen to letrozole a few weeks before the reaction occurred.

1. Chia WK, *et al.* Toxic epidermal necrolysis in patient with breast cancer receiving letrozole. *Lancet Oncol* 2006; **7**: 184–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies letrozole 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 05/09/11)

Interactions

Tamoxifen. In a study[1] of postmenopausal women with breast cancer, the addition of tamoxifen reduced letrozole plasma concentrations by a mean of about 38%, but the effect of letrozole on hormone concentrations was unchanged. The mechanism and possible clinical effect of this interaction are unknown.

1. Dowsett M, *et al.* Impact of tamoxifen on the pharmacokinetics and endocrine effects of the aromatase inhibitor letrozole in postmenopausal women with breast cancer. *Clin Cancer Res* 1999; **5**: 2338–43.

Pharmacokinetics

Letrozole is rapidly and completely absorbed from the gastrointestinal tract. Food decreases the rate but not the extent of absorption. About 60% of letrozole in the circulation is bound to plasma protein, mainly albumin. Letrozole is rapidly and extensively distributed to tissues. *In vitro* data suggest that it is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2A6. Most of an oral dose is slowly metabolised to an inactive carbinol metabolite, which is then excreted as the glucuronide in the urine. Letrozole has a terminal elimination half-life of about 2 days, and steady-state concentrations occur within 2 to 6 weeks.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cendalon; Pecinole; Femara; Kebirzol; Letrofarm; Veuen; ***Austral.***: Femara; Fera; ***Austria***: Femara; ***Belg.***: Femara; ***Braz.***: Femara; ***Canad.***: Femara; ***Chile***: Femara; ***China***: Femara (弗隆); Fu Rui (芙瑞); ***Cz.***: Aletro; Arofek; Attozette; Brenea; Britagal; Britapons; Clarzole; Dracenax; Etruzil; Femara; Femtozette†; Garion; Helzette; Lerana; Lestara; Letmylan; Letride; Letrogen†; Letromedac; Letrovena; Letrozette; Loosyn; Loxelza; Luro; Mamira; Ninivet;

OncoZol; Oralet; Symletrol; Trozara; Trozel; ***Denm.***: Femar; Femara; Letregio; ***Fin.***: Femar; Letrolan; ***Fr.***: Femara; ***Ger.***: Femara; Letro-cell; Letroarom; Letroblock; Letromedac; ***Gr.***: Aramef; Aromed; Femaplex; Femara; Leoncon; Letrafem; Letropen; Letrozin; Levinox; Linol; Mimor; Religan; Stefaplex; Trezor; Viobrest; ***Hong Kong***: Femara; ***Hung.***: Etruzil; Famos; Femara; Letromataz; Letronorm; Lexeroll; Ninivet; Picozone; ***India***: Femara; Fempro; Feofer; Letocor; Letoripe; Letroz; Lets; Letz; Letzol; Momazol; Oncolet; Oreta; Trozet; ***Indon.***: Femara; ***Irl.***: Eirfem; Femara; Letzo; ***Israel***: Femara; Femozol; ***Ital.***: Femara; ***Jpn***: Femara; ***Malaysia***: Femara; ***Mex.***: Femara; Zolstro; ***Neth.***: Etruzil; Femara; Letarist†; Letrazan; Letregio; Letroman; Letromedica; Letronofi; Letroregiozol; Letroveres; Letrozin; Regioletrozol; ***Norw.***: Femar; Femara; ***NZ***: Femara; Letara; Letraccord; ***Philipp.***: Femara; Hentrozole; Letoripe; Lezol; Trozet; ***Pol.***: Apo-Letro; Aromek; Clarzole; Etruzil; Femara; Lametta; Letralan; Letrodotril; Letrofem; Lostar; Mionic; Trozel; ***Port.***: Cetezol; Femara; Lambda; Loosyn; Nucleus†; ***Rus.***: Extraza (Экстраза); Femara (Фемара); Letrose (Летроза); Letrotera (Летротера); ***S.Afr.***: Femara; Femzole; Laradex; ***Singapore***: Femara; ***Spain***: Devazol; Femara; Galdar; Loxifan; ***Swed.***: Femar; ***Switz.***: Femara; ***Thai.***: Femara; Trozet; ***Turk.***: Femara; Letroks; ***UK***: Femara; ***Ukr.***: Femara (Фемара); Letromara (Летромара); ***USA***: Femara; ***Venez.***: Femara.

Pharmacopoeial Preparations
USP 36: Letrozole Tablets.

Lintuzumab *(rINN)*

HuM-195; Lintuzumabum; SGN-33; Линтузумаб.
Immunoglobulin G1, anti-(human CD33 (antigen)) (human-mouse monoclonal HuM195γ1-chain), disulfide with human-mouse monoclonal HuM195κ-chain, dimer.
CAS — 166089-32-3.

Profile

Lintuzumab is a humanised anti-CD33 monoclonal antibody that is under investigation for the treatment of myelodysplastic syndromes and acute myeloid leukaemia.

References.

1. **Feldman EJ, *et al.*** Phase III randomized multicenter study of a humanized anti-CD33 monoclonal antibody, lintuzumab, in combination with chemotherapy, versus chemotherapy alone in patients with refractory or first-relapsed acute myeloid leukemia. *J Clin Oncol* 2005; 23: 4110–16.

Lobaplatin *(rINN)*

D-19466; Lobaplatine; Lobaplatino; Lobaplatinum; Лобаплатин.
cis-[*trans*-1,2-Cyclobutanebis(methylamine)][(*S*)-lactato-O^1,O^2]platinum.
$C_9H_{18}N_2O_3Pt$=397.3
CAS — 135558-11-1.
UNII — OX5XK1JD8C.

Profile

Lobaplatin is a platinum derivative that is used as an antineoplastic in the treatment of breast cancer, small cell lung cancer, and chronic myelogenous leukaemia. The main adverse effect is thrombocytopenia. Lobaplatin is reported to show some cytotoxic effect upon cisplatin-resistant cells.

References.

1. **Welink J, *et al.*** Pharmacokinetics and pharmacodynamics of lobaplatin (D-19466) in patients with advanced solid tumors, including patients with impaired renal or liver function. *Clin Cancer Res* 1999; 5: 2349–58.
2. **McKeage MJ.** Lobaplatin: a new antitumour platinum drug. *Expert Opin Invest Drugs* 2001; 10: 119–28.
3. **Anonymous.** Lobaplatin: D 19466. *Drugs R D* 2003; 4: 369–72.
4. **Zhou B, *et al.*** Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. *J Vasc Interv Radiol* 2010; 21: 333–8.

Lomustine *(BAN, USAN, rINN)*

CCNU; Lomustiini; Lomustin; Lomustina; Lomustinas; Lomustinum; Lomustyna; Lomusztin; NSC-79037; RB-1509; WR-139017; Ломустин.
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea.
$C_9H_{16}ClN_3O_2$=233.7
CAS — 13010-47-4.
ATC — L01AD02.
ATC Vet — QL01AD02.
UNII — 7BRF0Z81KG.

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

Ph. Eur. 8: (Lomustine). A yellow, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Lomustine). A yellow crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone, and in dichloromethane. Store at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Lomustine is a nitrosourea with actions and uses similar to those of carmustine (p. 761.2). It has been used in the treatment of brain tumours (p. 701.2) and resistant or relapsed Hodgkin's disease and other lymphomas (p. 696.1), and also lung cancer (p. 710.2), malignant melanoma (p. 714.3), and various solid tumours.

When given as a single agent, lomustine is licensed for oral use in adults and children as a single dose of 120 to 130 mg/m^2; division of the dose over 3 consecutive days may reduce gastrointestinal effects. A dose of 100 mg/m^2 should be given to patients with compromised bone-marrow function. Doses are also generally reduced when lomustine is given as part of a combination regimen. Providing blood counts have returned to acceptable levels, doses may be repeated every 6 to 8 weeks, and should be adjusted according to the haematological response (see also Bone-marrow Depression, p. 730.3).

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

Adverse Effects, Treatment, and Precautions

As for Carmustine, p. 761.3. Neurological reactions such as confusion and lethargy have been reported.

Handling and disposal. A method for the destruction of lomustine *waste* by reaction with hydrobromic acid in glacial acetic acid has been described.[1] The residue produced by the degradation of lomustine by this method showed no mutagenicity. This method is not suitable for the degradation of carmustine.

1. **Castegnaro M, *et al.*, eds.** Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.

Overdosage. A patient who inadvertently received 200 mg of lomustine for 7 days instead of a single 200-mg dose developed pancytopenia and subsequent multiorgan dysfunction including liver dysfunction, abdominal pain, pulmonary toxicity with tachypnoea and hypoxaemia, and CNS toxicity leading to confusion and disorientation.[1] Although the white cell count recovered other signs of toxicity did not and the patient developed fever and hypotension and died 59 days after the initial dose of lomustine. In another case of accidental overdose, a 30-year old female received a cumulative dose of 28 mg/kg over 7 days.[2] Severe myelosuppression developed soon after the overdose and lasted for 50 days. The patient was treated with granulocyte colony-stimulating factor and antibacterial cover, norethisterone (to prevent menstruation), and acetylcysteine (to protect against organ toxicity). Gastrointestinal necrosis occurred, and liver enzymes remained elevated even after recovery from the overdose, but the patient survived and her tumour regressed without further chemotherapy.

1. **Trent KC, *et al.*** Multiorgan failure associated with lomustine overdose. *Ann Pharmacother* 1995; 29: 384–6.
2. **Abele M, *et al.*** CCNU overdose during PCV chemotherapy for anaplastic astrocytoma. *J Neurol* 1998; 245: 236–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lomustine 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 28/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Cimetidine. For a report of a possible interaction between lomustine and cimetidine, see under Carmustine, p. 762.1.

Theophylline. Leucopenia and thrombocytopenia in a 45-year-old woman were believed to have been secondary to an interaction between theophylline and lomustine.[1]

1. **Zeltzer PM, Feig SA.** Theophylline-induced lomustine toxicity. *Lancet* 1979; ii: 960–1.

Pharmacokinetics

Lomustine is absorbed from the gastrointestinal tract and is rapidly metabolised, with peak plasma concentrations of metabolites occurring within 4 hours of an oral dose. Metabolites have a prolonged plasma half-life reported to range from 16 to 48 hours. Active metabolites readily cross the blood-brain barrier and appear in the CSF in concentrations higher than those in plasma. About half a dose is excreted as metabolites in the urine within 24 hours and about 75% is excreted within 4 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: CeeNU; ***Austral.***: CeeNU; ***Braz.***: Citostal; ***Canad.***: CeeNU; ***Chile***: CeeNU†; ***Cz.***: CeeNU; ***Fr.***: Belustine; ***Ger.***: Cecenu; ***Gr.***: Cecenu; CeeNU; Praxa; ***India***: Lomtin; Lustine; ***Mex.***: CeeNU; ***Neth.***: Belustine; ***NZ***: CeeNU; ***Philipp.***: CeeNU†; ***S.Afr.***: CeeNU†; ***Singapore***: CeeNU; ***Switz.***: CeeNU†; ***UK***: CCNU; ***USA***: CeeNU.

Pharmacopoeial Preparations
BP 2014: Lomustine Capsules;
USP 36: Lomustine Capsules.

Lonidamine *(BAN, rINN)*

AF-1890; Diclondazolic Acid; Lonidamina; Lonidaminum; T-H-070; Лонидамин.
1-(2,4-Dichlorobenzyl)indazole-3-carboxylic acid.
$C_{15}H_{10}Cl_2N_2O_2$=321.2
CAS — 50264-69-2.
ATC — L01XX07.
ATC Vet — QL01XX07.
UNII — U78804BIDR.

Profile

Lonidamine is an antineoplastic that is thought to act by inhibiting mitochondrial function in tumour cells. It has been given orally in the treatment of various solid neoplasms, including those of the lung, breast, prostate, and brain. It has also been used as a radiosensitiser.

Lumiliximab *(USAN, rINN)*

Gomiliximab; IDEC-152; Lumiliximabum; Лумиликсимаб.
Immunoglobulin G1, anti-(human immunoglobulin E receptor type II) (human-*Macaca irus* monoclonal IDEC-152 γ1-chain), disulfide with human-*Macaca irus* monoclonal IDEC-152 κ-chain, dimer.
CAS — 357613-86-6.
UNII — 8Z13529R5A.

Profile

Lumiliximab is a chimeric anti-CD23 monoclonal antibody that is under investigation for the treatment of chronic lymphocytic leukaemia.

References.

1. **Byrd JC, *et al.*** Phase 1 study of lumiliximab with detailed pharmacokinetic and pharmacodynamic measurements in patients with relapsed or refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2007; 13: 4448–55.
2. **Byrd JC, *et al.*** Phase 1/2 study of lumiliximab combined with fludarabine, cyclophosphamide, and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia. *Blood* 2010; 115: 489–95.

Mafosfamide *(rINN)*

Mafosfamid; Mafosfamida; Mafosfamidi; Mafosfamidum; Мафосфамид.
(±)-2-([2-[Bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorin-4-yl]thio)ethanesulphonic acid *P*-*cis* oxide.
$C_9H_{19}Cl_2N_2O_5PS_2$=401.3
CAS — 88859-04-5.
UNII — 5970HH9923.

Profile

Mafosfamide is a derivative of cyclophosphamide (p. 771.1) that has been used to treat bone marrow for transplantation. Intrathecal mafosfamide has been investigated for the treatment of meningeal tumours.

Marimastat *(BAN, USAN, rINN)*

BB-2516; Marimastatum; TA-2516; Маримастат.
(2*S*,3*R*)-3-[(*S*)-[2,2-Dimethyl-1-(methylcarbamoyl)propyl]carbamoyl]-2-hydroxy-5-methylhexanohydroxamic acid.
$C_{15}H_{29}N_3O_5$=331.4
CAS — 154039-60-8.
UNII — D5EQV23TDS.

Profile

Marimastat is an oral inhibitor of matrix metalloproteinases, enzymes which are thought to play a role in the metastasis of cancer cells. It has been investigated in various malignant disorders.

Masitinib *(rINN)*

AB-1010; Masitinibum; Маситиниб.
4-[(4-Methylpiperazin-1-yl)methyl]-*N*-(4-methyl-3-([4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino)phenyl)benzamide.
$C_{28}H_{30}N_6OS$=498.6
CAS — 790299-79-5.
ATC — L01XE22.
ATC Vet — QL01XE22.
UNII — M59NC4E26P.

Profile

Masitinib is a tyrosine kinase inhibitor active against c-kit and platelet-derived growth factor tyrosine kinases, that is under investigation for the treatment of malignancies such as gastrointestinal stromal tumours, pancreatic cancer, and multiple myeloma. It is also being investigated in inflammatory conditions such as asthma, mastocytosis, and rheumatoid arthritis.

Melphalan *(BAN, USAN, rINN)*

CB-3025; Melfalaani; Melfalan; Melfalán; Melphalanum; NSC-8806 (melphalan hydrochloride); PAM; Phenylalanine Mustard; Phenylalanine Nitrogen Mustard; L-Sarcolysine; WR-19813; Мелфалан.
4-Bis(2-chloroethyl)amino-L-phenylalanine.
$C_{13}H_{18}Cl_2N_2O_2$=305.2
CAS — 148-82-3 (melphalan); 3223-07-2 (melphalan hydrochloride).
ATC — L01AA03.
ATC Vet — QL01AA03.
UNII — Q41OR9510P.

NOTE. Merphalan (CB-3007; NSC-14210; sarcolysine) is the racemic form of melphalan; Medphalan (CB-3026; NSC-35051) is the D-isomer of melphalan.

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

Ph. Eur. 8: (Melphalan). A white or almost white, hygroscopic powder. Practically insoluble in water; slightly soluble in methyl alcohol; dissolves in dilute mineral acids. Store in airtight containers. Protect from light.

USP 36: (Melphalan). An off-white to buff powder with a faint odour. Practically insoluble in water, in chloroform, and in ether; slightly soluble in alcohol and in methyl alcohol; soluble in dilute mineral acids. Store in airtight, glass containers. Protect from light.

Stability. A study of the stability of melphalan 40 and 400 micrograms/mL in infusion fluids reported that the time for a 10% loss of drug at 20 degrees in sodium chloride 0.9% injection was 4.5 hours, compared with 2.9 hours in lactated Ringer's injection, which has a considerably lower chloride ion content, and only 1.5 hours in glucose 5% injection.[1] At 25 degrees the corresponding figures were 2.4, 1.5, and 0.6 hours, and at 37 degrees they were 0.6, 0.4, and 0.3 hours. It was concluded that melphalan is sufficiently stable at 20 degrees in sodium chloride injection to permit infusion, but that increased temperature and decreased chloride ion concentration were associated with faster degradation rates.[1] Another study recommended that solutions of melphalan be handled at temperatures above 5 degrees for the minimum time but found that a solution containing 20 micrograms/mL in sodium chloride 0.9% could be stored for at least 6 months at -20 degrees without significant deterioration.[2] A more recent study, while recommending storage at 4 degrees between preparation and use of the infusion, considered that giving it at a room temperature of 20 degrees or below, and use of hypertonic (3%) saline as a diluent, would be sufficient to allow prolonged infusion.[3] The practicalities of such a procedure were not addressed.

1. Tabibi SE, Cradock JC. Stability of melphalan in infusion fluids. *Am J Hosp Pharm* 1984; **41**: 1380–2.
2. Bosanquet AG. Stability of melphalan solutions during preparation and storage. *J Pharm Sci* 1985; **74**: 348–51.
3. Pinguet F, *et al.* Effect of sodium chloride concentration and temperature on melphalan stability during storage and use. *Am J Hosp Pharm* 1994; **51**: 2701–4.

Uses and Administration

Melphalan is an antineoplastic that acts as a bifunctional alkylating agent. It is used mainly in the treatment of multiple myeloma. Melphalan has also been given to patients with carcinoma of the breast and ovary, neuroblastoma, Hodgkin's disease, and in polycythaemia vera, and has been given by intra-arterial regional perfusion for malignant melanoma and soft-tissue sarcomas. See also the cross-references given below. Melphalan is also used in the treatment of amyloidosis, see below.

Melphalan is usually given orally as a single daily dose or in divided doses; it is also given intravenously as the hydrochloride. Doses are calculated in terms of the base; 1.12 mg of melphalan hydrochloride is equivalent to about 1 mg of melphalan. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration; p. 732.3.* Frequent blood counts are essential and dosage should be adjusted according to haematological response. Therapy should be interrupted if the platelet or white cell count fall below acceptable levels (see also Bone-marrow Depression, p. 730.3). It should be given with great caution if the neutrophil count has recently been depressed by chemotherapy or radiotherapy.

Many conventional-dose regimens have been tried for the treatment of multiple myeloma and there is still uncertainty as to the best schedule. Melphalan is usually combined with corticosteroids. Licensed **oral** dosage regimens that have been used include:

- 150 micrograms/kg daily in divided doses for 4 days, repeated at 6-week intervals
- 150 micrograms/kg daily for 7 days followed by a rest period of at least 14 days, or as long as 5 to 6 weeks; a maintenance dose of 50 micrograms/kg daily or less is given when the white blood cells and platelet counts increase with further adjustments according to the blood count
- 250 micrograms/kg daily for 4 days *or* 200 micrograms/kg daily for 5 days, for a total dose per course of 1 mg/kg; the course is repeated at intervals of 4 to 6 weeks according to the blood count
- 6 mg daily for 2 to 3 weeks adjusted according to the blood count; treatment is then stopped for up to 4 weeks until the white blood cells and platelet counts increase, after which a maintenance dose of 2 mg daily may be started
- 10 mg daily for 7 to 10 days followed by a maintenance dose of 2 mg daily when the white blood cells and platelet counts exceed 4000 cells/mm^3 and 100 000 cells/mm^3, respectively; the dose should then be further adjusted to 1 to 3 mg daily, according to blood counts

For optimum effect, therapy is usually adjusted to produce a moderate leucopenia, with white cell counts in the range 3000 to 3500 cells/mm^3.

In the treatment of breast cancer, licensed doses of 150 micrograms/kg daily or 6 mg/m^2 daily for 5 days, repeated every 6 weeks have been used. Doses of 200 micrograms/kg daily for 5 days every 4 to 8 weeks may be given to patients with ovarian carcinoma.

In patients with polycythaemia vera, doses of 6 to 10 mg daily for 5 to 7 days, and then 2 to 4 mg daily, have been used for remission induction; a dose of 2 to 6 mg weekly has been used for maintenance.

Melphalan is also given **intravenously**; for ovarian adenocarcinoma a single dose of 1 mg/kg, repeated at 4-week intervals if the platelet and neutrophil counts permit, may be given as monotherapy. It can be infused in sodium chloride 0.9% or injected slowly into the tubing of a fast-running drip; when given by infusion the time from reconstitution of the solution to completion of infusion should not exceed 1.5 hours and prolonged infusions should be carried out with several batches of solution, each freshly prepared. In multiple myeloma, the licensed dose for use as a single agent is an intravenous dose of 400 micrograms/kg or 16 mg/m^2, infused over 15 to 20 minutes; the first 4 doses may be given at 2-week intervals, but further doses should be given at 4-week intervals depending on toxicity.

High-dose melphalan has been given intravenously in some malignancies: doses of 100 to 240 mg/m^2 have been licensed in neuroblastoma, and 100 to 200 mg/m^2 in multiple myeloma, generally followed by autologous stem cell rescue, which becomes essential where doses exceed 140 mg/m^2. High doses should be given through a central venous catheter.

Melphalan may be given by **regional arterial perfusion** in the management of melanoma and soft-tissue sarcomas. A typical dosage range for hyperthermic regional perfusion for upper extremity perfusions is 0.6 to 1 mg/kg, whereas for lower extremity perfusions doses of 0.8 to 1.5 mg/kg (in melanoma) or 1 to 1.4 mg/kg (in sarcoma) are typically used.

The dose of melphalan should be reduced in patients with **renal impairment** (see below).

Administration in the elderly. Higher toxicity, mainly myelosuppression, has been reported when melphalan is used in patients older than 70 years, but a review concluded that dose modification is not recommended on the basis of age alone.[1] Dose reduction of melphalan is recommended for declining renal function (see Administration in Renal Impairment, below).

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25**: 1832–43.

Administration in renal impairment. The initial dose of intravenous melphalan should be reduced by about 50% in patients with renal impairment and dosage reduction should be considered when giving it orally. For high-dose intravenous melphalan regimens (melphalan 100 to 140 mg/m^2) given **without** stem cell rescue to patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min), UK licensed product information advises that the dose is also usually reduced by 50%.

High-dose intravenous melphalan (up to 200 mg/m^2) **with** stem cell rescue has been used successfully without dose reductions in patients with severe renal impairment (creatinine clearance less than 20 mL/min), including those on dialysis.[1]

1. Bird JM, *et al.* The clinical outcome and toxicity of high-dose chemotherapy and autologous stem cell transplantation in patients with myeloma or amyloid and severe renal impairment: a British Society of Blood and Marrow Transplantation study. *Br J Haematol* 2006; **134**: 385–90.

Amyloidosis. Amyloidosis refers to a group of conditions characterised by accumulation of a waxy proteinaceous infiltrate within body tissues.[1-3] They include:

- primary or AL amyloidosis, in which the amyloid is derived from immunoglobulin light chains
- ATTR amyloidosis (a familial form), in which amyloid is derived from transthyretin
- AA amyloidosis, which is most often secondary to chronic inflammation, such as that associated with rheumatoid arthritis, tuberculosis, or familial Mediterranean fever (p. 605.1)

Symptoms vary, depending on where the amyloid is deposited. The organs most commonly affected are the heart and kidneys. Renal amyloidosis can present as proteinuria, leading to nephrotic syndrome and renal failure. While renal disease is common in the AA and AL forms, it is less prevalent in ATTR amyloidosis, which commonly presents with neuropathy. Cardiac involvement, rare in AA amyloidosis, is variable in the ATTR form, and common in the AL form; it manifests as restrictive cardiomyopathy, leading to congestive heart failure. Painful peripheral sensory neuropathy and carpal tunnel syndrome also occur frequently. Amyloid deposition in the gastrointestinal tract can lead to malabsorption. Hepatomegaly is common. Macroglossia, due to deposition of amyloid in the tongue, occurs only in the AL form.[1,2]

Management depends to some extent upon the type of amyloidosis involved, and the site, but no drug or combination of drugs is unequivocally effective.

Liver transplantation is the definitive therapy for patients with ATTR amyloidosis.[1,4] Tafamidis meglumine is used for the treatment of ATTR amyloidosis in adult patients with symptomatic polyneuropathy to delay peripheral neurological impairment; it is used before liver transplantation.

Treatment for AA amyloidosis secondary to chronic inflammation is aimed at the underlying disease; immunosuppressants such as chlorambucil, cyclophosphamide, and methotrexate have been used, as well as inhibitors of tumour necrosis factor and interleukin-1 receptor antagonists.[5] Colchicine is effective in the treatment of AA amyloidosis complicating familial Mediterranean fever, but is not considered to be of benefit in other forms of amyloidosis.[1,6]

Melphalan plus prednisone or prednisolone has been shown to increase median survival in primary amyloidosis patients.[7] It is considered the treatment of choice in AL amyloidosis for patients in whom more intensive chemotherapy is not appropriate; evidence of benefit from the addition of a corticosteroid has not been evaluated and in some patients, it may be reasonable not to include a corticosteroid.[6] Melphalan, prednisone, and colchicine was found to be more effective than colchicine alone in the treatment of AL amyloidosis,[8] but a later study[9] found no benefit in adding colchicine to the standard therapy.

Addition of multiple alkylating agents such as vincristine, carmustine, and cyclophosphamide to the standard therapy[10] did not improve survival or response. Evidence to support the use of alkylating-based combination chemotherapy for primary amyloidosis is lacking.[6] Alternatively, cycles of vincristine, doxorubicin, and dexamethasone (VAD) may be effective, but patients with cardiac amyloidosis may be at increased risk of anthracycline toxicity.[11] In the UK, VAD is considered as first-line therapy in patients under the age of 70 years who do not have cardiac failure, autonomic neuropathy, or peripheral neuropathy.[6]

High-dose intravenous melphalan with autologous haematopoietic stem cell transplantation (HSCT) has been used;[12] it may result in complete remission of primary amyloidosis.[13-15] Some[1] consider it the treatment of choice, but while it may improve renal disease,[13] the therapy remains very toxic; patient selection on the basis of limited organ disease and no significant cardiac involvement may reduce morbidity and mortality.[6,14] The outcome of treatment with high-dose intravenous melphalan with

autologous HSCT was not superior to standard-dose oral melphalan plus oral dexamethasone in patients with newly diagnosed AL amyloidosis.[16]

High-dose dexamethasone or thalidomide may be considered in patients in whom other regimens may not be feasible due to expected toxicity or in those refractory to chemotherapy;[6] good results have been reported in patients with AL amyloidosis given a regimen combining cyclophosphamide with dexamethasone and thalidomide.[17] Local application or oral dosage of dimethyl sulfoxide, and 4'-iodo-4'-deoxydoxorubicin has been investigated.[1,11]

Symptomatic management is also important. Care must be taken to avoid digitalis toxicity when cardiac amyloid is present, as well as to avoid salt and water depletion through injudicious use of diuretics. Calcium-channel blockers and beta blockers should be avoided.[1] Renal transplantation may be considered in end-stage renal failure due to amyloidosis, but unless amyloid production has been stopped disease is likely to recur in the new kidney. Cardiac transplantation, and subsequent chemotherapy with epirubicin, carmustine, and cyclophosphamide to suppress the underlying disease and control amyloid deposition in the graft has also been described.[18]

Because amyloid deposits contain a plasma glycoprotein serum amyloid P component (SAP) that contributes to the stability of the deposits, and thus contributes to the pathogenesis of amyloidosis, future therapeutic approaches include the targeting of SAP to deplete it from the tissues and clear it from the plasma. Ro-63-8695 (CPHPC) is being investigated.[3,19] Eprodisate disodium is under investigation for AA amyloidosis.[20]

1. Khan MF, Falk RH. Amyloidosis. *Postgrad Med J* 2001; 77: 686–93.
2. Falk RH, Skinner M. The systemic amyloidoses: an overview. *Adv Intern Med* 2000; 45: 107–37.
3. Gillmore JD, Hawkins PN. Drug Insight: emerging therapies for amyloidosis. *Nat Clin Pract Nephrol* 2006; 2: 263–70.
4. Suhr OB, *et al.* Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transpl* 2000; 6: 263–76.
5. Lachmann HJ, *et al.* Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; 356: 2361–71.
6. British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. *Br J Haematol* 2004; 125: 681–700. Also available at: http://www.bcshguidelines.com/pdf/ALamyloidosis_210604.pdf (accessed 07/03/06)
7. Gertz MA, Rajkumar SV. Primary systemic amyloidosis. *Curr Treat Options Oncol* 2002; 3: 261–71.
8. Skinner M, *et al.* Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996; 100: 290–8.
9. Kyle RA, *et al.* A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med* 1997; 336: 1202–7.
10. Gertz MA, *et al.* Prospective randomized trial of melphalan and prednisone versus vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of primary systemic amyloidosis. *J Clin Oncol* 1999; 17: 262–7.
11. Sezer O, *et al.* New therapeutic approaches in primary systemic AL amyloidosis. *Ann Hematol* 2000; 79: 1–6.
12. Sanchorawala V, Seldin DC. An overview of high-dose melphalan and stem cell transplantation in the treatment of AL amyloidosis. *Amyloid* 2007; 14: 261–9.
13. Dember LM, *et al.* Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis-associated renal disease. *Ann Intern Med* 2001; 134: 746–53.
14. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood* 2002; 99: 4276–82.
15. Skinner M, *et al.* High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med* 2004; 140: 85–93.
16. Jaccard A, *et al.* Myélome Autogreffe (MAG) and Intergroupe Francophone du Myélome (IFM) Intergroup. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007; 357: 1083–93.
17. Wechalekar AD, *et al.* Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; 109: 457–64.
18. Hall R, *et al.* Cardiac transplantation for AL amyloidosis. *BMJ* 1994; 309: 1135–7.
19. Pepys MB, *et al.* Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* 2002; 417: 254–9.
20. Dember LM, *et al.* Eprodisate for AA Amyloidosis Trial Group. Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med* 2007; 356: 2349–60.

Bone disorders, non-malignant. Fibrogenesis imperfecta ossium is a rare progressive bone disease in which disorders of bone collagen and mineralisation, and subsequent abnormal bone structure, result in bone pain and fractures. A patient responded to melphalan 10 mg and prednisolone 20 or 30 mg given daily, in 7-day courses every 2 months.[1,2] Another showed some improvement with intermittent 5-day courses of melphalan 10 mg daily and prednisolone 40 mg daily.[3] However, melphalan alone was reported to be ineffective in 2 other patients; both had bone-marrow depression.[3,4]

1. Stamp TCB, *et al.* Fibrogenesis imperfecta ossium: remission with melphalan. *Lancet* 1985; i: 582–3.
2. Ralphs JR, *et al.* Ultrastructural features of the osteoid of patients with fibrogenesis imperfecta ossium. *Bone* 1989; 10: 243–9.
3. Carr AJ, *et al.* Fibrogenesis imperfecta ossium. *J Bone Joint Surg Br* 1995; 77: 820–9.
4. Lafage-Proust M-H, *et al.* Fibrogenesis imperfecta ossium: ineffectiveness of melphalan. *Calcif Tissue Int* 1996; 59: 240–4.

Malignant neoplasms. The important role played by melphalan in the management of multiple myeloma is discussed on p. 699.2. Melphalan is also used as part of salvage regimens for relapsed Hodgkin's disease (see p. 696.1), in ovarian cancer (p. 711.2), and for local perfusion of melanoma (p. 714.3).

Organ and tissue transplantation. Melphalan is used as part of non-myeloablative or reduced intensity conditioning regimens before haematopoietic stem cell transplantation, see p. 1937.1.

Adverse Effects and Treatment

For general discussions see Antineoplastics, p. 726.1 and p. 730.2.

The onset of neutropenia and thrombocytopenia is variable; the nadir of bone-marrow depression usually occurs at 2 to 3 weeks after starting treatment with melphalan, with recovery after 4 to 5 weeks.

Skin rashes and hypersensitivity reactions, including anaphylaxis, may occur. Cardiac arrest has been reported in association with such effects. Gastrointestinal disturbances may sometimes occur, particularly at high doses where diarrhoea, vomiting, and stomatitis may become dose-limiting. Haemolytic anaemia, vasculitis, pulmonary fibrosis, and hepatic disorders including hepatitis and jaundice have been reported. Suppression of ovarian function is common in premenopausal women; temporary or permanent sterility may occur in male patients. Extravasation of melphalan injection can cause skin ulceration and necrosis. As with other alkylating agents, melphalan also has carcinogenic, mutagenic, and teratogenic potential.

Mucositis. Amifostine has been shown to reduce the frequency and severity of melphalan-induced oral mucositis.[1]

1. Spencer A, *et al.* Prospective randomised trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. *Bone Marrow Transplant* 2005; 35: 971–7.

Overdosage. A 12-month old child given melphalan 140 mg intravenously (a tenfold overdose) developed pronounced lymphopenia within 24 hours but had no other significant adverse effects until the seventh day, when neutropenia, thrombocytopenia, oral ulceration, and diarrhoea developed.[1] Bone marrow recovered within 40 days. Treatment was by vigorous hyperalimentation and close surveillance during this period and the patient subsequently remained well 9 months afterwards, without complications. Cases of intravenous melphalan overdose have also been reported in adults,[2] resulting in bone-marrow depression, haemorrhagic diarrhoea, and electrolyte disturbances. Bone-marrow depression has also been reported after cumulative oral doses of 360 mg over 3 weeks,[3] and 560 mg over 2 weeks.[4] Filgrastim was used in one of these cases to stimulate bone-marrow recovery.[4]

1. Coates TD. Survival from melphalan overdose. *Lancet* 1984; ii: 1048.
2. Jost LM. Überdosierung von Melphalan (Alkeran): Symptome und Behandlung: eine Übersicht. *Onkologie* 1990; 13: 96–101.
3. Grimes DJ, *et al.* Complete remission of paraproteinaemia and neuropathy following iatrogenic oral melphalan overdose. *Br J Haematol* 1993; 83: 675–7.
4. Jirillo A, *et al.* Accidental overdose of melphalan per os in a 69-year-old woman treated for advanced endometrial carcinoma. *Tumori* 1998; 84: 611.

Precautions

For general discussions see Antineoplastics, p. 732.2.

Care is required in patients with impaired renal function.

Handling and disposal. *Urine and faeces* produced for up to 48 hours and 7 days respectively after an oral dose of melphalan should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies melphalan 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 28/09/11)

Interactions

Use of nalidixic acid with high-dose intravenous melphalan in children has resulted in fatal haemorrhagic enterocolitis.

Ciclosporin. For reference to enhanced toxicity when melphalan was given with ciclosporin, see under Ciclosporin, p. 1957.2.

Food. The bioavailability of oral melphalan is significantly reduced, by up to 45%, by food. Some recommend that melphalan should not be taken with food, and that if dosage is switched from after to before food patients should be monitored for increased toxicity.[1]

1. Nathan C, Betmouni R. Melphalan: avoid with food. *Pharm J* 1996; 257: 264.

Interferons. The fever induced by interferon alfa resulted in a reduction in the area under the plasma concentration-time curve for melphalan in a study of 10 patients, although the peak plasma concentration and time to peak concentration were not affected.[1] The effect was thought to represent increased chemical reactivity of melphalan at the elevated temperature.

1. Ehrsson H, *et al.* Oral melphalan pharmacokinetics: influence of interferon-induced fever. *Clin Pharmacol Ther* 1990; 47: 86–90.

Pharmacokinetics

Absorption of melphalan from the gastrointestinal tract is variable; the mean bioavailability is reported to be 56% but it may range from 25 to 89%. Absorption is reduced by the presence of food (see above). On absorption it is rapidly distributed throughout body water with a volume of distribution of about 0.5 litres/kg, and has been reported to be inactivated mainly by spontaneous hydrolysis. About 60 to 90% is bound to plasma proteins, mainly albumin. The terminal plasma half-life of melphalan has been reported to be about 30 to 150 minutes. Melphalan is excreted in the urine, about 10% as unchanged drug.

References.
1. Nath CE, *et al.* Melphalan pharmacokinetics in children with malignant disease: influence of body weight, renal function, carboplatin therapy and total body irradiation. *Br J Clin Pharmacol* 2005; 59: 314–24.
2. Nath CE, *et al.* Population pharmacokinetics of melphalan in paediatric blood or marrow transplant recipients. *Br J Clin Pharmacol* 2007; 64: 151–64.
3. Padussis JC, *et al.* Pharmacokinetics and drug resistance of melphalan in regional chemotherapy: ILP versus ILI. *Int J Hyperthermia* 2008; 24: 239–49.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alkerana; Eriolan; Melfoma: *Austral.*: Alkeran; *Austria*: Alkeran; *Belg.*: Alkeran; *Braz.*: Alkeran; *Canad.*: Alkeran; *Chile*: Alkeran; *China*: Alkeran (爱克兰); *Cz.*: Alkeran; *Denm.*: Alkeran; *Fin.*: Alkeran; *Fr.*: Alkeran; *Ger.*: Alkeran; *Gr.*: Alkeran; *Hong Kong*: Alkeran; *India*: Alkacel; Alkeran; Alphalan; *Irl.*: Alkeran; *Israel*: Alkeran; *Ital.*: Alkeran; *Malaysia*: Alkeran; *Mex.*: Alkeran; *Neth.*: Alkeran; *Norw.*: Alkeran; *NZ*: Alkeran; *Philipp.*: Alkeran; *Pol.*: Alkeran; *Port.*: Alkeran; *Rus.*: Alkeran (Алкеран); Sarcolysin (Сарколизин); *S.Afr.*: Alkeran; *Singapore*: Alkeran; *Swed.*: Alkeran; *Switz.*: Alkeran; *Thai.*: Alkeran; *Turk.*: Alkeran; *UK*: Alkeran; *USA*: Alkeran.

Pharmacopoeial Preparations

BP 2014: Melphalan Injection; Melphalan Tablets;
USP 36: Melphalan Tablets.

Mercaptopurine *(BAN, rINN)*

6MP; Mercaptopurin; Mercaptopurina; Mercaptopurinum; Mercaptopurinum Monohydricum; Merkaptopurilni; Merkaptopürin; Merkaptopurin; Merkaptopurin monohydrát; Merkaptopurinas; Merkaptopuryna; NSC-755; Purinethiol; WR-2785; Меркаптопурин.

6-Mercaptopurine monohydrate; Purine-6-thiol monohydrate; 1,7-Dihydro-6*H*-purine-6-thione monohydrate.

$C_5H_4N_4S,H_2O$=170.2

CAS — 50-44-2 (anhydrous mercaptopurine); 6112-76-1 (mercaptopurine monohydrate).

ATC — L01BB02.

ATC Vet — QL01BB02.

UNII — E7WED276I5 (mercaptopurine); PKK6MUZ20G (anhydrous mercaptopurine).

NOTE. In the UK, the CSM noted in October 2004 that confusion had arisen between mercaptopurine and mercaptamine (formerly cysteamine, p. 2554.3) after the switch from prescribing by British Approved Name to prescribing by International Nonproprietary Name. Particular care should be taken to distinguish the two, since they are available in oral dosage forms of similar strength.

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

Ph. Eur. 8: (Mercaptopurine). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 36: (Mercaptopurine). A yellow, odourless or practically odourless, crystalline powder. Insoluble in water, in acetone, and in ether; soluble in hot alcohol and in dilute alkali solutions; slightly soluble in 2*N* sulfuric acid. Store in airtight containers. Protect from light.

Uses and Administration

Mercaptopurine is an antineoplastic that acts as an antimetabolite. It is an analogue of the natural purines hypoxanthine and adenine. After the intracellular conversion of mercaptopurine to active tioguanine nucleotides, including thioinosinic acid, it appears to have a variety of actions including interfering with nucleic acid synthesis. It also has immunosuppressant properties. Its actions are specific for cells in S phase.

Mercaptopurine is used, usually with other agents, in the treatment of leukaemia. It can be used for remission induction in acute lymphoblastic and myeloid leukaemias (p. 692.3 and p. 693.1, respectively) but other agents are generally preferred and its main use is in maintenance programmes, commonly with methotrexate. It may also be effective in chronic myeloid leukaemia (p. 694.2). There is cross-resistance between mercaptopurine and tioguanine (p. 872.1).

Mercaptopurine has been used for its immunosuppressant properties in the treatment of auto-immune disorders such as inflammatory bowel disease (see below for doses) but has been largely replaced by azathioprine.

Mercaptopurine is given orally usually as tablets; although oral suspensions are available, they are not bioequivalent to tablets and close haematological monitoring is advised when changing between formulations. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* The usual initial antineoplastic dose of mercaptopurine is 2.5 mg/kg or 50 to 75 mg/m^2 daily but dose and duration depend on the combination regimen used; dosage is adjusted according to individual response and tolerance. In maintenance schedules the dose may vary from 1.5 to 2.5 mg/kg daily. Blood counts should be taken daily during remission induction and weekly during maintenance; if there is a steep fall in the white cell count or severe bone-marrow depression mercaptopurine should be stopped immediately.

For dose reductions when mercaptopurine is used with allopurinol, see Interactions, below.

It has been used intravenously as mercaptopurine sodium. Thioinosine (mercaptopurine riboside) has also been used.

Administration in children. Mercaptopurine is given to children for the treatment of leukaemias in the same dose by weight or surface area as that used for adults (see Uses and Administration, above).

There is evidence[1] that the maintenance dosage of mercaptopurine should be tailored individually to achieve an appropriate systemic exposure in children with acute lymphoblastic leukaemia (although this would involve determining mercaptopurine pharmacokinetics in each child). Improvements in survival since 1980 may be associated with changes in the prescribing of mercaptopurine which have resulted in greater cumulative doses being given;[2] some children may have been undertreated in the past because of variations in the pharmacokinetics of mercaptopurine (particularly boys, who tolerate mercaptopurine better than girls,[3] but who have a poorer prognosis).[2] The concentration of tioguanine nucleotide metabolites in the erythrocytes has been shown to be directly related to the risk of relapse in children with acute lymphoblastic leukaemia.[4] Thiopurine methyltransferase (TPMT) activity (which results in methylation and inactivation of mercaptopurine rather than the formation of active nucleotides) may play a substantial role in this variation,[5] but titration of the dose of mercaptopurine until myelotoxicity occurs may prevent the problem;[2] despite gaps in therapy caused by more frequent drug withdrawal, it appears to result in greater accumulation of tioguanine nucleotides in the cells.[6] A pharmacokinetic model has been proposed as offering a more rational approach for mercaptopurine dosing in children, by taking into account body-surface as well as TPMT genotype.[7]

Mercaptopurine is also used for inflammatory bowel disease in children, see below.

1. Koren G, *et al.* Systemic exposure to mercaptopurine as a prognostic factor in acute lymphocytic leukemia in children. *N Engl J Med* 1990; 323: 17–21.
2. Hale JP, Lilleyman JS. Importance of 6-mercaptopurine dose in lymphoblastic leukaemia. *Arch Dis Child* 1991; 66: 462–6.
3. Lilleyman JS, *et al.* Childhood lymphoblastic leukaemia: sex difference in 6-mercaptopurine utilization. *Br J Cancer* 1984; 49: 703–7.
4. Lilleyman JS, Lennard L. Mercaptopurine metabolism and risk of relapse in childhood lymphoblastic leukaemia. *Lancet* 1994; 343: 1188–90.
5. Lennard L, *et al.* Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukaemia. *Lancet* 1990; 336: 225–9.
6. Lennard L, *et al.* Mercaptopurine in childhood leukaemia: the effects of dose escalation on thioguanine nucleotide metabolites. *Br J Clin Pharmacol* 1996; 42: 525–7.
7. Hawwa AF, *et al.* Population pharmacokinetic and pharmacogenetic analysis of 6-mercaptopurine in paediatric patients with acute lymphoblastic leukaemia. *Br J Clin Pharmacol* 2008; 66: 826–37.

Administration in hepatic or renal impairment. Both UK and US licensed product information suggest that consideration be given to reducing the dosage of mercaptopurine in patients with hepatic or renal impairment, but no specific dose recommendations are given.

Inflammatory bowel disease. Mercaptopurine has been reported to be of benefit in ulcerative colitis[1,2] (although the quality of the evidence was considered low by a systematic review[3]) and Crohn's disease,[4–6] although azathioprine has generally been preferred (see p. 1945.1). Although unlicensed in the UK, the *BNF* and the *BNFC* state that mercaptopurine may be given to adults and children from 2 years of age for severe Crohn's disease or ulcerative colitis in an oral dose of 1 to 1.5 mg/kg once daily; in children up to 18 years of age an initial maximum of 50 mg daily is advised, increasing only up to 75 mg daily if necessary.

1. Adler DJ, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990; 85: 717–22.
2. George J, *et al.* The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996; 91: 1711–14.
3. Timmer A, *et al.* Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 07/07/10).
4. Peyrin-Biroulet L, *et al.* Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2009; 104: 2089–96.
5. Prefontaine E, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 07/07/10).
6. Prefontaine E, *et al.* Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 07/07/10).

Polymyositis. Mercaptopurine has been tried in a few patients with polymyositis but has not been formally assessed.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression with mercaptopurine, manifesting as leucopenia, thrombocytopenia, and anaemia, may be delayed; hypoplasia may occur. Mercaptopurine is less toxic to the gastrointestinal tract than the folic acid antagonists or fluorouracil but gastrointestinal disturbances may occur. Hepatotoxicity has been reported, with cholestatic jaundice and necrosis, sometimes fatal. Gastrointestinal and hepatic toxicity are reported to be more frequent in adults than in children, and are more likely at higher doses. Crystalluria with haematuria has been seen rarely as have skin disorders including hyperpigmentation. Fever may occur.

Mercaptopurine should be used with care in patients with impaired hepatic or renal function. Hepatic function should be monitored periodically.

Breast feeding. For information about the use of mercaptopurine during breast-feeding, see Azathioprine, p. 1946.3.

Effects on the blood. Measurement of the activity of thiopurine methyltransferase (TPMT) or the concentration of its substrate, tioguanine nucleotide, has been suggested as a way of predicting those individuals likely to have severe myelotoxicity with mercaptopurine and related drugs (see Azathioprine, p. 1946.2). Patients with an inherited deficiency of the TPMT enzyme may be at increased risk of myelosuppression from mercaptopurine. TPMT testing may be carried out in patients with evidence of toxicity; dose reductions should be considered in those with TPMT deficiency, although optimal initial doses have not been established for these patients. Tests for TPMT deficiency have not been shown to identify all patients at risk of severe toxicity; close monitoring of blood counts should still be performed.

Effects on the pancreas. Pancreatitis occurred in 13 of 396 patients given mercaptopurine for inflammatory bowel disease.[1] Symptoms resolved on withdrawal but recurred in 7 who were re-challenged with mercaptopurine or azathioprine. Acute pancreatitis has also been reported in 2 children given mercaptopurine during maintenance chemotherapy for acute lymphoblastic leukaemia.[2] They had also suffered pancreatitis from asparaginase during earlier therapy, and the authors suggested that subclinical damage to the pancreas by asparaginase may have been exacerbated by mercaptopurine, but also noted that most patients who develop asparaginase-induced pancreatitis receive mercaptopurine without developing this complication.

1. Present DH, *et al.* 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989; 111: 641–9.
2. Willert JR, *et al.* Recurrent mercaptopurine-induced acute pancreatitis: a rare complication of chemotherapy for acute lymphoblastic leukemia in children. *Med Pediatr Oncol* 2002; 38: 73–4.

Handling and disposal. A method for the destruction of mercaptopurine or tioguanine in *wastes* by oxidation with potassium permanganate in sulfuric acid.[1] Residues produced by this method had no mutagenic activity. *Urine and faeces* produced for up to 48 hours and 5 days, respectively after a dose of mercaptopurine should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Overdosage. Despite substantial overdose, no acute renal or hepatic toxicity occurred in 2 children. In one case, in which no specific detoxification measures were implemented, neutrophils reached a nadir on day 11 followed by a gradual recovery to normal by day 46. In the other case, gastric lavage was performed and activated charcoal was given; no evidence of neutropenia was seen. The authors recommended that management of acute accidental ingestion should include gastric lavage if the patient presents within 1 hour or if the amount ingested is large. Haemodialysis may be considered if the patient presents within 3 hours of ingestion. Liver function should be monitored. Severe myelosuppression may be managed with granulocyte colony-stimulating factor and a bone-marrow harvest may be of benefit if performed within several hours of the overdose.[1]

1. Chow LML, *et al.* Toxic ingestion of 6-mercaptopurine by young siblings of pediatric oncology patients. *J Pediatr* 2004; 144: 669–71.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mercaptopurine 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 29/09/11)

Pregnancy. For discussion of the safety of mercaptopurine in pregnancy, see Azathioprine, p. 1947.1.

Interactions

Mercaptopurine should be given with particular caution with other hepatotoxic drugs. Its effects are enhanced by allopurinol and the dose of mercaptopurine should be reduced to one-third to one-quarter of the usual dose when allopurinol is also given.

Allopurinol. Mercaptopurine plasma concentrations were markedly increased by allopurinol when mercaptopurine was given orally but not when it was given intravenously.[1] The results appear to indicate that allopurinol inhibits the first-pass metabolism of mercaptopurine.

The use of allopurinol to promote formation of 6-thioguanine nucleotides rather than 6-methylmercaptopurine nucleotides in patients with preferential metabolism via the latter has been investigated.[2,3]

1. Zimm S, *et al.* Inhibition of first-pass metabolism in cancer chemotherapy: interaction of 6-mercaptopurine and allopurinol. *Clin Pharmacol Ther* 1983; 34: 810–17.
2. Gerich ME, *et al.* A prospective evaluation of the impact of allopurinol in pediatric and adult IBD patients with preferential metabolism of 6-mercaptopurine to 6-methylmercaptopurine. *J Crohns Colitis* 2010; 4: 546–52.
3. Gardiner SJ, *et al.* Allopurinol might improve response to azathioprine and 6-mercaptopurine by correcting an unfavorable metabolite ratio. *J Gastroenterol Hepatol* 2011; 26: 49–54.

Anticoagulants. For reference to mercaptopurine diminishing the activity of *warfarin*, see p. 1532.2.

Antineoplastics. For a suggestion that *doxorubicin* might enhance the hepatotoxicity of mercaptopurine, see under Daunorubicin Hydrochloride, p. 779.3.

Giving mercaptopurine with low-dose oral *methotrexate* increased mean peak plasma concentrations of mercaptopurine by 26% compared with the same dose of mercaptopurine alone in a study in 14 patients with acute lymphoblastic leukaemia.[1] The effect was probably due to inhibition of the first-pass metabolism of mercaptopurine by methotrexate, which is a potent inhibitor of xanthine oxidase. In another study[2] of 10 children with acute lymphoblastic leukaemia, high-dose intravenous methotrexate (2 or 5 g/m^2) increased the peak plasma concentrations of mercaptopurine by 108 and 121% respectively. However, the clinical effect of this pharmacokinetic interaction is probably only minor because of the low, and highly variable, mercaptopurine bioavailability and the lack of correlation between mercaptopurine plasma concentrations and effect.[3] Mercaptopurine and methotrexate have been widely used in combination chemother-

apy regimens for acute lymphoblastic leukaemia for their synergistic pharmacodynamic interaction.

1. Balis FM, *et al.* The effect of methotrexate on the bioavailability of oral 6-mercaptopurine. *Clin Pharmacol Ther* 1987; 41: 384–7.
2. Innocenti F, *et al.* Clinical and experimental pharmacokinetic interaction between 6-mercaptopurine and methotrexate. *Cancer Chemother Pharmacol* 1996; 37: 409–14.
3. Giverhaug T, *et al.* The interaction of 6-mercaptopurine (6-MP) and methotrexate (MTX). *Gen Pharmacol* 1999; 33: 341–6.

Azathioprine. For a report of a fatality when a patient was prescribed mercaptopurine and azathioprine by separate practitioners, see Interactions, under Azathioprine, p. 1947.2.

Gastrointestinal drugs. The enzyme thiopurine methyltransferase is inhibited *in vitro* by *sulfasalazine* and *mesalazine*, raising the possibility of an interaction in patients treated simultaneously with an aminosalicylate and a thiopurine such as mercaptopurine or azathioprine.[1] Myelotoxicity has been reported in a patient receiving mercaptopurine and *olsalazine*.[2] Similarly, severe pancytopenia has occurred in a 13-year-old boy when azathioprine was added to mesalazine therapy.[3] In a study[4] of 34 patients with Crohn's disease in which *balsalazide*, mesalazine, or sulfasalazine was added to established azathioprine or mercaptopurine therapy, mild leucopenia was common in patients given mesalazine or sulfasalazine, and whole blood concentrations of tioguanine nucleotide were found to be increased, probably due to thiopurine methyltransferase inhibition. These effects were not statistically significant in patients given balsalazide.

1. Szumlanski C, Weinshilboum RM. Sulfasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. *Br J Clin Pharmacol* 1995; 39: 456–9.
2. Lewis LD, *et al.* Olsalazine and 6-mercaptopurine-related bone marrow suppression: a possible drug-drug interaction. *Clin Pharmacol Ther* 1997; 62: 464–75.
3. Chouraqui JP, *et al.* Azathioprine toxicity in a child with ulcerative colitis: interaction with mesalazine. *Gastroenterology* 1996; 110 (suppl): A883.
4. Lowry PW, *et al.* Leucopenia resulting from a drug interaction between azathioprine or 6-mercaptopurine and mesalamine, sulphasalazine, or balsalazide. *Gut* 2001; 49: 656–64.

Pharmacokinetics

Mercaptopurine is variably and incompletely absorbed from the gastrointestinal tract; about 50% of an oral dose has been reported to be absorbed, but the absolute bioavailability is somewhat lower, probably due to gastrointestinal or first-pass metabolism, and is also subject to wide interindividual variation. Once absorbed it is widely distributed throughout body water and tissues. Plasma half-lives ranging from about 20 to 90 minutes have been reported after intravenous injection and the drug is not found in plasma after about 8 hours but this is of limited significance since mercaptopurine is activated intracellularly by conversion to nucleotide derivatives which persist for much longer. It is rapidly and extensively metabolised in the liver, by methylation and oxidation as well as by the formation of inorganic sulfates. Thiol methylation is catalysed by the enzyme thiopurine methyltransferase (TPMT). TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. Patients with little or no detectable enzyme activity may accumulate excessive cellular concentrations of active tioguanine nucleotides, predisposing them to mercaptopurine toxicity. Considerable amounts of mercaptopurine are also oxidised to thiouric acid by the enzyme xanthine oxidase. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

Mercaptopurine crosses the blood-brain barrier to some extent and is found in the CSF, but only in subtherapeutic concentrations.

Therapeutic drug monitoring. For a discussion of therapeutic drug monitoring for mercaptopurine, see under Azathioprine, p. 1947.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Puri-Nethol; Varimer; *Austral.*: Puri-Nethol; *Austria*: Puri-Nethol; *Belg.*: Puri-Nethol; *Braz.*: Puri-Nethol; *Canad.*: Purinethol; *Chile*: Puri-Nethol; *Cz.*: Puri-Nethol; *Denm.*: Xaluprine; *Fr.*: Puri-Nethol; *Ger.*: Puri-Nethol; *Gr.*: Puri-Nethol; *Hong Kong*: Puri-Nethol; *India*: Empurine; Mercapto; Puri-Nethol; *Irl.*: Puri-Nethol; *Israel*: Puri-Nethol; *Ital.*: Puri-Nethol; *Mex.*: Puri-Nethol; *Neth.*: Puri-Nethol; Xaluprine; *Norw.*: Puri-Nethol; Xaluprine; *NZ*: Puri-Nethol; *Philipp.*: Capmerin; Empurine; Merpurin; Puri-Nethol; *Rus.*: Puri-Nethol (Пури-нетол); *S.Afr.*: Puri-Nethol; *Singapore*: Puri-Nethol; Purinetone; *Swed.*: Puri-Nethol; *Switz.*: Puri-Nethol; *Thai.*: Empurine†; Puri-Nethol; *Turk.*: Puri-Nethol; *UK*: Puri-Nethol†; Xaluprine; *USA*: Purinethol.

Pharmacopoeial Preparations

BP 2014: Mercaptopurine Oral Suspension; Mercaptopurine Tablets;

USP 36: Mercaptopurine Tablets.

Methotrexate *(BAN, USAN, rINN)*

Amethopterin; Ametopterina; 4-Amino-4-deoxy-10-methylpteroyl-L-glutamic Acid; 4-Amino-10-methylfolic Acid; CL-14377; α-Methopterin; Methotrexat; Methotrexát; Méthotrexate; Methotrexatum; Metotreksaatti; Metotreksatas; Metotrexat; Metotrexát; Metotrexato; MTX; NSC-740; WR-19039; Метотрексат.

N-[4-[(2,4-Diamino-6-pteridinylmethyl)methylamino]benzoyl]-L-glutamic acid.

$C_{20}H_{22}N_8O_5$=454.4

CAS — 59-05-2.

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.

UNII — YL5FZ2Y5U1.

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

Ph. Eur. 8: (Methotrexate). A yellow or orange, hygroscopic, crystalline powder. It contains not more than 13% of water. Practically insoluble in water, in alcohol, and in dichloromethane; dissolves in dilute solutions of mineral acids and of alkali hydroxides and carbonates. Store in airtight containers. Protect from light.

USP 36: (Methotrexate). It is a mixture of 4-amino-10-methylfolic acid and closely related substances; it contains not less than 98% and not more than 102% of $C_{20}H_{22}N_8O_5$, calculated on the anhydrous basis. A yellow or orange-brown crystalline powder. It contains not more than 12% of water. Practically insoluble in water, in alcohol, in chloroform, and in ether; freely soluble in dilute solutions of alkali hydroxides and carbonates; slightly soluble in 6N hydrochloric acid. Store in airtight containers. Protect from light.

Methotrexate Sodium *(BANM, rINNM)*

Méthotrexate de Sodium; Methotrexate Disodium; Metotreksat Sodyum; Metotrexate sodium; Metotrexato disódico; Metotrexato sódico; Natrii Methotrexatum; Натрий Метотрексат.

$C_{20}H_{20}N_8Na_2O_5$=498.4

CAS — 7413-34-5 (methotrexate disodium); 15475-56-6 (methotrexate sodium, xNa).

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.

UNII — 3KG1E710ZN.

Incompatibility. Methotrexate sodium has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate;[1] however, another study suggests it is compatible with fluorouracil.[2] Furthermore a mixture of methotrexate sodium with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25 degrees, although precipitation did occur on storage for several days.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; 33: 1010–13.
2. Vincké BJ, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; 54: 181–9.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; 41: 1802–6.

Stability to light. Methotrexate undergoes photodegradation when stored in the light in diluted solutions, although undiluted commercial preparations are reported to show negligible photodegradation.[1] The bicarbonate ion catalyses this reaction and such admixtures should be avoided if possible, although they may be stable in light for 12 hours. Storage of solutions diluted in sodium chloride 0.9% injection in PVC bags was reported to protect against photodegradation although the length of the study was only 4 hours.[2] Photodegradation can take place under normal lighting, but is more rapid in direct sunlight, with about 11% drug loss from a 1 mg/mL solution after 7 hours; storage under normal lighting resulted in little change in drug concentration over 24 hours with a decrease of up to 12% by 48 hours.[3] Loss was greatest from unprotected polybutadiene tubing, with almost 80% drug loss in 48 hours.

1. Chatterji DC, Gallelli JF. Thermal and photolytic decomposition of methotrexate in aqueous solutions. *J Pharm Sci* 1978; 67: 526–31.
2. Dyvik O, *et al.* Methotrexate in infusion solutions—a stability test for the hospital pharmacy. *J Clin Hosp Pharm* 1986; 11: 343–8.
3. McElnay JC, *et al.* Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; 47: 239–47.

Uses and Administration

Methotrexate is an antimetabolite antineoplastic that acts as an antagonist of folic acid. It also has immunosuppressant properties. Within the cell, folic acid is reduced to dihydrofolic and then tetrahydrofolic acid. Methotrexate competitively inhibits the enzyme dihydrofolate reductase and prevents the formation of tetrahydrofolate which is necessary for purine and pyrimidine synthesis and consequently the formation of DNA and RNA. It is most active against cells in the S phase of the cell cycle. Folinic acid (the 5-formyl derivative of tetrahydrofolic acid) has been given after high doses to bypass the block in tetrahydrofolate production in normal cells and prevent the adverse effects of methotrexate. A suggested schedule for *folinic acid rescue* is described under Folinic Acid, p. 2067.1 (See also Treatment of Adverse Effects, p. 826.3). Methotrexate, in very high doses, followed by folinic acid rescue, is used in treating some malignant diseases.

Methotrexate is used in the management of acute lymphoblastic leukaemia. It is seldom used for the induction of remission but is employed in maintenance programmes and in the prophylaxis and treatment of meningeal leukaemia. It may be used for Burkitt's and other non-Hodgkin's lymphomas. In the solid neoplasms it is an important part of curative regimens for choriocarcinoma and other gestational trophoblastic tumours, and for the adjuvant therapy of osteosarcoma and breast cancer. It may also be used in other malignant neoplasms, see Malignant Neoplasms, p. 824.1.

Methotrexate is of value in the treatment of psoriasis but because of the risks associated with this use, it should only be given when the disease is severe and has not responded to other forms of treatment. It is widely used as a disease-modifying antirheumatic drug in rheumatoid arthritis. Methotrexate may be used to prevent graft-versus-host disease after bone marrow transplantation and may be used as a cytotoxic immunosuppressant and corticosteroid-sparing agent in non-malignant diseases.

Methotrexate has a role in the management of ectopic pregnancy (see p. 823.3) and in the termination of early pregnancy (see p. 824.3).

Methotrexate may be given *orally* as the base or the sodium salt, or by *injection* as the sodium salt. Doses are calculated in terms of methotrexate. Methotrexate sodium 16.5 mg is equivalent to about 15 mg of methotrexate. The doses and regimens used vary enormously, and may need to be adjusted according to bone marrow or other toxicity (see also under Bone-marrow Depression, p. 730.3). *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Methotrexate regimens are often described as low-, moderate-, and high-dose, although what is meant by these terms may vary slightly. Some UK licensed product information has defined them as follows:

- low-dose: individual doses under 100 mg/m²
- moderate-dose: individual doses between 100 mg/m² and 1 g/m²
- high-dose: individual doses above 1 g/m²

Doses larger than 100 mg are usually given partly or wholly by intravenous infusion over not more than 24 hours.

Some common methotrexate doses are as follows:

For maintenance therapy in **acute lymphoblastic leukaemia**:

- 15 mg/m² orally or intramuscularly twice weekly
- 20 to 30 mg/m² orally or intramuscularly twice weekly
- 2.5 mg/kg intravenously every 14 days

For **meningeal leukaemia**:

- 12 mg/m² intrathecally once weekly for 2 weeks, then once monthly
- 200 to 500 micrograms/kg intrathecally at intervals of 2 to 5 days until the cell count of the CSF returns to normal; one additional dose is advised thereafter
- 12 mg intrathecally once weekly until the cell count of the CSF returns to normal; one additional dose is advised thereafter

For **Burkitt's lymphoma**:

- stages I to II: 10 to 25 mg orally daily for 4 to 8 days
- stage III (with other drugs): 0.625 to 2.5 mg/kg orally daily

In all stages, courses are usually repeated several times at intervals of 7 to 10 days.

For **lymphosarcoma**:

- (with other drugs): 0.625 to 2.5 mg/kg intravenously or intramuscularly daily

For **choriocarcinoma** and similar trophoblastic diseases:

- 15 to 30 mg orally or intramuscularly daily for 5 days, repeated after an interval of 1 week or longer, for 3 to 5 courses

For **osteosarcoma**:

- 8 to 12 g/m² intravenously once weekly, with folinic acid rescue

For **breast cancer**:
- (with *cyclophosphamide* and *fluorouracil* in the CMF regimen, see Table 1, p. 719) 40 mg/m² intravenously on days 1 and 8
- (with other drugs in cyclical regimens) 10 to 60 mg/m² intravenously

For **mycosis fungoides**:
- 2.5 to 10 mg orally daily for weeks or months, adjusted according to response and toxicity
- 50 mg intramuscularly weekly, as a single dose, or in two divided doses

For **psoriasis**:
- 10 to 25 mg orally, intramuscularly, or intravenously once weekly, adjusted according to response and toxicity; a suggested test dose in the range of 5 to 10 mg is recommended one week before the start of therapy
- 7.5 to 20 mg (increased as needed to a maximum of 25 to 30 mg) orally weekly, given as 3 divided doses over 24 hours, or as 3 divided doses at 12-hour intervals, or as 4 divided doses at 8-hour intervals; some suggest a test dose of 2.5 to 5 mg
- 2 to 5 mg (maximum 6.25 mg) orally daily for 5 days, followed by an interval of at least 2 days

For **rheumatoid arthritis**:
- 7.5 mg once weekly, given as a single oral, subcutaneous, intramuscular, or intravenous dose, or as 2.5 mg orally every 12 hours for 3 doses, adjusted according to response to a usual maximum of 20 mg weekly

In psoriasis and rheumatoid arthritis, once an adequate response is seen, the dose should be reduced to the lowest possible effective dose.

For doses in children, see below.

It is essential that blood counts and tests of renal and liver function should be made before, during, and after each course of treatment with methotrexate (see Precautions, p. 827.1). For further information on dosing in hepatic and renal impairment, see below.

Administration in children. Methotrexate is used in some countries for cancer chemotherapy in children, either alone or in combination regimens, and in juvenile idiopathic arthritis, for patients with active polyarticular rheumatoid disease.

For use in cancer chemotherapy such as for **acute lymphoblastic leukaemia** dosage is usually based on body-weight or body-surface in similar doses to those used in adults (see Uses and Administration, p. 822.3); alternatively, an oral or parenteral dose of methotrexate 15 mg/m² once weekly (with other drugs) has been suggested. For **meningeal leukaemia**, some UK licensed product information states that the dose of intrathecal methotrexate is constant regardless of age or body-surface in patients over the age of 3 years, and that those under 3 years be treated in accordance with combination chemotherapy protocols. For **non-Hodgkin's lymphoma** in children, methotrexate is given according to the disease phase and histological type; single intravenous doses range from 300 mg/m² to 5 g/m².

For juvenile **rheumatoid arthritis** the recommended starting oral or parenteral dose in the USA is 10 mg/m² once weekly. Dosage is adjusted gradually to achieve an optimal response. Children have been given doses up to 30 mg/m² weekly, but data are too limited to assess how doses over 20 mg/m² weekly might affect the risk of serious toxicity, although there is some suggestion that children given 20 to 30 mg/m² weekly (0.65 to 1 mg/kg weekly) may have better absorption and fewer gastrointestinal adverse effects if methotrexate is given either intramuscularly or subcutaneously. In the UK, methotrexate is licensed for children aged 3 to 16 years in the treatment of polyarticular juvenile idiopathic arthritis; a usual dose of 10 to 15 mg/m² once weekly by subcutaneous or intramuscular injection can be increased up to a maximum of 20 mg/m² once weekly. While stating that methotrexate is not licensed for use in children with other non-malignant conditions, the *BNFC* recommends a dose for juvenile idiopathic arthritis, juvenile dermatomyositis, vasculitis, uveitis, SLE, localised scleroderma, and sarcoidosis; children aged 1 month to 18 years may be given 10 to 15 mg/m² once weekly initially, increased if needed to a maximum of 25 mg/m² once weekly. Doses may be given orally, subcutaneously, or intramuscularly.

Methotrexate injectable formulations containing the preservative benzyl alcohol are not recommended for use in neonates. See also Neonates, under Benzyl Alcohol, p. 1741.1.

For **psoriasis**, although methotrexate is unlicensed in the UK for this use in children, the *BNFC* allows for specialist use in severe uncontrolled refractory disease. Children aged 2 to 18 years may be given an initial oral dose of 200 micrograms/kg (maximum 10 mg) once weekly, increased according to response to 400 micrograms/kg (maximum 25 mg) once weekly.

For suggested doses in the treatment of **Crohn's disease** in children, see Inflammatory Bowel Disease, p. 824.1.

Administration in the elderly. Licensed product information states that methotrexate should be used with extreme caution in the elderly, and that dosage reduction should be considered. Folate reserves are lower in older people and dosage reduction may be needed based on reduced liver and kidney function. Concomitant disease or drug therapy may contribute to these factors. There is some suggestion that adverse effects such as bone marrow suppression, thrombocytopenia, and pneumonitis may be increased in elderly patients.

A review[1] also states that increased toxicity has been seen in elderly patients given long-term low-dose methotrexate, and that half-life and clearance are significantly prolonged in older patients. A dose reduction based on renal function is recommended, and an alternative dosing formula using creatinine clearance (CC) has been proposed, namely:

$$\text{adjusted dose} = \text{normal dose} \times CC / 70$$

See also Administration in Renal Impairment, below.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; **25**: 1832–43.

Administration in hepatic impairment. Methotrexate is hepatotoxic, and liver function should be monitored during therapy (see Precautions, p. 827.1). Methotrexate should not be given to patients with severe or significant hepatic impairment, or to those with liver disease, including fibrosis, cirrhosis, or hepatitis. UK licensed product information for one injectable formulation (*Metoject; Medac, UK*) specifies that methotrexate should not be used if the bilirubin concentration is greater than 5 mg per 100 mL (85.5 micromoles/litre). Most UK licensed product information advises that methotrexate therapy be suspended for at least 2 weeks if substantial hepatic function abnormalities develop.

Administration in renal impairment. Methotrexate is renally excreted, and renal function should be monitored before, during, and after treatment. High-dose methotrexate therapy can affect the kidneys, and measures to prevent this may be required, see Effects on the Kidneys, p. 825.2.

Most UK licensed product information contra-indicates use in severe or significant renal impairment and states that doses of methotrexate should be reduced in patients with renal impairment, but gives no specific dose recommendations. However, licensed product information for one injectable formulation (*Metoject; Medac, UK*) gives the following recommendations based on creatinine clearance (CC):
- CC > 50 mL/min: 100% of the usual dose
- CC between 20 and 50 mL/min: 50% of the usual dose
- CC < 20 mL/min: use contra-indicated

Some advise adjustment of dose according to the CC and serum methotrexate concentrations. For a suggested dose in elderly patients based on CC, see Administration in the Elderly, above.

Asthma. Various immunosuppressants, including methotrexate, have been tried for their anti-inflammatory and corticosteroid-sparing properties in chronic asthma (p. 1195.2), but because of fears about toxicity are largely reserved for certain patients dependent upon systemic corticosteroids. Results of individual studies with methotrexate have been conflicting, but it appears that some patients may benefit from the corticosteroid-sparing effects of methotrexate.[1-5] However, some reviewers considered that the reduction in corticosteroid dose was insufficient to offset the adverse effects of methotrexate.[6] Methotrexate therapy must be given for at least 3 months for an adequate assessment of efficacy.

1. Shulimzon TR, Shiner RJ. A risk-benefit assessment of methotrexate in corticosteroid-dependent asthma. *Drug Safety* 1996; **15**: 283–90.
2. Marin MG. Low-dose methotrexate spares steroid usage in steroid-dependent asthmatic patients: a meta-analysis. *Chest* 1997; **112**: 29–33.
3. Corrigan CJ, *et al.* Methotrexate therapy of oral corticosteroid-dependent asthmatics reduces serum immunoglobulins: correlation with clinical response to therapy. *Clin Exp Allergy* 2005; **35**: 579–84.
4. Comet R, *et al.* Benefits of low weekly doses of methotrexate in steroid-dependent asthmatic patients: a double-blind, randomized, placebo-controlled study. *Respir Med* 2006; **100**: 411–19.
5. Domingo C, *et al.* Twelve years' experience with methotrexate for GINA treatment step 5 asthma patients. *Curr Med Res Opin* 2009; **25**: 367–74.
6. Davies H, *et al.* Methotrexate as a steroid sparing agent for asthma in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 12/05/05).

Connective tissue and muscular disorders. Reports in a limited number of patients indicate that methotrexate given once weekly in low to moderate doses may be of benefit in patients with SLE (p. 1613.3), with benefit reported particularly for joint and mucocutaneous symptoms.[1,2] In a retrospective analysis of patients with cutaneous lupus erythematosus, low doses of methotrexate significantly decreased disease activity.[3]

Methotrexate therapy has been investigated for its potential corticosteroid-sparing properties in polymyalgia rheumatica (p. 1610.3). Different regimens have been tried and although one study[4] reported benefit, others[5,6] found no evidence of clinical efficacy or a corticosteroid-sparing effect. *Guidelines from the 3E Initiative*[2] considered it effective and recommended its use as a corticosteroid-sparing agent in polymyalgia rheumatica and giant-cell arteritis.

Methotrexate is widely used in rheumatoid arthritis (see p. 824.2) and in polymyositis (p. 1611.1), and has been tried in Cogan's syndrome (p. 1603.2).

1. Sato EI. Methotrexate therapy in systemic lupus erythematosus. *Lupus* 2001; **10**: 162–4.
2. Visser K, *et al.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; **68**: 1086–93.
3. Wenzel J, *et al.* Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. *Br J Dermatol* 2005; **153**: 157–62.
4. Ferraccioli G, *et al.* Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. *J Rheumatol* 1996; **23**: 624–8.
5. Feinberg HL, *et al.* The use of methotrexate in polymyalgia rheumatica. *J Rheumatol* 1996; **23**: 1550–2.
6. van der Veen MJ, *et al.* Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatica and giant cell arteritis? *Ann Rheum Dis* 1996; **55**: 218–23.

Ectopic pregnancy. Ectopic pregnancy occurs when the fertilised ovum implants outside the uterus, usually in the fallopian tube itself (tubal pregnancy). Earlier detection has become possible due to improved diagnostic techniques. In many countries, there has been a rise in the rate of ectopic pregnancies followed by a decline; this may be partly due to increasing rates of infection with *Chlamydia*, followed by the effect of prevention, and changes in the popularity of intra-uterine devices.[1] Although ectopic pregnancies may spontaneously abort early, without clinical sequelae, the potential adverse effects are serious, ranging from pelvic pain and bleeding at 5 to 6 weeks of gestation (indistinguishable from spontaneous abortion), to potentially fatal intra-abdominal haemorrhage later in the course of an otherwise asymptomatic pregnancy.

Laparoscopic surgery remains the standard treatment.[1-4] In some countries non-surgical methods are increasing in popularity because of earlier diagnosis.[1,5] Perhaps the most experience of the latter has been with methotrexate. Management with intramuscular methotrexate may be appropriate for selected women with small unruptured tubal pregnancies who are haemodynamically stable, have low serum-chorionic gonadotrophin concentrations, and lack contra-indications to methotrexate use.[2-7] Surgery is preferred where there is cardiac activity in the conceptus, since a living embryo increases resistance to methotrexate.[6,7] Two regimens of intramuscular methotrexate have been described. A multiple-dose regimen of 1 mg/kg on 4 alternate days, with folinic acid rescue,[1] has similar efficacy to surgery.[3] A single dose of 50 mg/m² can be used instead[1,3] but systematic reviews have indicated that it has a higher failure rate than surgery[3,8] and about 20% of patients will require more than one cycle of treatment.[3] Some suggest that it is best reserved for women with serum-chorionic gonadotrophin concentrations below 1.5 units/mL.[4] The addition of an oral dose of mifepristone to single-dose methotrexate has been investigated[1,9,10] and may reduce treatment failure rates.

Methotrexate has been given by local injection directly into the ectopic (salpingocentesis). Doses of 1 mg/kg or 50 mg have been used[11] but this technique is significantly less successful than surgery.[3] Systemic methotrexate (with folinic acid rescue) has also been reported to be effective in resolving persistent ectopic pregnancy unsuccessfully treated with surgery.

The role of other agents in the management of ectopic pregnancy is less well established. Local instillation of glucose 50% by salpingocentesis has also been used in the treatment of ectopic pregnancy,[11,12] but one study was stopped because of a higher failure rate with glucose treatment compared with local methotrexate.[13]

Methotrexate may also be used in the termination of early uterine pregnancy (see p. 824.3).

1. Farquhar CM. Ectopic pregnancy. *Lancet* 2005; **366**: 583–91.
2. Tay JI, *et al.* Ectopic pregnancy. *BMJ* 2000; **320**: 916–9. Correction. *ibid.*; **321**: 424.
3. Hajenius PJ, *et al.* Interventions for tubal ectopic pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 19/05/08).
4. Mol F, *et al.* Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis. *Hum Reprod Update* 2008; **14**: 309–19.
5. Lipscomb GH, *et al.* Nonsurgical treatment of ectopic pregnancy. *N Engl J Med* 2000; **343**: 1325–9.
6. Lipscomb GH, *et al.* Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med* 1999; **341**: 1974–8.
7. American College of Obstetricians and Gynecologists. ACOG practice bulletin: medical management of tubal pregnancy. Number 3, December 1998. *Int J Gynecol Obstet* 1999; **65**: 97–103.

8. Parker J, *et al.* A systematic review of single-dose intramuscular methotrexate for the treatment of ectopic pregnancy. *Aust N Z J Obstet Gynaecol* 1998; 38: 145–50.
9. Gazvani MR, *et al.* Mifepristone in combination with methotrexate for the medical treatment of tubal pregnancy: a randomized, controlled trial. *Hum Reprod* 1998; 13: 1987–90.
10. Perdu M, *et al.* Treating ectopic pregnancy with the combination of mifepristone and methotrexate: a phase II nonrandomized study. *Am J Obstet Gynecol* 1998; 179: 640–3.
11. Natofsky JG, *et al.* Ultrasound-guided injection of ectopic pregnancy. *Clin Obstet Gynecol* 1999; 42: 39–47.
12. Lang PFJ, *et al.* Laparoscopic instillation of hyperosmolar glucose vs. expectant management of tubal pregnancies with serum hCG≤2500 mIU/mL. *Acta Obstet Gynecol Scand* 1997; 76: 797–800.
13. Sadan O, *et al.* Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001; 265: 82–4.

Inflammatory bowel disease. Methotrexate (given intramuscularly once weekly in a dose of 25 mg) was reported to improve symptoms and reduce corticosteroid requirements in a large controlled study in patients with chronic active *Crohn's disease*.[1] Those patients who were in remission after 16 weeks of methotrexate treatment were entered into a further placebo-controlled study[2] of methotrexate 15 mg weekly by intramuscular injection. During 40 weeks of follow-up, a higher proportion of patients receiving methotrexate remained in remission, and had fewer relapses. Smaller studies have also reported modest benefit for oral methotrexate 12.5 to 22.5 mg/week in chronic active disease.[3,4] Subcutaneous methotrexate has also been used.[5] A review[6] concluded that low-dose methotrexate could be recommended for induction of remission and for its corticosteroid-sparing effect in refractory and corticosteroid-dependent Crohn's disease, although the precise indications, dose, and route for its use were still unclear.

Although methotrexate is unlicensed in the UK for Crohn's disease, the *BNF* suggests the following doses in adults over 18 years of age with severe disease:

- induction of remission: 25 mg intramuscularly once weekly
- maintenance of remission: 10 to 25 mg orally once weekly, or 15 mg intramuscularly once weekly

The *BNFC* suggests the following doses for children aged 7 to 18 years:

- induction of remission: 15 mg/m^2 (maximum 25 mg) once weekly, by subcutaneous or intramuscular injection
- maintenance of remission: 15 mg/m^2(maximum 25 mg) once weekly, either orally or by subcutaneous or intramuscular injection; the dose is reduced according to response to the lowest effective dose

The value of methotrexate in *ulcerative colitis* is doubtful: although benefits have been seen in some patients,[5,7] a study in active ulcerative colitis found no significant differences between oral methotrexate 12.5 mg/week and placebo.[8] For a discussion of inflammatory bowel disease, see p. 1811.3.

1. Feagan BG, *et al.* Methotrexate for the treatment of Crohn's disease. *N Engl J Med* 1995; 332: 292–7.
2. Feagan BG, *et al.* A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. *N Engl J Med* 2000; 342: 1627–32.
3. Oren R, *et al.* Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997; 92: 2203–9.
4. Arora S, *et al.* Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999; 46: 1724–9.
5. Egan LJ, *et al.* A randomized dose-response and pharmacokinetic study of methotrexate for refractory inflammatory Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 1999; 13: 1597–1604.
6. Egan LJ, Sandborn WJ. Methotrexate for inflammatory bowel disease: pharmacology and preliminary results. *Mayo Clin Proc* 1996; 71: 69–80.
7. Kozarek RA. Methotrexate for refractory Crohn's disease: preliminary answers to definitive questions. *Mayo Clin Proc* 1996; 71: 104–5.
8. Oren R, *et al.* Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996; 110: 1416–21.

Malignant neoplasms. Methotrexate is extensively used in the management of malignant disease. In acute lymphoblastic leukaemia it is used for maintenance therapy, and intrathecally for prophylaxis of CNS relapse, as discussed on p. 692.3, while it also forms part of several regimens used for non-Hodgkin's lymphomas such as Burkitt's lymphoma (p. 697.3), mycosis fungoides (p. 698.3) and those associated with AIDS (p. 697.2). In the solid neoplasms it is an important part of curative regimens for gestational trophoblastic tumours (p. 691.2), the adjuvant therapy of osteosarcoma (p. 717.3) and is used in regimens for tumours of the bladder (p. 700.2), brain (p. 701.2), breast (p. 702.1), stomach (p. 706.1), and head and neck (p. 708.1).

Multiple sclerosis. Results suggest that oral methotrexate 7.5 mg weekly may be of benefit[1] in slowing the progression of multiple sclerosis (p. 996.3). Although the results of studies of immunosuppressant therapy in this condition have tended to be disappointing, it has been pointed out that benefit was assessed differently in the methotrexate study,[2] which may have a bearing on its more favourable conclusions.

1. Goodkin DE, *et al.* Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol* 1995; 37: 30–40.
2. Whitaker JN, *et al.* Clinical outcomes and documentation of partial beneficial effects of immunotherapy for multiple sclerosis. *Ann Neurol* 1995; 37: 5–6.

Myasthenia gravis. Methotrexate has been tried in the management of myasthenia gravis (p. 684.1) in patients who require immunosuppression but are intolerant of or unresponsive to corticosteroids and azathioprine.

Organ and tissue transplantation. For reference to the use of methotrexate (usually with ciclosporin) in bone marrow transplantation, see Haematopoietic Stem Cell Transplantation, p. 1937.1.

Primary biliary cirrhosis. Like other drugs used for primary biliary cirrhosis (p. 2638.3) methotrexate has been associated with biochemical improvement but evidence of clinical and in particular histological improvement is harder to show, and the toxicity of immunosuppressants such as methotrexate is problematic. A randomised study comparing methotrexate with colchicine found a slightly lower survival with methotrexate after 10 years of treatment;[1] a systematic review[2] concluded that methotrexate had no effect on mortality or the need for liver transplantation in patients with primary biliary cirrhosis and that there was no evidence to support its use.

1. Kaplan MM, *et al.* A randomized controlled trial of colchicine plus ursodiol versus methotrexate plus ursodiol in primary biliary cirrhosis: ten-year results. *Hepatology* 2004; 39: 915–23.
2. Giljaca V, *et al.* Methotrexate for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews: Issue 5. Chichester: John Wiley; 2010 (accessed 07/07/10).

Psoriatic arthritis. Methotrexate may be useful for severe or progressive cases of psoriatic arthritis (see under Spondyloarthropathies, p. 14.3) when the arthritis is not controlled by physical therapy and NSAIDs, although toxicity may limit long-term use in some patients.

Retroperitoneal fibrosis. There are reports[1,2] of success with low-dose weekly methotrexate in the treatment of retroperitoneal fibrosis (p. 1612.1); corticosteroids were also given, but tapered off in one case.[1]

1. Scavalli AS, *et al.* Long-term follow-up of low-dose methotrexate therapy in one case of idiopathic retroperitoneal fibrosis. *Clin Rheumatol* 1995; 14: 481–4.
2. Vaglio A, *et al.* Post-treatment residual tissue in idiopathic retroperitoneal fibrosis: active residual disease or silent "scar"? A study using ^{18}F-fluorodeoxyglucose positron emission tomography. *Clin Exp Rheumatol* 2005; 23: 231–4.

Rheumatoid arthritis. Therapy of rheumatoid arthritis (p. 13.2) is conventionally begun with an analgesic and an NSAID for symptomatic relief, to which a disease-modifying antirheumatic drug (DMARD) is subsequently added in an attempt to retard the disease process. It is now clear that irreversible joint damage commonly occurs in early disease and rheumatologists now generally add the DMARD shortly after rheumatoid arthritis has been diagnosed. Methotrexate is widely used,[1] and is the DMARD of first choice in many patients. Systematic review has confirmed that methotrexate has significant benefit in the short-term treatment of the disease.[2] Multinational recommendations for its use[3] produced by the 3E Initiative included beginning oral therapy at 10 to 15 mg weekly and increasing this dose by 5 mg every 2 to 4 weeks up to a maximum of 20 to 30 mg weekly (this is somewhat higher than the licensed doses recommended in Uses and Administration, p. 822.3); the Initiative also considered that at least 5 mg of folic acid weekly should be given as a supplement. These recommendations considered that monotherapy was preferable to combination of methotrexate with other DMARDs in DMARD-naive patients,[3] with methotrexate-based combinations used when monotherapy was ineffective. Methotrexate has been tried with ciclosporin, hydroxychloroquine and sulfasalazine, leflunomide, etanercept, and infliximab. Studies have shown improved responses to these combinations compared with methotrexate alone, but long-term efficacy and safety has not been studied.[4] For debate on the value of initial combination therapy versus monotherapy see p. 13.2. A randomised controlled study[5] found that subcutaneous methotrexate was significantly more effective than the same dose of oral methotrexate in patients with active rheumatoid arthritis.

Methotrexate may be of benefit[6-8] in juvenile idiopathic arthritis (p. 12.1): for doses, see Administration in Children, p. 823.1.

Methotrexate may also be of value in the management of associated uveitis (see p. 825.1).

1. Anonymous. Modifying disease in rheumatoid arthritis. *Drug Ther Bull* 1998; 36: 3–6.
2. Suarez-Almazor ME, *et al.* Methotrexate for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 15/10/09).
3. Visser K, *et al.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; 68: 1086–93.
4. Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Ann Intern Med* 2001; 134: 695–706.
5. Braun J, *et al.* MC-MTX.6/RH Study Group. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; 58: 73–81.
6. Ravelli A, *et al.* Radiologic progression in patients with juvenile chronic arthritis treated with methotrexate. *J Pediatr* 1998; 133: 262–5.
7. Takken T, *et al.* Methotrexate for treating juvenile idiopathic arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 15/10/09).
8. Ramanan AV, *et al.* Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child* 2003; 88: 197–200.

Sarcoidosis. Where therapy is required for sarcoidosis (p. 1612.2) corticosteroids are the first choice of drug; methotrexate is one of the preferred second-line immunosuppressants.

References.
1. Webster GF, *et al.* Methotrexate therapy in cutaneous sarcoidosis. *Ann Intern Med* 1989; 111: 538–9.
2. Soriano FG, *et al.* Neurosarcoidosis: therapeutic success with methotrexate. *Postgrad Med J* 1990; 66: 142–3.
3. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995; 155: 846–51.
4. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. *Thorax* 1999; 54: 742–6.

Scleroderma. There is some evidence of benefit with methotrexate in patients with scleroderma (p. 1942.3), particularly for cutaneous symptoms, although not all studies have shown clear value.

References.
1. van den Hoogen FH, *et al.* Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br J Rheumatol* 1996; 35: 364–72.
2. Seyger MMB, *et al.* Low-dose methotrexate in the treatment of widespread morphea. *J Am Acad Dermatol* 1998; 39: 220–5.
3. Uziel Y, *et al.* Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000; 136: 91–5.
4. Pope JE, *et al.* A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001; 44: 1351–8.
5. Weibel L, *et al.* Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children. *Br J Dermatol* 2006; 155: 1013–20.

Skin disorders, non-malignant. Methotrexate is widely used in the treatment of severe refractory psoriasis. As discussed on p. 1688.1 the aim of such therapy is to bring the disease under control, enabling a return to other therapy. For use in psoriatic arthritis see above. Methotrexate is also used with corticosteroids in the management of pemphigus and pemphigoid (p. 1687.1).

Termination of pregnancy. Methotrexate has been investigated as an alternative to mifepristone for use with misoprostol for the termination of early pregnancy (p. 2131.3). Intramuscular methotrexate followed 3 days later by intravaginal misoprostol was more effective than misoprostol alone for termination at 56 days or less;[1] the combination was reported to be less successful after 57 to 63 days of gestation.[2] Later studies[3,4] however found the combination to be safe and effective in terminating pregnancies up to 63 days of gestation; in these the misoprostol was given up to 7 days after the methotrexate. Oral methotrexate is also effective.[5-7] However, the efficacy of methotrexate followed by misoprostol does appear to diminish with increasing gestational age,[8] and the time to complete abortion generally takes longer with regimens using methotrexate compared with mifepristone.[9] The American College of Obstetricians and Gynecologists[10] recommends that methotrexate with misoprostol may be used in pregnancies of up to 49 days of gestation, the usual regimen being methotrexate, either 50 mg/m^2 intramuscularly or 50 mg orally, followed 3 to 7 days later by misoprostol 800 micrograms vaginally. The College also advises that it may take up to 4 weeks for complete abortion to occur in about 1% to 25% of women given such regimens.

For the role of methotrexate in the management of ectopic pregnancy, see p. 823.3.

1. Creinin MD, Vittinghoff E. Methotrexate and misoprostol vs misoprostol alone for early abortion: a randomized controlled trial. *JAMA* 1994; 272: 1190–5.
2. Creinin MD. Methotrexate and misoprostol for abortion at 57-63 days' gestation. *Contraception* 1994; 50: 511–15.
3. Hausknecht RU. Methotrexate and misoprostol to terminate early pregnancy. *N Engl J Med* 1995; 333: 537–40.
4. Creinin MD, *et al.* A randomized trial comparing misoprostol three and seven days after methotrexate for early abortion. *Am J Obstet Gynecol* 1995; 173: 1578–84.
5. Creinin MD. Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1996; 54: 15–18.
6. Creinin MD, *et al.* Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997; 90: 611–16.
7. Carbonell JLL, *et al.* Oral methotrexate and vaginal misoprostol for early abortion. *Contraception* 1998; 57: 83–8.

8. Creinin MD, *et al.* Methotrexate and misoprostol for early abortion: a multicenter trial. *Contraception* 1996; 53: 321–7.
9. Wiebe E, *et al.* Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. *Obstet Gynecol* 2002; 99: 813–19.
10. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, October 2005). *Obstet Gynecol* 2005; 106: 871–82.

Uveitis. Methotrexate has been reported to be safe and effective[1-3] when used to treat uveitis (p. 1615.1) in small numbers of patients.

1. Samson CM, *et al.* Methotrexate therapy for chronic noninfectious uveitis: analysis of a case series of 160 patients. *Ophthalmology* 2001; 108: 1134–9.
2. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005; 32: 362–5.
3. Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. *Br J Ophthalmol* 2005; 89: 806–8.

Vasculitic syndromes. In giant cell arteritis (p. 1604.2), improved clinical response and a corticosteroid-sparing effect have been reported with the addition of methotrexate to corticosteroid therapy,[1] but other studies using different designs and dosages[2,3] have failed to find any benefit. Guidelines from the 3E Initiative[4] considered it effective and recommended its use as a corticosteroid-sparing agent in polymyalgia rheumatica and giant-cell arteritis. For the use of methotrexate in Takayasu's arteritis and Wegener's granulomatosis see p. 1614.3 and p. 1615.2, respectively.

1. Jover JA, *et al.* Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001; 134: 106–14.
2. Spiera RE, *et al.* A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol* 2001; 19: 495–501.
3. Hoffman GS, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; 46: 1309–18.
4. Visser K, *et al.* Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; 68: 1086–93.

Adverse Effects

For general discussions see Antineoplastics, p. 726.1.

The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leucopenia, thrombocytopenia, and anaemia may all occur. The nadir of the platelet and white-blood cell counts is usually around 5 to 10 days after a bolus dose, with recovery between about 14 to 28 days, but some sources suggest that leucocytes may show an early fall and rise, followed by a second nadir and recovery, within this period. Ulceration of the mouth and gastrointestinal disturbances are also early signs of toxicity: stomatitis and diarrhoea during treatment indicate that it may need to be interrupted, otherwise haemorrhagic enteritis, intestinal perforation, and death may follow.

Methotrexate is associated with liver damage, both acute (notably after high doses) and, more seriously, chronic (generally after long-term use). Hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity, and have led to eventual death.

Other adverse effects include renal failure and tubular necrosis after high doses, pulmonary reactions including life-threatening interstitial lung disease, skin reactions (sometimes severe), alopecia, and ocular irritation. Neurotoxicity may be seen: leukoencephalopathy, paresis, demyelination are associated particularly with intrathecal use and are more likely when cranial irradiation is also given. Intrathecal use may also produce arachnoiditis, an acute syndrome of headache, nuchal rigidity, back pain, and fever. Other rarer reactions may include megaloblastic anaemia, osteoporosis, precipitation of diabetes, arthralgias, necrosis of soft tissue and bone, and anaphylaxis.

Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired (this may be reversible). Like other folate inhibitors it is teratogenic, and it has been associated with fetal deaths. Lymphomas (generally reversible on withdrawal of treatment) have occasionally been reported with methotrexate therapy, although the association has been questioned (see Carcinogenicity, below).

Carcinogenicity. There are reports of lymphomas associated with low-dose methotrexate therapy for rheumatic disorders,[1-4] which in some cases have been associated with concomitant Epstein-Barr virus infection.[2] Transitional cell bladder cancer has also been associated with such therapy.[5] However, a retrospective analysis involving 16 263 patients with rheumatoid arthritis found no evidence of a relationship between the use of methotrexate as an antirheumatic and the development of haematological malignancy.[6] Nonetheless, the spontaneous remission of lymphoma after withdrawal of methotrexate in some patients seems to support an association[7] A later prospective study[8] of all new cases of lymphoma, detected over 3 years in patients treated with methotrexate for rheumatoid arthritis, also found a higher incidence of Hodgkin's disease compared with the general population. An Australian cohort study[9] in rheumatoid arthritis patients treated with methotrexate found an overall increased incidence of malignancy with a fivefold increased risk of non-Hodgkin's lymphoma, a threefold increased risk of lung cancer, and a threefold increased risk of melanoma relative to the general population. Further investigation was considered necessary to determine whether the findings with respect to melanoma were unique to Australia and what role methotrexate, immunosuppression, and environmental factors such as exposure to UV radiation have in the development thereof. The carcinogenic risk with antimetabolites such as methotrexate has generally been considered less than with alkylating agents (p. 726.2).

1. Zimmer-Galler I, Lie JT. Choroidal infiltrates as the initial manifestation of lymphoma in rheumatoid arthritis after treatment with low-dose methotrexate. *Mayo Clin Proc* 1994; 69: 258–61.
2. Kamel OW, *et al.* Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993; 328: 1317–21.
3. Viraben R, *et al.* Reversible cutaneous lymphoma occurring during methotrexate therapy. *Br J Dermatol* 1996; 135: 116–18.
4. Ebeo CT, *et al.* Methotrexate-induced pulmonary lymphoma. *Chest* 2003; 123: 2150–3.
5. Millard RJ, McCredie S. Bladder cancer in patients on low-dose methotrexate and corticosteroids. *Lancet* 1994; 343: 1222–3.
6. Moder KG, *et al.* Hematologic malignancies and the use of methotrexate in rheumatoid arthritis: a retrospective study. *Am J Med* 1995; 99: 276–81.
7. Georgescu L, Paget SA. Lymphoma in patients with rheumatoid arthritis: what is the evidence of a link with methotrexate? *Drug Safety* 1999; 20: 475–87.
8. Mariette X, *et al.* Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood* 2002; 99: 3909–15.
9. Buchbinder R, *et al.* Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 2008; 59: 794–9.

Effects on the blood. Although serious and sometimes fatal blood dyscrasias are a well-known consequence of high-dose methotrexate therapy the UK CSM[1] stated in September 1997 that it was also aware of 83 reports of blood dyscrasias associated with low-dose methotrexate used to treat psoriasis or rheumatoid arthritis; there were 36 fatalities. Many of the cases had contributing factors such as advanced age, renal impairment, or use with interacting drugs.

1. CSM/MCA. Blood dyscrasias and other ADRs with low-dose methotrexate. *Current Problems* 1997; 23: 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 03/04/06)

MEGALOBLASTIC ANAEMIA. Megaloblastic anaemia, usually with marked macrocytosis, has been reported in mainly elderly patients given long-term weekly methotrexate therapy.[1-3] It has been suggested that therapy should be withdrawn if the mean corpuscular volume exceeds 106 femtolitres.[1] Symptoms appear to be associated with folate depletion by methotrexate,[2,4,5] probably due to increased excretion,[6] and in one case megaloblastic anaemia developed after starting a weight-reducing diet poor in folate.[4] Folate supplementation, conversely, may permit continuation of methotrexate therapy with resolution of the anaemia.[5]

1. Dodd HJ, *et al.* Megaloblastic anaemia in psoriatic patients treated with methotrexate. *Br J Dermatol* 1985; 112: 630.
2. Dahl MGC. Folate depletion in psoriatics on methotrexate. *Br J Dermatol* 1984; 111 (suppl 26): 18.
3. Casserly CM, *et al.* Severe megaloblastic anemia in a patient receiving low-dose methotrexate for psoriasis. *J Am Acad Dermatol* 1993; 29: 477–80.
4. Fulton RA. Megaloblastic anaemia and methotrexate treatment. *Br J Dermatol* 1986; 114: 267–8.
5. Oxholm A, Thomsen K. Megaloblastic anaemia and methotrexate treatment. *Br J Dermatol* 1986; 114: 268–9.
6. Duhra P, *et al.* Intestinal folate absorption in methotrexate treated psoriatic patients. *Br J Dermatol* 1988; 119: 327–32.

Effects on the gastrointestinal tract. Although gastrointestinal toxicity is well recognised as an effect of high-dose regimens, oral ulceration has also been reported after low-dose (weekly) methotrexate use.[1,2] In some instances it was related to overdosage; symptoms resolved upon correction of the dose and with folate supplementation.[1] Folate deficiency may increase the oral toxicity of methotrexate, and folate supplementation may also avoid the need to stop low-dose methotrexate.[2]

1. Deeming GMJ, *et al.* Methotrexate and oral ulceration. *Br Dent J* 2005; 198: 83–5.
2. Kalantzis A, *et al.* Oral effects of low-dose methotrexate treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 100: 52–62.

Effects on the kidneys. High-dose methotrexate therapy can result in supersaturation of the urine with methotrexate and its metabolites leading to crystal formation.[1] These crystals can cause intrarenal obstruction and are a factor in the development of acute renal failure. Risk factors for crystal formation are acid urine, volume depletion, and renal impairment. Adequate hydration, and urinary alkalinisation with sodium bicarbonate or acetazolamide play an important role in minimising nephrotoxicity in high-dose methotrexate regimens. A study found that the incidence of severe toxicity was reduced in patients given greater hydration and alkalinisation. However, this more intensive hydration regimen also significantly lowered methotrexate plasma concentrations.[2] Glucarpidase, a recombinant glutamate carboxypeptidase, is used in the management of methotrexate-induced renal dysfunction when methotrexate concentrations are very high (see Treatment of Adverse Effects, p. 826.3).[3]

1. Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999; 106: 459–65.
2. Christensen ML, *et al.* Effect of hydration on methotrexate plasma concentrations in children with acute lymphocytic leukemia. *J Clin Oncol* 1988; 6: 797–801.
3. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist* 2006; 11: 694–703.

Effects on the liver. Methotrexate is well established as a cause of hepatotoxicity, including periportal fibrosis, when given in relatively high doses as an antineoplastic, and it has become clear that its long-term use in lower doses for disorders such as psoriasis and rheumatoid arthritis can also be associated with liver toxicity.[1,2] There has been some difficulty in these patients in distinguishing the effects of the drug from the effects of the disease, but there is good evidence that the risk is increased in patients given doses on a daily rather than a weekly regimen, and in those with a high alcohol intake.[1] Pre-existing liver disease, obesity (especially if associated with diabetes mellitus), renal impairment, and increasing total cumulative dose may also increase the risk of hepatotoxicity.[1] A lower incidence of hepatotoxicity in patients with rheumatoid arthritis (compared with older studies in patients with psoriasis) may be due to improved dosage regimens and greater awareness of the risks.[1]

In order to minimise the risks of serious liver damage various guidelines and recommendations have been issued for the use of methotrexate in psoriasis and rheumatoid arthritis, and the appropriate monitoring.

- For patients with *psoriasis*, 1988 US guidelines[3] recommended a liver biopsy at the beginning of treatment and after each cumulative dose of 1 to 1.5 g, with monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, and albumin. However, the need to repeat routine liver biopsies was questioned[4] and some[5] recommended omitting the baseline biopsy in patients with no risk factors. A 2009 consensus[6] suggests that patients being considered for methotrexate therapy be divided into 2 groups based on their risk factors for liver injury. Patients with a low risk for hepatotoxicity are monitored similarly to rheumatoid arthritis patients (see below), with an option for liver biopsy upon reaching a cumulative dose of 3.5 to 4 g. For those with one or more risk factors for hepatotoxicity, guidelines remain more stringent, with the first consideration being the feasibility of using another drug. If methotrexate is used, it is advisable that a liver biopsy be performed, at or near the start of therapy; since some patients will stop methotrexate after 2 to 6 months because of adverse effects or lack of efficacy, the liver biopsy may be postponed until after this period. A repeat biopsy should be performed after a cumulative dose of 1 to 1.5 g, and with every additional 1 to 1.5 g thereafter. Methotrexate should be stopped if liver changes are moderate to severe. Practice in the UK has focused on monitoring of the aminoterminal peptide of type III procollagen (PIIINP), a serological marker of hepatic fibrosis,[7] and this is recommended by the British Association of Dermatologists[8] as a safer alternative to liver biopsy. PIIINP values should be determined before starting methotrexate and then every 2 to 3 months during treatment. A liver biopsy may then be considered in those with persistently abnormal values. However, some[7] have said that larger studies of the value of PIIINP assays should be undertaken before definitive recommendations can be made.
- In patients with *rheumatoid arthritis* US guidelines[9,10] suggest an initial biopsy only in patients with a history of excessive alcohol consumption, persistently abnormal AST or ALT values or chronic hepatitis B or C infection. All patients should have liver function tests (LFTs) monitored monthly for the first 6 months and then every 1 to 2 months thereafter. For minor elevations in AST or ALT (less than twofold the upper limit of normal), LFTs are repeated in 2 to 4 weeks; for moderate elevations in AST or ALT (greater than twofold but less than threefold the upper limit of normal), close monitoring, repeat LFTs in 2 to 4 weeks, and reduction of the dose as needed are advocated. A biopsy should be performed if 5 of 9 (or 6 of 12) measurements of AST are elevated in a 12-month

interval or if there is a decline in serum albumin (with normal nutritional status) below the normal range; if liver changes are moderate to severe, methotrexate should be stopped. Options for patients with normal findings include continuing to follow the above guidelines without biopsy, or the first biopsy may be performed at a cumulative dose of 3.5 to 4 g of methotrexate, or methotrexate can be stopped after this cumulative dose, or patients switched to alternative therapy. However, some rheumatologists[11,12] consider that less stringent monitoring may be warranted, especially in those with no risk factors for hepatotoxicity. Similarly, although these guidelines have been widely adopted for use in children with juvenile idiopathic arthritis, some[13] consider that routine blood tests every 4 to 8 weeks are unnecessarily frequent.

The UK CSM advised in 1997 that LFTs (with blood count and renal-function testing) should be performed before beginning long-term low-dose methotrexate therapy and repeated weekly until therapy was stabilised, and thereafter every 2 to 3 months.[14]

1. West SG, *et al.* Methotrexate hepatotoxicity. *Rheum Dis Clin North Am* 1997; 23: 883–915.
2. Visser K, van der Heijde DM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. *Clin Exp Rheumatol* 2009; 27: 1017–25.
3. Roenigk HH, *et al.* American Academy of Dermatology. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988; 19: 145–6.
4. Boffa MJ, *et al.* Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. *Br J Dermatol* 1995; 133: 774–8.
5. Roenigk HH, *et al.* Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 1998; 38: 478–85.
6. Kalb RE, *et al.* Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol* 2009; 60: 824–37.
7. Maurice PDL, *et al.* Monitoring patients on methotrexate: hepatic fibrosis not seen in patients with normal serum assays of aminoterminal peptide of type III procollagen. *Br J Dermatol* 2005; 152: 451–8.
8. British Association of Dermatologists. Psoriasis—General Management—Methotrexate. Available at: http://www.bad.org.uk/site/1121/default.aspx (accessed 20/07/10)
9. Kremer JM, *et al.* American College of Rheumatology. Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994; 37: 316–28.
10. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum* 2002; 46: 328–46.
11. Yazici Y, *et al.* Monitoring by rheumatologists for methotrexate-, etanercept-, infliximab-, and anakinra-associated adverse events. *Arthritis Rheum* 2003; 48: 2769–72.
12. Yazici Y, *et al.* Methotrexate use in rheumatoid arthritis is associated with few clinically significant liver function test abnormalities. *Clin Exp Rheumatol* 2005; 23: 517–20.
13. Ortiz-Alvarez O,*et al.* Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol* 2004; 31: 2501–6.
14. CSM/MCA. Blood dyscrasias and other ADRs with low-dose methotrexate. *Current Problems* 1997; 23: 12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023240&RevisionSelectionMethod=LatestReleased (accessed 03/04/06)

Effects on the lungs. Pulmonary toxicity due to methotrexate has been well described.[1-3] A review[1] of over 120 reports of methotrexate pneumonitis found that onset usually occurred during treatment, presenting as dyspnoea, cough, and fever. Examination often found tachypnoea and crackles, eosinophilia, reduced pulmonary function, interstitial and alveolar infiltrates on chest radiography, and interstitial inflammation and fibrosis. The majority of cases were managed with cessation of methotrexate with or without corticosteroid therapy; most patients improved, but there were 16 deaths caused by respiratory disease. Methotrexate was restarted in 16 patients, and pneumonitis recurred in 4 of these.

Up to 25 April 2003, the UK CSM had received 90 reports of parenchymal lung disorders, including 52 reports of pneumonitis, 21 of pulmonary fibrosis, 5 of interstitial lung disease, and 3 of interstitial pneumonitis. The CSM has suggested that patients should seek medical attention if symptoms such as dyspnoea, dry, nonproductive cough, or fever develop; methotrexate should be stopped and corticosteroids given in the event of suspected pneumonitis.[4]

A multicentre case-control study[5] which examined 29 cases of methotrexate-induced lung injury among rheumatoid arthritis patients found that risk factors included age over 60 years, pleuropulmonary disease (or to a lesser extent other extra-articular disease), previous use of other disease-modifying antirheumatic drugs, and low serum-albumin; an association with smoking, nonsedentary occupations, and diabetes mellitus was also noted. The mechanisms of methotrexate-induced pulmonary inflammation have been investigated *in vitro*,[6] and suggested to be due to stimulation of the p38 mitogen-activated protein kinase pathway, with increased production of the pro-inflammatory cytokines interleukin-1β and interleukin-8, and inhibition of the anti-inflammatory interleukin-4.

1. Imokawa S, *et al.* Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J* 2000; 15: 373–81.
2. Lateef O, *et al.* Methotrexate pulmonary toxicity. *Expert Opin Drug Safety* 2005; 4: 723–30.
3. Kim Y-J, *et al.* Mechanisms underlying methotrexate-induced pulmonary toxicity. *Expert Opin Drug Safety* 2009; 8: 451–8.
4. CSM/MHRA. Methotrexate and pneumonitis. *Current Problems* 2003; 29: 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074506&RevisionSelectionMethod=LatestReleased (accessed 31/07/08)
5. Alarcón GS, *et al.* Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis: a multicenter, case-control study. *Ann Intern Med* 1997; 127: 356–64.
6. Kim Y-J, *et al.* Inflammation in methotrexate-induced pulmonary toxicity occurs via the p38 MAPK pathway. *Toxicology* 2009; 256: 183–90.

Effects on mental function. Children who had received intrathecal methotrexate with cranial irradiation for the prophylaxis of CNS leukaemia, had a significant intellectual deficit compared with their siblings.[1] There was no corresponding significant reduction in IQ in a group of children who had received systemic chemotherapy and radiotherapy when compared with their sibling controls. The results suggest that intrathecal methotrexate and cranial irradiation cause intellectual problems, particularly on the higher, more complex and integrated intellectual functions, and that the repercussions are greater in younger children. Subsequent results in these patients indicated that although the lowering of IQ had persisted, it had not progressed since the original study.[2] A further study confirmed the adverse neurological effects of leukaemia treatment, and its effects on IQ, and did not find a reduced radiation dose to be any less toxic.[3] Neurotoxicity appeared to be greater when systemic therapy with intramuscular rather than oral methotrexate was given with CNS prophylaxis. A study[4] of children who underwent surgery, chemotherapy, and craniospinal radiotherapy for medulloblastoma also found that those patients who received intrathecal methotrexate had significantly worse cognitive deficits than those who did not, and all patients performed worse than a control group of cousins and siblings.

In a small study[5] of children treated for leukaemia with chemotherapy that included intrathecal methotrexate, but without irradiation, there were lower cognitive scores in some measures compared with a group of healthy controls, but overall no major cognitive impairment was found.

A study in 20 patients receiving intermittent oral methotrexate for psoriasis found no evidence of psychological impairment.[6]

1. Twaddle V, *et al.* Intellectual function after treatment for leukaemia or solid tumours. *Arch Dis Child* 1983; 58: 949–52.
2. Twaddle V, *et al.* Intellect after malignancy. *Arch Dis Child* 1986; 61: 700–2.
3. Chessells JM, *et al.* Neurotoxicity in lymphoblastic leukaemia: comparison of oral and intramuscular methotrexate and two doses of radiation. *Arch Dis Child* 1990; 65: 416–22.
4. Riva D, *et al.* Intrathecal methotrexate affects cognitive function in children with medulloblastoma. *Neurology* 2002; 59: 48–53.
5. Kingma A, *et al.* No major cognitive impairment in young children with acute lymphoblastic leukemia using chemotherapy only: a prospective longitudinal study. *J Pediatr Hematol Oncol* 2002; 24: 106–14.
6. Duller P, van de Kerkhof PCM. The impact of methotrexate on psychoorganic functioning. *Br J Dermatol* 1985; 113: 503–4.

Effects on the nervous system. Methotrexate has a cumulative toxic effect on the nervous system, and generalised and focal neurotoxic reactions are associated with intrathecal and high-dose intravenous use.[1] An immediate, usually transient, effect occurring within a day of high intravenous doses can cause nausea and vomiting, headache, somnolence, lethargy, confusion, disorientation, seizures, and increased intracranial pressure. Reversible acute meningitis can follow intrathecal use, with similar results.[1] Aseptic meningitis has also been reported after intramuscular methotrexate.[2] Spinal cord myelopathy resulting in transient or permanent paraplegia has also followed intrathecal methotrexate use, especially if other neurotoxic treatments have also been used. A subacute form of toxic reaction can occur up to several weeks after treatment. It is usually transient and characterised by seizures, varying degrees of paresis, aphasia, anaesthesia, blurred vision, and pseudobulbar palsy. A more delayed syndrome occurs weeks to months after treatment and is of variable severity, but can progress to lethargy, seizures, spasticity, paresis, drooling, and dementia. This condition is characterised by leukoencephalopathy and chronic calcification of brain tissue. It is dose-related, and more severe if the patient has also received radiotherapy.[1]

See also Effects on Mental Function, above.

1. Shuper A, *et al.* Methotrexate treatment protocols and the central nervous system: significant cure with significant neurotoxicity. *J Child Neurol* 2000; 15: 573–80.
2. Hawboldt J, Bader M. Intramuscular methotrexate-induced aseptic meningitis. *Ann Pharmacother* 2007; 41: 1906–11.

Effects on the skin. There are rare reports[1,2] of painful erythema of the hands and feet, particularly the fingertips, with progression to blistering and desquamation (palmar-plantar erythrodysesthesia syndrome, p. 730.1) after the use of high-dose intravenous methotrexate. Purpuric skin lesions due to vasculitis have occurred after both high-dose[3] and low-dose[4,5] methotrexate. Accelerated rheumatoid nodulosis has been reported[6,7] after the use of methotrexate in patients with rheumatoid arthritis. Erosion of psoriatic plaques, accompanied by pain and erythema, has been seen[8,9] after low-dose methotrexate therapy; blistering and necrosis consistent with toxic epidermal necrolysis has occurred.[8] Possible exacerbation of a photosensitivity reaction to ciprofloxacin has been described,[10] and reactivation of sunburn has also been reported[11] in several cases where methotrexate was given within 2 to 5 days after the initial sunburn.

1. Doyle LA, *et al.* Erythema and desquamation after high-dose methotrexate. *Ann Intern Med* 1983; 98: 611–12.
2. Millot F, *et al.* Acral erythema in children receiving high-dose methotrexate. *Pediatr Dermatol* 1999; 16: 398–400.
3. Navarro M, *et al.* Leukocytoclastic vasculitis after high-dose methotrexate. *Ann Intern Med* 1986; 105: 471–2.
4. Marks CR, *et al.* Small-vessel vasculitis and methotrexate. *Ann Intern Med* 1984; 100: 916.
5. Torner O, *et al.* Methotrexate related cutaneous vasculitis. *Clin Rheumatol* 1997; 16: 108–9.
6. Williams FM, *et al.* Accelerated cutaneous nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. *J Am Acad Dermatol* 1998; 39: 359–62.
7. Filosa G, *et al.* Accelerated nodulosis during methotrexate therapy for refractory rheumatoid arthritis: a case report. *Adv Exp Med Biol* 1999; 455: 521–4.
8. Reed KM, Sober AJ. Methotrexate-induced necrolysis. *J Am Acad Dermatol* 1983; 8: 677–9.
9. Pearce HP, Wilson BB. Erosion of psoriatic plaques: an early sign of methotrexate toxicity. *J Am Acad Dermatol* 1996; 35: 835–8.
10. Nedorost ST, *et al.* Drug-induced photosensitivity reaction. *Arch Dermatol* 1989; 125: 433–4.
11. Khan AJ, *et al.* Methotrexate and the photodermatitis reactivation reaction: a case report and review of the literature. *Cutis* 2000; 66: 379–82.

Hypersensitivity. There are rare reports of anaphylactic reactions in patients given methotrexate. Reactions have usually occurred in patients who had previous exposure to methotrexate, but there are also reports of reaction during initial exposure to high-dose intravenous therapy.[1] Serious reactions have also been described after low-dose intravenous[2] and intrathecal[3] use. Desensitisation may be possible.[4] A 9-year-old patient with osteosarcoma who had previously tolerated 5 courses of high-dose methotrexate (12 g/m² over 4 hours) developed urticaria, repeated on rechallenge, but no oedema or respiratory symptoms during the sixth. She was successfully managed by premedication with diphenhydramine and corticosteroids, followed by 1/1000 of the total methotrexate dose over 90 minutes, 1/100 over 90 minutes, 1/10 over 6 hours, and the remainder over 18 hours.[4]

1. Alkins SA, *et al.* Anaphylactoid reactions to methotrexate. *Cancer* 1996; 77: 2123–6.
2. Cohn JR, *et al.* Systemic anaphylaxis from low dose methotrexate. *Ann Allergy* 1993; 70: 384–5.
3. Devecioğlu Ö, *et al.* Systemic near-fatal anaphylactic reaction after intrathecal methotrexate administration. *Med Pediatr Oncol* 2000; 34: 151–2.
4. Bouchireb K, *et al.* Management and successful desensitization in methotrexate-induced anaphylaxis. *Pediatr Blood Cancer* 2009; 52: 295–7.

Treatment of Adverse Effects

For general guidelines, see p. 730.2.

Folinic acid neutralises the immediate toxic effects of methotrexate on the bone marrow. It is given as sodium or calcium folinate orally, intramuscularly, by intravenous bolus injection, or by infusion. When overdosage is suspected the dose of folinate should be at least as high as that of methotrexate and should be given as soon as possible; further doses are given as required preferably based on serum-methotrexate concentrations. Folinate should be continued until serum-methotrexate concentrations fall below 0.05 to 0.1 micromol/litre, which may necessitate prolonged treatment in patients with delayed elimination. Other dosage regimens, given intramuscularly or orally, may be appropriate for more modest toxicity associated with conventional doses of methotrexate. For details, see under Folinic Acid, p. 2067.1. After intrathecal overdose, the drainage of 30 mL of CSF within 15 minutes removes about 95% of methotrexate; but methotrexate rapidly enters the systemic circulation and folinic acid treatment should be based on serum-methotrexate concentrations.

Folinic acid is usually given with high-dose methotrexate regimens to prevent damage to normal tissue ('folinic acid rescue') and this is discussed in Uses and Administration, p. 822.3.

An adequate flow of alkaline urine should be maintained after high doses of methotrexate to prevent precipitation of methotrexate or its metabolites in the renal tubules; in addition to adequate hydration, the use of acetazolamide or sodium bicarbonate is recommended.

The recombinant glutamate carboxypeptidase glucarpidase (p. 1555.1) is used in addition to folinic acid in the management of methotrexate toxicity. It rapidly hydrolyses methotrexate to its inactive metabolites 4-deoxy-4-amino-N^{10}-methylpteroic acid and glutamate which are metabo-

lised by the liver thus providing a non-renal pathway for methotrexate elimination.

Desensitisation. For mention of desensitisation to the drug in a patient with methotrexate-induced anaphylaxis see Hypersensitivity, p. 826.3.

Folate supplementation. A discussion of the selection of the appropriate route for folinic acid rescue with *high-dose methotrexate* regimens.[1] The general objective is to give folinic acid (as folinate) at doses that maintain plasma concentrations of reduced folates at a level equivalent to or greater than the plasma-methotrexate concentration. In any clinical situation suggesting impaired gastrointestinal function calcium folinate should be given by injection. Although absorption of intramuscular doses is relatively complete and rapid the intravenous route is usually preferable for other reasons, such as a reduced risk of bleeding at injection sites. In the absence of impaired gastrointestinal function, and where there are no concomitant risk factors for methotrexate toxicity, the oral route may be used provided that methotrexate concentrations are expected to be less than 1 micromol/litre. For very high dose methotrexate regimens it is generally appropriate to begin folinic acid rescue intravenously to ensure adequate initial therapy, but the majority of the dosage regimen can generally be given orally.

There is no consensus on the use of folate supplementation in patients taking *low-dose methotrexate*,[2] although reviews have concluded that supplementation with either folic or folinic acid reduces adverse effects related to the liver function tests, gastrointestinal tract and oral mucosa.[2,3] However, a study found that while folate supplementation reduced the incidence of methotrexate-related liver enzyme elevations, it had no effect on incidence, severity, or duration of other adverse effects.[4] Effects of folate supplementation on the efficacy of methotrexate have been inconclusive;[3] some consider the effect to be small.[4,5] There is some suggestion that folinic acid, but not folic acid, may reduce the efficacy of methotrexate.[2] However, an analysis[6] of two studies found a reduction in efficacy with folic acid supplementation. The issue of supplementation remains controversial, with some recommending routine folic acid,[2,5,7] and others suggesting that folate only be added when demand for folate increases, such as during infection or with antibacterial use.[8]

1. Rodman JH, Crom WR. Selecting an administration route for leucovorin rescue. *Clin Pharm* 1989; 8: 617, 621.
2. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)* 2004; 43: 267–71.
3. Ortiz Z, *et al.* Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 1999 (accessed 08/02/06).
4. van Ede AE, *et al.* Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight-week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001; 44: 1515–24.
5. Griffith SM, *et al.* Do patients with rheumatoid arthritis established on methotrexate and folic acid 5 mg daily need to continue folic acid supplements long term? *Rheumatology (Oxford)* 2000; 39: 1102–9.
6. Khanna D, *et al.* Reduction of the efficacy of methotrexate by the use of folic acid: post hoc analysis from two randomized controlled studies. *Arthritis Rheum* 2005; 52: 3030–8.
7. Hornung N, *et al.* Folate, homocysteine, and cobalamin status in patients with rheumatoid arthritis treated with methotrexate, and the effect of low dose folic acid supplement. *J Rheumatol* 2004; 31: 2374–81.
8. Manna R, *et al.* Folic acid supplementation during methotrexate treatment: nonsense? *Rheumatology (Oxford)* 2005; 44: 563–4.

Other drugs. Pretreatment with fluorouracil is reported to reduce the toxicity of methotrexate sufficiently to permit high-dose methotrexate without the need for folinic acid rescue.[1] Methotrexate has also been given before fluorouracil to modulate its activity (see Administration, in Fluorouracil, p. 796.1).

The acute neurotoxic effects of methotrexate have been reported to be relieved by intravenous aminophylline or oral theophylline in some children.[2]

For reference to the inefficacy of diltiazem in preventing the nephrotoxicity due to high-dose methotrexate, see Kidney Disorders, under Diltiazem p. 1360.1.

For evidence that colestyramine might decrease serum-methotrexate concentrations, see Interactions, p. 828.1. For reference to the use of glucarpidase to manage methotrexate-induced renal toxicity see Effects on the Kidneys, p. 825.2.

1. White RM. 5-Fluorouracil modulates the toxicity of high dose methotrexate. *J Clin Pharmacol* 1995; 35: 1156–65.
2. Bernini JC, *et al.* Aminophylline for methotrexate-induced neurotoxicity. *Lancet* 1995; 345: 544–7.

Precautions

For general discussions see p. 732.2.

Methotrexate should be used with great care in patients with bone-marrow, hepatic, or renal impairment. It should also be used cautiously in ulcerative disorders of the gastrointestinal tract, and in the elderly and the very young. Pleural or ascitic effusions may act as a depot for methotrexate and produce enhanced toxicity, and should be drained before treatment.

Regular monitoring of haematological, renal, and hepatic function, and gastrointestinal toxicity is advisable. Treatment should be interrupted if myelosuppression, diarrhoea, or stomatitis occur. Dyspnoea or cough may be a sign of pulmonary toxicity and patients should be advised to contact their doctor if they develop these symptoms. Treatment should be withdrawn and the patient investigated to exclude infection. If methotrexate-induced lung disease is suspected corticosteroid therapy may be started and further treatment with methotrexate should not be given. Patients or their carers should report any symptoms or signs suggestive of infection, especially sore throat.

In patients receiving **low-dose methotrexate for psoriasis or rheumatoid arthritis** full blood counts and renal and liver function tests should be performed before starting treatment and repeated regularly thereafter (for discussion of guidelines for monitoring in these patients see Effects on the Liver, p. 825.3). Treatment should be interrupted if myelosuppression, stomatitis, or any abnormality of liver function is detected. Methotrexate should not be used to treat rheumatoid arthritis or psoriasis in patients with alcoholism, liver disease or persistent abnormal liver function tests, or in those with significant renal impairment, immunodeficiency, or blood disorders. A test dose has been recommended. Severe or fatal toxicity has resulted from overdosage when doses intended for a low-dose weekly regimen were mistakenly taken daily, and particular care should be taken to avoid confusion about dosage frequency.

With **high-dose regimens**, serum concentrations of methotrexate should be monitored. Maintenance of an adequate flow of alkaline urine is essential (see Treatment of Adverse Effects, p. 826.3).

Methotrexate is a potent teratogen and should be avoided in **pregnancy**. While some licensed product information includes advice that conception should be avoided for at least 6 months after therapy some considers 3 months adequate.

Blood products. Enhanced toxicity was seen in 2 of 14 patients receiving methotrexate by 24-hour infusion when packed red cells were transfused immediately after the methotrexate infusion.[1] Erythrocytes act as reservoirs for methotrexate and probably resulted in the prolonged high serum-methotrexate concentrations seen in these patients. Great care should be exercised whenever packed red blood cells and methotrexate are given concurrently.

1. Yap AKL, *et al.* Methotrexate toxicity coincident with packed red cell transfusions. *Lancet* 1986; ii: 641.

Breast feeding. Methotrexate has been detected in breast milk in low concentrations.[1] The American Academy of Pediatrics considers[2] that methotrexate may interfere with cellular metabolism, causing neutropenia and possibly immunosuppression in the nursing infant, and has unknown effects on growth, and an association with carcinogenesis.

1. Johns DG, *et al.* Secretion of methotrexate into human milk. *Am J Obstet Gynecol* 1972; 112: 978–80.
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 30/06/04)

Handling and disposal. Care should be taken to avoid inhalation of methotrexate or contact with skin and mucous membranes. It may cause irritation of the eyes.

Methods have been published for the oxidative destruction of methotrexate *wastes* using potassium permanganate and sulfuric acid, aqueous alkaline potassium permanganate, or sodium hypochlorite.[1] The first method may also be used for dichloromethotrexate. Residues produced by the degradation of methotrexate by these methods showed no mutagenicity *in vitro*.

Urine and faeces produced for up to 72 hours and 7 days respectively after a dose of methotrexate should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.* eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1983; 235: 289–91.

Hepatitis. Reactivation of hepatitis B infection, with the development of hepatocellular necrosis and fulminant hepatic failure requiring liver transplantation, developed on stopping low-dose methotrexate therapy in a patient with rheumatoid arthritis who was also an asymptomatic chronic hepatitis B carrier.[1] It was suggested that all patients being considered for low-dose methotrexate therapy should be screened for the presence of serum HBsAg before beginning therapy. However, a similar case of fatal reactivation has been reported[2] in a patient negative for HBsAg.

1. Flowers MA, *et al.* Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990; 112: 381–2.
2. Gwak GY, *et al.* Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. *Clin Exp Rheumatol* 2007; 25: 888–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methotrexate 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 29/09/11)

Pregnancy. The use of methotrexate in pregnancy is contra-indicated (see Precautions, above). There is a report of a healthy infant born to a woman who was treated with *intrathecal* methotrexate, see Pregnancy, under Teniposide, p. 867.2.

PUVA. Of a total of 94 patients with psoriasis and 38 with mycosis fungoides treated with PUVA therapy (methoxsalen and ultraviolet light) 2 of the former also given methotrexate developed skin cancers.[1] It was suggested that the combination of methotrexate and PUVA may be synergistic in inducing cutaneous malignancy. However, in a cohort study[2] of patients with severe psoriasis, exposure to methotrexate for at least 4 years was associated with an increase in risk of squamous cell carcinoma but not basal cell carcinoma, and no interaction was found between methotrexate and PUVA.

1. Fitzsimons CP, *et al.* Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. *Lancet* 1983; i: 235–6.
2. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; 73: 2759–64.

Radiation. Analysis of neutrophil counts for 18 months in children with acute lymphoblastic leukaemia showed that methotrexate-induced neutropenia was significantly greater in patients given CNS irradiation and was considered to have contributed to 3 of 5 deaths during remission.[1]

For the effect of cranial irradiation and intrathecal methotrexate on intellectual development, see Effects on Mental Function, p. 826.2.

1. Report to the Medical Research Council of the Working Party on Leukaemia in Childhood. Analysis of treatment in childhood leukaemia: I—predisposition to methotrexate-induced neutropenia after craniospinal irradiation. *BMJ* 1975; 3: 563–6.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. The effects of methotrexate may be enhanced by drugs that decrease its renal excretion, such as NSAIDs and salicylates, probenecid, and some penicillins. Fatal toxicity has occurred in patients given NSAIDs with methotrexate (see p. 828.2). Severe toxicity has occurred rarely when co-trimoxazole or trimethoprim was given with methotrexate. Use with other myelotoxic, hepatotoxic, or nephrotoxic agents may increase the risk of toxicity. Folic acid and its derivatives may decrease the efficacy of methotrexate, although they are often used together to reduce methotrexate toxicity (see Treatment of Adverse Effects, p. 826.3).

Animal studies suggested methotrexate toxicity may be increased by chloramphenicol, para-aminobenzoic acid, and hypoglycaemics, but there does not appear to be any evidence of this clinically.

Antibacterials. The oral *aminoglycosides* neomycin[1] and paromomycin[2] have been reported to reduce the gastrointestinal absorption of methotrexate. Various *penicillins* have been reported to markedly decrease the clearance of methotrexate given intravenously for treatment of neoplasms,[3-6] although *ceftazidime* may not.[4] There have also been a few reports of penicillins possibly exacerbating the toxicity of low-dose methotrexate in patients being treated for psoriasis or rheumatoid arthritis, but a small study found that although fludoxacillin decreased methotrexate clearance slightly, this was not clinically significant.[7] Methotrexate toxicity has been reported in a patient receiving low-dose methotrexate after a course of *tetracycline*.[8] In a patient receiving high-dose methotrexate, giving *doxycycline* before the eleventh cycle was believed to be responsible for an exacerbation of methotrexate toxicity, with raised plasma concentrations and reduced clearance of methotrexate.[9] *Sulfonamides* such as sulfafurazole and sulfamethoxazole may displace methotrexate from binding sites[10] and reduce renal clearance.[11] Megaloblastic pancytopenia has been reported on several occasions when methotrexate was given with *co-trimoxazole*[12-14] or *trimethoprim*;[13,15,16] possible mechanisms involved include an addi-

tive antifolate effect, in addition to the effect of the sulfamethoxazole component in the case of co-trimoxazole.

1. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; 3: 1–13.
2. Cohen MH, *et al.* Effect of oral prophylactic broad spectrum nonabsorbable antibiotics on the gastrointestinal absorption of nutrients and methotrexate in small cell bronchogenic carcinoma patients. *Cancer* 1976; 38: 1556.
3. Bloom EJ, *et al.* Delayed clearance (CL) of methotrexate (MTX) associated with antibiotics and antiinflammatory agents. *Clin Res* 1986; 34: 560A.
4. Yamamoto K, *et al.* Delayed elimination of methotrexate associated with piperacillin administration. *Ann Pharmacother* 1997; 31: 1261–2.
5. Dean R, *et al.* Possible methotrexate-mezlocillin interaction. *Am J Pediatr Hematol Oncol* 1992; 14: 88–9.
6. Ronchera CL, *et al.* Pharmacokinetic interaction between high-dose methotrexate and amoxycillin. *Ther Drug Monit* 1993; 15: 375–9.
7. Herrick AL, *et al.* Lack of interaction between flucloxacillin and methotrexate in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1996; 41: 223–7.
8. Turck M. Successful psoriasis treatment then sudden 'cytotoxicity'. *Hosp Pract* 1984; 19: 175–6.
9. Tortajada-Ituren JJ, *et al.* High-dose methotrexate—doxycycline interaction. *Ann Pharmacother* 1999; 33: 804–8.
10. Liegler DG, *et al.* The effect of organic acids on renal clearance of methotrexate in man. *Clin Pharmacol Ther* 1969; 10: 849–57.
11. Ferrazzini G, *et al.* Interaction between trimethoprim-sulfamethoxazole and methotrexate in children with leukemia. *J Pediatr* 1990; 117: 823–6.
12. Liddle BJ, Marsden JR. Drug interactions with methotrexate. *Br J Dermatol* 1989; 120: 582–3.
13. Jeurissen ME, *et al.* Pancytopenia and methotrexate with trimethoprim-sulfamethoxazole. *Ann Intern Med* 1989; 111: 261.
14. Groenendal H, Rampen FHJ. Methotrexate and trimethoprim–sulphamethoxazole—a potentially hazardous combination. *Clin Exp Dermatol* 1990; 15: 358–60.
15. Steuer A, Gumpel JM. Methotrexate and trimethoprim: a fatal interaction. *Br J Rheumatol* 1998; 37: 105–6.
16. Govert JA, *et al.* Pancytopenia from using trimethoprim and methotrexate. *Ann Intern Med* 1992; 117: 877–8.

Antiepileptics. For mention of the reduction in serum-*valproate* concentration produced by methotrexate see p. 557.3.

Antineoplastics. Enhanced methotrexate toxicity might be expected with nephrotoxic agents (such as *cisplatin*) that can reduce methotrexate excretion by impairing renal function. Sequential use of methotrexate and *fluorouracil* may result in synergistic enhancement of effect (see Administration, in Fluorouracil, p. 796.1), and equally, fluorouracil before methotrexate may reduce its toxicity (see Other Drugs, under Treatment of Adverse Effects, p. 827.1), but if *asparaginase* (p. 744.3) is given before methotrexate the cytotoxic effect of methotrexate may be reduced.

Methotrexate may increase the bioavailability of *mercaptopurine*, probably by interference with first-pass metabolism (see p. 821.3).

Colestyramine. Serum-methotrexate concentrations were markedly reduced in 3 patients given colestyramine to treat methotrexate toxicity.[1,2] Colestyramine appears to bind methotrexate and reduce its enterohepatic recirculation.

1. Ertmann R, Landbeck G. Effect of oral cholestyramine on the elimination of high-dose methotrexate. *J Cancer Res Clin Oncol* 1985; 110: 48–50.
2. Shinozaki T, *et al.* Successful rescue by oral cholestyramine of a patient with methotrexate nephrotoxicity: nonrenal excretion of serum methotrexate. *Med Pediatr Oncol* 2000; 34: 226–8.

Dantrolene. Dantrolene was considered to have caused methotrexate toxicity in a patient given high-dose methotrexate.[1]

1. André N, *et al.* Can dantrolene contribute to methotrexate toxicity? *Ann Pharmacother* 2006; 40: 1695–6.

Gastrointestinal drugs. Elevated serum concentrations of methotrexate were reported when it was given to 2 patients also receiving *omeprazole*.[1,2] The effect was not seen with subsequent cycles of methotrexate therapy once omeprazole had been stopped. In another case[3] however, raised methotrexate concentrations were thought to be due to an interaction with omeprazole, but were identical during a second cycle after omeprazole had been withdrawn. Severe generalised myalgia and bone pain were reported in a patient who received methotrexate and *pantoprazole*.[4] The same reaction occurred on rechallenge with the combination, but not with methotrexate alone. Although methotrexate concentrations were unchanged, concentrations of the metabolite 7-hydroxymethotrexate were raised suggesting an interaction with its renal elimination. *Lansoprazole* has been reported not to affect the pharmacokinetics of methotrexate.[5] A Japanese study found that use of proton pump inhibitors (including omeprazole, lansoprazole, and *rabeprazole*) was associated with delayed plasma elimination of methotrexate in patients given high-dose methotrexate therapy.[6]

1. Reid T, *et al.* Impact of omeprazole on the plasma clearance of methotrexate. *Cancer Chemother Pharmacol* 1993; 33: 82–4.
2. Beorlegui B, *et al.* Potential interaction between methotrexate and omeprazole. *Ann Pharmacother* 2000; 34: 1024–7.
3. Whelan J, *et al.* Omeprazole does not alter plasma methotrexate clearance. *Cancer Chemother Pharmacol* 1999; 44: 88–9.
4. Tröger U, *et al.* Severe myalgia from an interaction between treatments with pantoprazole and methotrexate. *BMJ* 2002; 324: 1497.
5. Vaklily M, *et al.* Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol* 2005; 45: 1179–86.
6. Suzuki K, *et al.* Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. *Br J Clin Pharmacol* 2009; 67: 44–9.

Glutamine. Drugs with the potential to lower urinary pH, such as glutamine, may decrease clearance of methotrexate and cause it to precipitate in the renal tubules. Acute nephrotoxicity[1] followed failure to adjust urinary pH during high-dose methotrexate infusion in a patient also taking glutamine. Urinary pH should be continually checked in patients receiving both drugs and adjusted with bicarbonate if necessary.

1. Marín Pozo JF, *et al.* Hazards of concomitant administration of methotrexate and glutamine. *Am J Health-Syst Pharm* 2010; 67: 601–2.

Immunosuppressants. For reports of enhanced toxicity with *ciclosporin* in patients who have received methotrexate see p. 1957.2.

Leflunomide. For a report of the effect of methotrexate in patients receiving leflunomide, see p. 82.3.

Nitrous oxide. Severe unpredictable myelosuppression and stomatitis have been attributed to the use of nitrous oxide anaesthesia in patients receiving methotrexate, potentiating the effects of methotrexate on folate metabolism.[1] The effect could be reduced by the use of folinic acid rescue.

1. Goldhirsch A, *et al.* Methotrexate/nitrous-oxide toxic interaction in perioperative chemotherapy for early breast cancer. *Lancet* 1987; ii: 151.

NSAIDs. Severe, and in some cases fatal, aggravation of methotrexate toxicity has been reported when it was given with various NSAIDs including *aspirin* and other *salicylates*,[1,2] *azapropazone*,[3] *diclofenac*,[4] *indometacin*,[4,5] and *ketoprofen*.[6] The mechanism is uncertain but may include both displacement of methotrexate from protein-binding sites or an effect of NSAIDs on the kidney resulting in reduced methotrexate excretion.[6,7] *Naproxen* has been reported not to affect the pharmacokinetics of methotrexate,[8,9] but a fatal interaction has nonetheless been reported.[10] Despite the risks, some commentators have pointed out that methotrexate and NSAIDs are frequently used together in the treatment of rheumatoid arthritis,[11,12] and that provided this is done with caution, in low doses, and patients are appropriately monitored and cautioned to avoid additional 'over-the-counter' analgesics, such combinations need not be contra-indicated. A study in patients receiving low-dose methotrexate for rheumatoid arthritis suggested that *flurbiprofen*, *ketoprofen*, or *piroxicam* did not influence methotrexate clearance.[13] A case of methotrexate toxicity has nevertheless been described[14] in an elderly woman when flurbiprofen was added to low-dose methotrexate therapy.

Manufacturers of methotrexate generally contra-indicate the use of NSAIDs with high-dose methotrexate.

1. Baker H. Intermittent high dose oral methotrexate therapy in psoriasis. *Br J Dermatol* 1970; 82: 65–9.
2. Zuik M, Mandel MA. Methotrexate-salicylate interaction: a clinical and experimental study. *Surg Forum* 1975; 26: 567–9.
3. Daly HM, *et al.* Methotrexate toxicity precipitated by azapropazone. *Br J Dermatol* 1986; 114: 733–5.
4. Gabrielli A, *et al.* Methotrexate and nonsteroidal anti-inflammatory drugs. *BMJ* 1987; 294: 776.
5. Maiche AG. Acute renal failure due to concomitant action of methotrexate and indomethacin. *Lancet* 1986; i: 1390.
6. Thyss A, *et al.* Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. *Lancet* 1986; i: 256–8.
7. Furst DE, *et al.* Effect of aspirin and sulindac on methotrexate clearance. *J Pharm Sci* 1990; 79: 782–6.
8. Stewart CF, *et al.* Coadministration of naproxen and low-dose methotrexate in patients with rheumatoid arthritis. *Clin Pharmacol Ther* 1990; 47: 540–6.
9. Vaklily M, *et al.* Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol* 2005; 45: 1179–86.
10. Singh RR, *et al.* Fatal interaction between methotrexate and naproxen. *Lancet* 1986; i: 1390.
11. Tully M. NSAIDs. *Pharm J* 1991; 247: 746.
12. Zachariae H. Methotrexate and nonsteroidal anti-inflammatory drugs. *Br J Dermatol* 1992; 126: 95.
13. Tracy TS, *et al.* Methotrexate disposition following concomitant administration of ketoprofen, piroxicam and flurbiprofen in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1994; 37: 453–6.
14. Frenia ML, Long KS. Methotrexate and nonsteroidal antiinflammatory drug interactions. *Ann Pharmacother* 1992; 26: 234–7.

Probenecid. Probenecid can produce two- to fourfold increases in serum-methotrexate concentrations,[1-3] presumably by inhibiting renal excretion of methotrexate. Although probenecid has been shown to reduce protein binding of methotrexate,[4] usual doses of probenecid are unlikely to significantly affect methotrexate elimination by this mechanism. A woman receiving low-dose weekly methotrexate for rheumatoid arthritis developed severe pancytopenia when probenecid was given for asymptomatic hyperuricaemia.[5]

1. Aherne GW, *et al.* Prolongation and enhancement of serum methotrexate concentrations by probenecid. *BMJ* 1978; 1: 1097–9.
2. Howell SB, *et al.* Effect of probenecid on cerebrospinal fluid methotrexate kinetics. *Clin Pharmacol Ther* 1979; 26: 641–6.
3. Lilly MB, Omura GA. Clinical pharmacology of oral intermediate-dose methotrexate with or without probenecid. *Cancer Chemother Pharmacol* 1985; 15: 220–2.
4. Paxton JW. Interaction of probenecid with the protein binding of methotrexate. *Pharmacology* 1984; 28: 86–9.
5. Basin KS, *et al.* Severe pancytopenia in a patient taking low dose methotrexate and probenecid. *J Rheumatol* 1991; 18: 609–10.

Retinoids. An increased risk of hepatotoxicity has been reported when methotrexate and *etretinate* are given together,[1] possibly due to increased plasma concentrations of methotrexate.[2,3]

1. Zachariae H. Dangers of methotrexate/etretinate combination therapy. *Lancet* 1988; i: 422.
2. Harrison PV, *et al.* Methotrexate and retinoids in combination for psoriasis. *Lancet* 1987; ii: 512.
3. Larsen FG, *et al.* Interaction of etretinate with methotrexate pharmacokinetics in psoriatic patients. *J Clin Pharmacol* 1990; 30: 802–7.

Xanthines. For mention of the effect of methotrexate on the clearance of theophylline, see Antineoplastics, under Interactions of Theophylline, p. 1235.2.

Pharmacokinetics

When given in low doses, methotrexate is rapidly absorbed from the gastrointestinal tract, but higher doses are less well absorbed. It is also rapidly and completely absorbed after intramuscular doses. Peak serum concentrations occur to 2 hours after an oral dose, and 30 to 60 minutes after an intramuscular one.

Methotrexate is distributed to tissues and extracellular fluid with a steady-state volume of distribution of 0.4 to 0.8 litres/kg; it penetrates ascitic fluid and effusions, which may act as a depot and thus enhance toxicity. Clearance from plasma is reported to be triphasic, with a terminal elimination half-life of between 3 and 10 hours after doses less than 30 mg/m^2 or 8 to 15 hours after high-dose parenteral therapy. It is about 50% bound to plasma protein. Methotrexate enters the cells in part by an active transport mechanism and is bound as polyglutamate conjugates: bound drug may remain in the body for several months, particularly in the liver.

Only small or insignificant amounts cross the blood-brain barrier and enter the CSF after oral or parenteral doses, although this may be increased by giving higher doses; however, after intrathecal doses there is significant passage into the systemic circulation.

Methotrexate has been detected in very small amounts in saliva and breast milk. It crosses the placenta.

Methotrexate does not appear to undergo significant metabolism at low doses; after high-dose therapy the 7-hydroxy metabolite has been detected. Methotrexate may be partly metabolised by the intestinal flora after oral doses. It is excreted mainly in the urine, by glomerular filtration and active tubular secretion. Small amounts are excreted in bile and found in faeces; there is some evidence for enterohepatic recirculation.

Considerable interindividual variation exists in the pharmacokinetics of methotrexate: those patients in whom clearance is delayed are at increased risk of toxicity.

References.
1. Shen DD, Azarnoff DL. Clinical pharmacokinetics of methotrexate. *Clin Pharmacokinet* 1978; 3: 1–13.
2. Balls FM, *et al.* Clinical pharmacokinetics of commonly used anticancer drugs. *Clin Pharmacokinet* 1983; 8: 202–32.
3. Wang Y-M, Fujimoto T. Clinical pharmacokinetics of methotrexate in children. *Clin Pharmacokinet* 1984; 9: 335–48.
4. Witter FR. Clinical pharmacokinetics in the treatment of rheumatoid arthritis in pregnancy. *Clin Pharmacokinet* 1993; 25: 444–9.
5. Bannwarth B, *et al.* Clinical pharmacokinetics of low-dose pulse methotrexate in rheumatoid arthritis. *Clin Pharmacokinet* 1996; 30: 19–210.
6. Chládek J, *et al.* Pharmacokinetics and pharmacodynamics of low-dose methotrexate in the treatment of psoriasis. *Br J Clin Pharmacol* 2002; 54: 147–56.
7. Grim J, *et al.* Pharmacokinetics and pharmacodynamics of methotrexate in non-neoplastic diseases. *Clin Pharmacokinet* 2003; 42: 139–51.
8. Aumente D, *et al.* Population pharmacokinetics of high-dose methotrexate in children with acute lymphoblastic leukaemia. *Clin Pharmacokinet* 2006; 45: 1227–38.
9. Thompson PA, *et al.* Methotrexate pharmacokinetics in infants with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* 2007; 59: 847–53.
10. Rider SL, *et al.* The pharmacogenetics of methotrexate. *Rheumatology (Oxford)* 2007; 46: 1520–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Artrait; Ervemin; Metodik; Trixate; Xantromid; *Austral.*: Ledertrexate†; Methoblastin; *Austria*: Ebetrexat; Metoject†; *Belg.*: Emthexate; Ledertrexate; *Braz.*: Biometrox; Emthexate†; Fauldmetro; Hytas; Metrexate; Miantrex; Reutrexato; Tecnomet; Tevametho; *Canad.*: Metoject; *Chile*: Metoject; Trixilem; *China*: Meisusheng (美素生) Midu (密都); *Cz.*: Metoject; Trexan; *Denm.*: Ebetrex; Emthex

ate; Metex; Metoject†; *Fin.*: Ebetrex; Emthexat†; Metoject; Trexan; *Fr.*: Imeth; Ledertrexate; Metoject; Novatrex; *Ger.*: Bendatrexat†; Lantarel; Metex; MTX; Neotrexat†; *Gr.*: Emthexate; Methobion; Methoblastin; Metoject; *Hung.*: Metoject; Trexan; *India*: Alltrex; Biotrexate; Caditrex; Dermatrex; Dermotrex; Folitrax; Hi-Trex; Imutrex; Merex; Methocel; Methocip; Methorex; Metorex; Metrex; Mexate; Neotrexate; Oncotrex; Onotrex; *Indon.*: Emthexate; *Irl.*: Metoject; *Israel*: Abitrexate; Metoject; *Ital.*: Reumaflex; Sactiva; Securact; *Jpn*: Metolate; *Malaysia*: Emthexate; *Mex.*: Atrexel; Ifamet†; Ledertrexate; Medsatrexate; Otaxem; Texate; Trixilem; *Neth.*: Ebetrexat†; Emthexate; Metoject; *Norw.*: Ebetrex; Metex; Metoject†; *NZ*: Emthexate; Methoblastin; *Philipp.*: Alltrex; Emthexate; Hextrate†; Methobax†; Pterin; Zexate; *Pol.*: Metex; Metoject; Trexan; *Port.*: Fauldexato; Ledertrexato; Metex; Metoject; *Rus.*: Metoject (Методжект); Zexat (Зексат); *S.Afr.*: Abitrexate; Emthexate†; Methacor; Methacor; *Singapore*: Abitrexate; Ebetrexat; Emthexate; MTX; *Spain*: Bertanel; Emthexate†; Metoject; *Swed.*: Ebetrex; Metoject; Metotab; *Switz.*: Metoject; *Thai.*: Abitrexate; Alltrex; Emthexate; Metrex; Neometho; Onkomet; Trixilem; Zexate†; *Turk.*: Emthexate; Metoart; Metoject; MTX; Trexan; *UK*: Ebetrex†; Matrex; Maxtrex; Metoject; *USA*: Otrexup; Rheumatrex; Trexall; *Venez.*: Zexate.

Pharmacopoeial Preparations

BP 2014: Methotrexate Injection; Methotrexate Tablets;
USP 36: Methotrexate for Injection; Methotrexate Injection; Methotrexate Tablets.

2-Methoxyoestradiol

2-ME2; 2-Methoxyestradiol; NSC-659853; 2-Метоксиэстрадиол.
(17β)-2-Methoxyestra-1,3,5(10)-triene-3,17-diol.
$C_{19}H_{26}O_3$=302.4
CAS — 362-07-2.
UNII — 6I2QW73SR5.

NOTE. The names Panzem and PulmoLAR have been used as trade marks for 2-methoxyoestradiol.

Profile

2-Methoxyoestradiol is a metabolite of oestradiol (p. 2271.1). It does not have direct oestrogenic activity, but works through multiple cellular pathways to produce antineoplastic effects, including inhibition of angiogenesis and induction of apoptosis. 2-Methoxyoestradiol is under investigation in the treatment of various diseases, including glioblastoma, multiple myeloma, carcinoid tumours, as well as ovarian, prostate, breast, and renal cell cancers. It is also under investigation for pulmonary arterial hypertension and rheumatoid arthritis.

Midostaurin *(USAN, rINN)*

Benzoylstaurosporine; CGP-41251; Midostaurina; Midostaurine; Midostaurinum; PKC-412; Мидостаурин.
N-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-Hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3′,2′,1′-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide.
$C_{35}H_{30}N_4O_4$=570.6
CAS — 120685-11-2.
UNII — ID912S5VON.

Profile

Midostaurin is a multikinase inhibitor effective against tyrosine kinase and protein kinase C, and those of receptors for growth factors including vascular endothelial growth factor and platelet-derived growth factor. It is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndrome, and systemic mastocytosis.

Mifamurtide *(BAN, rINN)*

Mifamurtida; Mifamurtidum; MTP-PE; Muramyl Tripeptide Phosphatidyl Ethanolamine; Muramyl Tripeptide Phosphatidyl Monoethanolamine; Мифамуртид.
2-[(*N*-[(2*R*)-[(2-Acetamido-2,3-dideoxy-D-glucopyranos-3-yl)oxy]propanoyl]-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexadecanoyloxy)propyl hydrogen phosphate.
$C_{59}H_{109}N_6O_{19}P$=1237.5
CAS — 83461-56-7.
ATC — L03AX15.
ATC Vet — QL03AX15.
UNII — 1LM890Q4FY.

NOTE. The name Mifamurtide has been used for both the base and the sodium salt. The name Junovan has been used as a trade mark for mifamurtide.

Mifamurtide Sodium *(rINNM)*

CGP-19835A; L-MTP-PE (liposomal mifamurtide sodium); Mifamurtida sódica; Mifamurtide (USAN); Mifamurtide Sodique; Mifamurtidum Natricum; Мифамуртид Натрий.
2-[(*N*-[(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(Acetylamino)-2,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yloxy]propanoyl]-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexanoyloxy)propyl sodium phosphate hydrate.
$C_{59}H_{108}N_6NaO_{19}P.xH_2O$=1259.5 (anhydrous)
CAS — 838853-48-8.

NOTE. The name Mifamurtide has been used for both the base and the sodium salt.

Uses and Administration

Mifamurtide is an immunomodulator that activates monocytes and macrophages to increase their capacity to destroy cancer cells. A liposomal formulation of mifamurtide is used with other chemotherapy to treat non-metastatic, resected osteosarcoma in patients from 2 to 30 years of age. The reconstituted suspension is filtered then diluted in 50 mL sodium chloride 0.9% and given by intravenous infusion over 1 hour. Mifamurtide 2 mg/m² is given twice weekly (at least 3 days apart) for 12 weeks, followed by once weekly for an additional 24 weeks. A total of 48 infusions is given in 36 weeks.

References.
1. Meyers PA. Muramyl tripeptide (mifamurtide) for the treatment of osteosarcoma. *Expert Rev Anticancer Ther* 2009; 9: 1035–49.
2. Frampton JE. Mifamurtide: a review of its use in the treatment of osteosarcoma. *Paediatr Drugs* 2010; 12: 141–53.
3. Chou AJ, *et al.* Addition of muramyl tripeptide to chemotherapy for patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group. *Cancer* 2009; 115: 5339–48.

Administration in children. Mifamurtide is given in a liposomal formulation to children aged from 2 years with osteosarcoma; see above for dosage details.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Common adverse effects with mifamurtide include blood disorders such as anaemia, thrombocytopenia, granulocytopenia, transient neutropenia, and leucopenia; CNS disorders such as headache, dizziness, paraesthesia, hypoaesthesia, somnolence or insomnia, tremor, fatigue, confusion, depression, and anxiety; musculoskeletal disorders such as pain, spasm, arthralgia, and myalgia; and skin disorders such as rash, pruritus, dry skin, alopecia, and hyperhidrosis. Gastrointestinal disturbances such as nausea, vomiting, diarrhoea or constipation, abdominal pain, and anorexia are very common.

Other adverse effects that occur commonly during treatment include infusion-site reactions, phlebitis, flushing, dehydration, hypokalaemia, vertigo, tinnitus, hearing loss, blurred vision, hepatic pain, dysmenorrhoea, haematuria, dysuria, pollakiuria, fever, chills, and oedema.

Common respiratory disorders include dyspnoea or tachypnoea, cough, haemoptysis, epistaxis, sinus or nasal congestion, pleural effusion, or pharyngolaryngeal pain. Respiratory distress has been reported occasionally in patients with pre-existing asthma; mifamurtide therapy should be stopped if a severe respiratory reaction occurs. Prophylactic bronchodilators may be considered in those with a history of reversible airways obstruction.

Cardiac disorders such as tachycardia and hypertension or hypotension are common. Subacute thrombosis has been reported very rarely. Patients with a history of venous thrombosis, vasculitis, or unstable cardiovascular disease should be closely monitored, and treatment delayed or stopped if symptoms are persistent or worsening. Clotting parameters should be monitored after the first dose and again after several doses.

Mifamurtide has occasionally been associated with an inflammatory response, including pericarditis and pleuritis, and it should be used with caution in those with a history of auto-immune disorders, inflammatory disease, or other collagen vascular diseases. Patients should be monitored for signs of uncontrolled inflammatory reactions such as arthritis or synovitis. Allergic reactions also have occurred occasionally with mifamurtide; symptoms include rash, dyspnoea, and severe hypertension.

Caution is required in patients with hepatic or renal impairment due to a lack of data; hepatic and renal function should be monitored until treatment is complete.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Mifamurtide modulates the immune system and its use is not recommended with calcineurin inhibitors or with regular use of corticosteroids. The use of mifamurtide with high-dose NSAIDs is also not recommended as *in vitro* studies have shown that high-dose NSAIDs can block the macrophage-activating action of mifamurtide.

Licensed product information suggests liposomal mifamurtide should not be administered at the same time as other lipophilic formulations.

Pharmacokinetics

Mifamurtide is rapidly cleared from the plasma after intravenous injection and is distributed into the liver, spleen, nasopharynx, thyroid, and to a lesser extent, into the lungs. The cells of the reticuloendothelial system clear mifamurtide liposomes by phagocytosis. The mean half-life is biphasic, that for the initial phase being about 15 minutes while the terminal half-life is about 18 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Mepact; *Cz.*: Mepact; *Denm.*: Mepact; *Ger.*: Mepact; *Gr.*: Mepact; *Irl.*: Mepact; *Israel*: Mepact; *Ital.*: Mepact; *Neth.*: Mepact; *Norw.*: Mepact; *Pol.*: Mepact; *Port.*: Mepact; *Spain*: Mepact; *Swed.*: Mepact; *Switz.*: Mepact; *UK*: Mepact.

Milatuzumab *(USAN, rINN)*

Immu-115; Milatuzumabum; Милатузумаб.
Immunoglobulin G1, anti-(human class II antigen invariant chain) (human-mouse monoclonal hLL1 heavy chain), disulfide with human-mouse monoclonal hLL1 κ-chain, dimer.
CAS — 899796-83-9.
UNII — 2OP4E0GC6V.

Profile

Milatuzumab is a humanised monoclonal antibody directed against the CD74 antigen. It is under investigation for the treatment of multiple myeloma, chronic lymphocytic leukaemia, and non-Hodgkin's lymphoma. Milatuzumab conjugated to doxorubicin (p. 782.3) is also being studied for multiple myeloma treatment.

References.
1. Berkova Z, *et al.* Milatuzumab—a promising new immunotherapeutic agent. *Expert Opin Invest Drugs* 2010; 19: 141–9.

Miltefosine *(BAN, rINN)*

D-18506; HDPC; Hexadecilfosfocolina; Hexadecylphosphocholine; Miltefosiini; Miltefosin; Miltefosina; Miltéfosine; Miltefosinum; Мильтефозин.
[2-(Trimethylammonio)ethyl][hexadecyloxyphosphonate].
$C_{21}H_{46}NO_4P$=407.6
CAS — 58066-85-6.
ATC — L01XX09.
ATC Vet — QL01XX09.
UNII — 53EY29W7EC.

Profile

Miltefosine is a phospholipid derivative that is structurally related to the phospholipid components of the cell membrane and is thought to exert its antineoplastic actions by disruption of cell-membrane function. A 6% solution is applied once or twice daily as a topical antineoplastic agent for skin metastases of breast cancer. Topical miltefosine is also being investigated for the treatment of cutaneous T-cell lymphoma and *Acanthamoeba* keratitis (p. 919.3); topical and oral formulations have been tried for disseminated amoebic infections (p. 920.1). Systemic miltefosine is being investigated for urticaria. Oral miltefosine is used for the treatment of visceral and cutaneous leishmaniasis in a dose of 1.5 to 2.5 mg/kg daily (maximum daily dose 150 mg) for 28 days.

Acanthamoeba infections. References[1,2] to the potential value of miltefosine against *Acanthamoeba* infections (p. 920.1).

1. Aichelburg AC, *et al.* Successful treatment of disseminated Acanthamoeba sp. infection with miltefosine. *Emerg Infect Dis* 2008; 14: 1743–6.
2. Walochnik J, *et al.* Anti-acanthamoeba efficacy and toxicity of miltefosine in an organotypic skin equivalent. *J Antimicrob Chemother* 2009; 64: 539–45.

Leishmaniasis. Miltefosine, given orally in doses of 50 to 150 mg daily, or about 2.5 mg/kg daily, for 28 days, appears to be of benefit[1-7] in the treatment of visceral leishmaniasis (p. 923.1), and has been licensed for this purpose in India and Germany. Benefit has also been reported in patients given similar doses for New World cutaneous leishmaniasis,[8] (p. 922.1) and it has also been licensed in some South American countries, but success may depend on the infecting *Leishmania* species.[9] A small

study[10] in Iran found oral miltefosine to be at least as good as intramuscular meglumine antimonate for the treatment of infections caused by *L. major*. Another retrospective, observational study[11] reported successful treatment with oral miltefosine in 30 of 34 patients (most of whom had not responded to initial treatment with intralesional antimony alone or with cryotherapy) for *L. major* infection acquired in northern Afghanistan. A further 4 patients were cured after receiving additional doses of either intralesional or intravenous antimony. The use of longer courses of miltefosine in the treatment of patients with both leishmaniasis and HIV infection has been reported.[12]

After recovery from visceral leishmaniasis caused by *L. donovani* patients may develop post-kala-azar dermal leishmaniasis; further treatment is needed in these patients as they represent a human reservoir for the disease. A small study[13] of 24 patients in Bihar, India reported that an oral dose of miltefosine 50 mg three times daily for 60 days (or 50 mg twice daily for 90 days in those who had intolerable adverse effects) achieved a cure in 96% of the patients. There were no relapses at 1-year follow-up.

1. Sundar S, *et al.* Trial of oral miltefosine for visceral leishmaniasis. *Lancet* 1998; 352: 1821–3.
2. Jha TK, *et al.* Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Engl J Med* 1999; 341: 1795–1800.
3. Thakur CP, *et al.* Miltefosine in a case of visceral leishmaniasis with HIV co-infection; and rising incidence of this disease in India. *Trans R Soc Trop Med Hyg* 2000; 94: 696–7.
4. Sundar S, *et al.* Short-course of oral miltefosine for treatment of visceral leishmaniasis. *Clin Infect Dis* 2000; 31: 1110–13.
5. Sundar S, *et al.* Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med* 2002; 347: 1739–46.
6. Bhattacharya SK, *et al.* Efficacy and tolerability of miltefosine for childhood visceral leishmaniasis in India. *Clin Infect Dis* 2004; 38: 217–21.
7. Ritmeijer K, *et al.* A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis* 2006; 43: 357–64.
8. Soto J, *et al.* Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. *Clin Infect Dis* 2001; 33: e57–e61. Available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/322689 (accessed 01/08/08)
9. Soto J, *et al.* Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis* 2004; 38: 1266–72.
10. Mohebali M, *et al.* Comparison of miltefosine and meglumine antimoniate for the treatment of zoonotic cutaneous leishmaniasis (ZCL) by a randomized clinical trial in Iran. *Acta Trop* 2007; 103: 33–40.
11. van Thiel PP, *et al.* Miltefosine treatment of *Leishmania major* infection: an observational study involving Dutch military personnel returning from northern Afghanistan. *Clin Infect Dis* 2010; 50: 80–3.
12. Sindermann H, *et al.* Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis* 2004; 39: 1520–3.
13. Ramesh V, *et al.* Miltefosine as an effective choice in the treatment of post-kala-azar dermal leishmaniasis. *Br J Dermatol* 2011; 165: 411–14.

Malignant neoplasms. References to the use of topical miltefosine in breast cancer.

1. Terwogt JM, *et al.* Phase II trial of topically applied miltefosine solution in patients with skin-metastasized breast cancer. *Br J Cancer* 1999; 79: 1158–61.
2. Smorenburg CH, *et al.* Phase II study of miltefosine 6% solution as topical treatment of skin metastases in breast cancer patients. *Anticancer Drugs* 2000; 11: 825–8.
3. Leonard R, *et al.* Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. *J Clin Oncol* 2001; 19: 4150–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies miltefosine 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 28/09/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Miltex; ***Braz.***: Miltex†; ***Chile***: Miltex; ***Fin.***: Miltex†; ***Fr.***: Miltex; ***Ger.***: Impavido; Miltex; ***Hung.***: Miltex; ***Israel***: Miltex†; ***Ital.***: Miltex; ***Philipp.***: Miltex†; ***Singapore***: Miltex; ***Spain***: Miltex†; ***Swed.***: Miltex†; ***UK***: Miltex†.

Miriplatin *(rINN)*

Miriplatine; Miriplatino; Miriplatinum; SM-11355; Мириплатин.
(SP-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-*N*,*N*']bis(tetradecanoato-*O*)platinum.
$C_{34}H_{68}N_2O_4Pt$=764.0
CAS — 141977-79-9.

Miriplatin Hydrate *(rINNM)*

D-06294; Miriplatine, Hydrate de; Miriplatini Hydratum; Miriplatino hidratada; Мириплатина Гидрат.
$C_{34}H_{68}N_2O_4Pt.H_2O$=782.0
CAS — 250159-48-9.

Profile

Miriplatin is a platinum derivative used as an antineoplastic in the treatment of hepatocellular carcinoma. It is given as the hydrate but doses are expressed as the base; 1 mg of miriplatin hydrate is equivalent to about 1.02 mg of miriplatin. A usual dose of 70 mg is given once daily by hepatic intra-arterial injection. Hepatic dysfunction, hepatobiliary disorders, and hepatic failure can occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Miripla.

Mitobronitol *(BAN, rINN)*

DBM; Dibromomannitol; Mitobronitolum; NSC-94100; R-54; WR-220057; Митобронитол.
1,6-Dibromo-1,6-dideoxy-D-mannitol.
$C_6H_{12}Br_2O_4$=308.0
CAS — 488-41-5.
ATC — L01AX01.
ATC Vet — QL01AX01.
UNII — 5UP30YED7N.

Pharmacopoeias. In *Br.*

BP 2014: (Mitobronitol). A white or almost white crystalline solid. Slightly soluble in water, in alcohol, and in acetone; practically insoluble in chloroform. Protect from light.

Profile

Mitobronitol is an antineoplastic that appears to act as an alkylating agent, perhaps by epoxide formation. It has been used in the management of thrombocythaemia, both primary, and secondary to chronic myeloid leukaemia or polycythaemia vera.

The usual oral dose is 250 mg daily until the platelet count falls to acceptable levels. Intermittent dosage has been given for maintenance therapy, adjusted according to the blood count. Frequent examination of the blood should be performed during treatment. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Mitobronitol is well absorbed from the gastrointestinal tract and is excreted through the liver into the bile, with reabsorption from the small intestine. It is eliminated as unchanged drug and some bromine-containing metabolites in the urine over several days.

Carcinogenicity. Long-term follow-up of a cooperative study[1] involving 350 patients with polycythaemia vera and treated with mitobronitol was thought to indicate that mitobronitol was less likely than phosphorus-32 or busulfan to induce acute myeloid leukaemia.

For a discussion of the usual management of polycythaemia vera, see p. 695.2.

1. Kelemen E, *et al.* Decreasing risk of leukaemia during prolonged follow-up after mitobronitol therapy for polycythaemia vera. *Lancet* 1987; ii: 625.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Myelobromol.

Pharmacopoeial Preparations
BP 2014: Mitobronitol Tablets.

Mitoguazone Dihydrochloride *(rINNM)*

Dihidrocloruro de mitoguazona; Methyl-GAG; Methylglyoxal Bisguanylhydrazone (mitoguazone); MGBG; Mitoguazona, dihidrocloruro de; Mitoguazone, Dichlorhydrate de; Mitoguazoni Dihydrochloridum; NSC-32946; Митогуазона Дигидрохлорид.
1,1'-[(Methylethanediylidene)dinitrilo]diguanidine dihydrochloride.
$C_5H_{12}N_8.2HCl$=257.1
CAS — 459-86-9 (mitoguazone); 7059-23-6 (mitoguazone dihydrochloride).
ATC — L01XX16.
ATC Vet — QL01XX16.
UNII — NNI098FX5Q.

Profile

Mitoguazone is an antineoplastic that may exert its cytotoxic effects by its ability to inhibit polyamine biosynthesis. It has been tried as the dihydrochloride monohydrate or the acetate, in the treatment of leukaemias, lymphomas, and some solid tumours.

Mitoguazone may produce hypoglycaemia and should be given dissolved in glucose-containing infusion fluids; sugar may be taken orally if hypoglycaemia develops during infusion. Granulocytopenia and thrombocytopenia are generally mild and reversible on stopping treatment. Gastrointestinal effects frequently occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Methyl-Gag†.

Mitolactol *(rINN)*

DBD; Dibromodulcitol; Mitolactolum; NSC-104800; WR-138743; Митолактол.
1,6-Dibromo-1,6-dideoxy-D-galactitol.
$C_6H_{12}Br_2O_4$=308.0
CAS — 10318-26-0.
UNII — LJ2P1SIK8Y.

Profile

Mitolactol is an antineoplastic that may act by alkylation, probably as epoxide metabolites including dianhydrogalactitol. It has been given orally in the treatment of metastatic breast and cervical carcinoma, although other drugs are usually preferred, and has also been tried in other malignant neoplasms, notably those of the brain. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In addition to myelosuppression, which is usually dose-limiting, and manifests chiefly as leucopenia and thrombocytopenia, adverse effects include gastrointestinal disturbances, skin rashes, grey pigmentation of the skin, transient disturbances of hepatic function, elevated blood-urea nitrogen (BUN), and hypersensitivity reactions. Blood counts should be taken regularly during treatment and mitolactol withdrawn if bone-marrow depression occurs.

Mitomycin *(BAN, USAN, rINN)*

Mitomicina; Mitomicina C; Mitomicinas; Mitomicinum; Mitomisin; Mitomycin C; Mitomycine; Mitomycine C; Mitomycinum; Mitomysiini; NSC-26980; Митомицин.
6-Amino-1,1a,2,8,8a,8b-hexahydro-8-hydroxymethyl-8a-methoxy-5-methylazirino[2',3':3,4]pyrrolo[1,2-*a*]indole-4,7-dione carbamate; (1*S*,2*S*,9*S*,9a*R*)-7-Amino-2,3,5,8,9,9a-hexahydro-9a-methoxy-6-methyl-5,8-dioxo-1,2-epimino-1-*H*-pyrrolo[1,2-*a*]indol-9-ylmethyl carbamate.
$C_{15}H_{18}N_4O_5$=334.3
CAS — 50-07-7.
ATC — L01DC03.
ATC Vet — QL01DC03.
UNII — 50SG953SK6.

Description. Mitomycin is an antineoplastic antibiotic produced by the growth of *Streptomyces caespitosus*.

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

Ph. Eur. 8: (Mitomycin). A substance produced by a strain of *Streptomyces caespitosus*. Blue-violet crystals or crystalline powder. Slightly soluble in water and in acetone; freely soluble in dimethylacetamide; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 5.5 to 7.5. Protect from light.

USP 36: (Mitomycin). A blue-violet crystalline powder. It has a potency of not less than 970 micrograms/mg. Slightly soluble in water; soluble in acetone, in butyl acetate, in cyclohexanone, and in methyl alcohol. A 0.5% suspension in water has a pH of 6.0 to 7.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Mitomycin may be incompatible with drugs that are acid in solution—for a report of incompatibility with topotecan, see p. 872.3.

Stability. Mitomycin undergoes degradation in acid solution,[1] and two studies[2,3] suggested that mitomycin was much less stable in glucose 5% injection than in sodium chloride 0.9%. These findings were queried by a manufacturer (*Bristol, USA*) whose own results suggested[4] that mitomycin was stable for 48 hours in glucose injection 5% at 25 degrees, and it is uncertain whether different manufacturers' formulations differ in stability, or, as has been suggested, that an unsuitable assay was used by the manufacturer to measure stability.[5]

1. Beijnen JH, Underberg WJM. Degradation of mitomycin C in acidic solution. *Int J Pharmaceutics* 1985; 24: 219–29.
2. Benvenuto JA, *et al.* Stability and compatibility of antitumour agents in glass and plastic containers. *Am J Hosp Pharm* 1981; 38: 1914–18.
3. Quebbeman EJ, *et al.* Stability of mitomycin admixtures. *Am J Hosp Pharm* 1985; 42: 1750–4.

4. Keller JH. Stability of mitomycin admixtures. *Am J Hosp Pharm* 1986; 43: 59,64.
5. Quebbeman EJ, Hoffman NE. Stability of mitomycin admixtures. *Am J Hosp Pharm* 1986; 43: 64.

Uses and Administration

Mitomycin is a highly toxic antibiotic with antineoplastic properties. It acts as an alkylating agent after activation *in vivo* and suppresses the synthesis of nucleic acids. It is a cell-cycle non-specific agent, but is most active in the late G_1 and early S phases.

Mitomycin is used, with other antineoplastic agents, in the treatment of many solid tumours including those of the bladder, breast, cervix, eye, stomach, and prostate as indicated by the cross-references given below. Mitomycin has been tried in other neoplasms including those of the gastrointestinal tract, head and neck, pancreas, in melanoma, sarcomas, and in leukaemias.

Dosage regimens include an initial dose of 10 to 20 mg/m² intravenously; subsequent doses are repeated at intervals of 6 to 8 weeks if blood counts permit, and should be reduced according to the previous haematological response. Usual doses in other regimens range from 4 to 10 mg (60 to 150 micrograms/kg) given at 1- to 6-week intervals. Other regimens may be used, particularly in combination.

Doses are adjusted according to the effect on bone marrow and treatment should not be repeated until the leucocyte and platelet counts are above acceptable levels (see also Bone-marrow Depression, p. 730.3).

Mitomycin is also used as a bladder instillation: 20 to 40 mg is instilled once weekly or three times a week for a total of 20 doses in the treatment of superficial bladder tumours. These doses are usually given in 20 to 40 mL of water for injection. The solution should be retained in the bladder for at least 1 hour. For the prevention of recurrent bladder tumours 20 mg may be instilled every 2 weeks, or 40 mg monthly or 3-monthly. Alternatively 4 to 10 mg has been instilled once weekly or three times a week.

Mitomycin has been given by the intra-arterial route in the treatment of liver tumours, sometimes as an infusion of microcapsules designed to produce localised embolisation.

Mitomycin is used for its effect on fibroblasts to improve outcomes and reduce scarring in certain types of surgery, notably in glaucoma (see below).

Mitomycin is also used topically in the form of 0.02% or 0.04% eye drops to treat conjunctival or corneal squamous cell carcinoma.

References.
1. Abraham LM, *et al.* Mitomycin: clinical applications in ophthalmic practice. *Drugs* 2006; 66: 321–40.
2. Bolenz C, *et al.* Intravesical mitomycin C for superficial transitional cell carcinoma. *Expert Rev Anticancer Ther* 2006; 6: 1273–82.
3. Tabaee A, *et al.* Mitomycin C and endoscopic sinus surgery: where are we? *Curr Opin Otolaryngol Head Neck Surg* 2007; 15: 40–3.
4. Warner D, Brietzke SE. Mitomycin C and airway surgery: how well does it work? *Otolaryngol Head Neck Surg* 2008; 138: 700–9.
5. Teus MA, *et al.* Mitomycin C in corneal refractive surgery. *Surv Ophthalmol* 2009; 54: 487–502.

Glaucoma. Mitomycin, like fluorouracil, is effective in improving the outcome of glaucoma filtering surgery in selected patients when used as an adjunct to prevent the formation of scar tissue (see p. 1999.1). Fluorouracil is usually given as a regimen of multiple injections but mitomycin given as a single intra-operative topical application in usual concentrations ranging from 200 to 500 micrograms/mL appears to be of similar efficacy.[1,2] A systematic review of 11 studies concluded that intra-operative mitomycin reduced the chances of failure in high-risk patients, and in those having their first trabeculectomy.[3] However it was noted that the nature of the data might have led to overestimation of the effect and that there was some evidence of an increased risk of cataract with mitomycin. Late hypotony is also a problem.[4] For other potential complications see Effects on the Eye, below.

1. Skuta GL, *et al.* Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1992; 99: 438–44.
2. Katz GJ, *et al.* Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery: extended follow-up. *Ophthalmology* 1995; 102: 1263–9.
3. Wilkins M, *et al.* Intra-operative mitomycin C for glaucoma surgery. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 25/04/06).
4. Bindlish R, *et al.* Efficacy and safety of mitomycin-C in primary trabeculectomy: five-year follow-up. *Ophthalmology* 2002; 109: 1336–42.

Keratectomy. Mitomycin has been used as an adjunct to laser keratectomy (photorefractive or phototherapeutic keratectomy) to prevent the subsequent formation of corneal haze due to fibroblast proliferation. Although earlier studies used brief intraoperative local application of a 0.02% solution, a lower dose solution (0.002%) also appears to be effective, and may reduce the risk of adverse effects.

References.
1. Kottler UB, Dick HB. Mitomycin C bei oberflächlichen Hornhautablationen mit dem Excimer-Laser: Eigene Erfahrungen und Literaturübersicht. *Klin Monbl Augenheilkd* 2005; 222: 499–504.
2. Wallau AD, *et al.* Mitomicina C e "Excimer laser". *Arq Bras Oftalmol* 2005; 68: 867–72.
3. Bedei A, *et al.* Photorefractive keratectomy in high myopic defects with or without intraoperative mitomycin C: 1-year results. *Eur J Ophthalmol* 2006; 16: 229–34.
4. Thornton I, *et al.* Low-dose mitomycin C as a prophylaxis for corneal haze in myopic surface ablation. *Am J Ophthalmol* 2007; 144: 673–681.
5. Thornton I, *et al.* Comparison of standard (0.02%) and low dose (0.002%) mitomycin C in the prevention of corneal haze following surface ablation for myopia. *J Refract Surg* 2008; 24: S68–S76.
6. Srinivasan S, *et al.* Photorefractive keratectomy with 0.02% mitomycin C for treatment of residual refractive errors after LASIK. *J Refract Surg* 2008; 24: S64–S67.
7. Lecciso tti A. Mitomycin C in photorefractive keratectomy: effect on epithelialization and predictability. *Cornea* 2008; 27: 288–91.
8. Wallau AD, Campos M. Photorefractive keratectomy with mitomycin C versus LASIK in custom surgeries for myopia: a bilateral prospective randomized clinical trial. *J Refract Surg* 2008; 24: 326–36.
9. Wallau AD, Campos M. One-year outcomes of a bilateral randomised prospective clinical trial comparing PRK with mitomycin C and LASIK. *Br J Ophthalmol* 2009; 93: 1634–8.
10. Virasch VV, *et al.* Reduced application time for prophylactic mitomycin C in photorefractive keratectomy. *Ophthalmology* 2010; 117: 885–9.
11. Shah RA, Wilson SE. Use of mitomycin-C for phototherapeutic keratectomy and photorefractive keratectomy surgery. *Curr Opin Ophthalmol* 2010; 21: 269–73.

Malignant neoplasms. Mitomycin is used in the prevention of recurrent bladder cancer (p. 700.2), in the palliative therapy of advanced breast cancer (p. 702.1), in malignancies of the cervix (p. 704.2), eye (p. 705.1), and stomach and anus (p. 706.1 and p. 708.1), and has been tried in advanced prostatic cancer (see p. 712.3).

Pterygium. Pterygium is a degenerative condition of subconjunctival tissues that results in a vascularised overgrowth of the conjunctiva and cornea. It is cosmetically unappealing but does not usually require treatment. However, if it affects the pupillary area it can be treated surgically. Pterygium often recurs after removal and methods used to prevent recurrence include radiotherapy or the topical application of mitomycin or thiotepa.[1]

Thiotepa has been applied postoperatively as 0.05% eye drops for several weeks, but pterygium may still recur[2] and adverse effects include conjunctival injection, granuloma, hypertrophic conjunctiva, and black deposits in the conjunctival fornix.[1] Depigmentation of the eyelids may also be a problem, so patients should avoid direct sunlight during thiotepa use.[1]

Mitomycin has been applied topically to the surgical site, or given as eye drops postoperatively.[1] The optimal intraoperative exposure time and concentration are uncertain: concentrations of 0.02 or 0.04% have been applied for up to 5 minutes,[1,3] and low-dose treatment with mitomycin 0.02% for 30 seconds has been reported to be effective with few complications.[4] Postoperative treatment has generally been given as 0.02, 0.04, or 0.1% eye drops for up to 2 weeks, but the higher concentrations and longer treatment periods have been associated with more adverse effects,[1] some of which may be severe and sight-threatening (see also Effects on the Eyes, below). Comparisons of intraoperative with postoperative use suggest that pterygium recurrence rates are similar.[1,5]

A range of β-irradiation doses and fractionation methods have been used. Long-term complications include posterior subcapsular changes of the lens, atrophy and ulceration of the sclera, and scleral necrosis leading to endophthalmitis.[1] In one retrospective study,[6] intra-operative use of 0.04% mitomycin was more effective than β-irradiation in preventing recurrence after surgery. In another study,[7] postoperative mitomycin 0.02% for one week was less effective than radiation therapy.

1. Hoffman RS, Power WJ. Current options in pterygium management. *Int Ophthalmol Clin* 1999; 39: 15–26.
2. Chapman-Smith JS. Pterygium treatment with triethylene thiophosphoramide. *Aust N Z J Ophthalmol* 1992; 20: 129–31.
3. Anduze AL. Pterygium surgery with mitomycin-C: ten-year results. *Ophthalmic Surg Lasers* 2001; 32: 341–5.
4. Cheng H-C, *et al.* Low-dose intraoperative mitomycin C as chemoadjuvant for pterygium surgery. *Cornea* 2001; 20: 24–9.
5. Oguz H, *et al.* Intraoperative application versus postoperative mitomycin C eye drops in pterygium surgery. *Acta Ophthalmol Scand* 1999; 77: 147–50.
6. Amano S, *et al.* Comparative study of intraoperative mitomycin C and β irradiation in pterygium surgery. *Br J Ophthalmol* 2000; 84: 618–21.
7. Şimşek T, *et al.* Comparative efficacy of β -irradiation and mitomycin-C in primary and recurrent pterygium. *Eur J Ophthalmol* 2001; 11: 126–32.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The main adverse effect of mitomycin is delayed cumulative bone-marrow suppression. Profound leucopenia and thrombocytopenia occurs after about 4 weeks with recovery in about 8 to 10 weeks after a dose. Therapy should be withheld until platelets and white blood cells recover to at least 100 000 cells/mm³ and 4000 cells/mm³, respectively. Blood counts may not recover in about one-quarter of patients. Other serious adverse effects include renal damage and pulmonary toxicity; a potentially fatal haemolytic-uraemic syndrome has been reported in some patients. US licensed product information states that the degree of renal impairment does not appear to be related to dose or duration of therapy although it has been suggested that the risk of renal toxicity is low with cumulative doses less than 50 mg/m², but increases with higher cumulative doses (see also Effects on the Kidneys, below). Gastrointestinal toxicity, dermatitis, alopecia, fever, malaise, and rarely cardiotoxicity may also occur. Local tissue necrosis, ulceration, and cellulitis may follow extravasation. Intra-arterial use can cause skin disorders such as pain, redness, erythema, blisters, erosion, and ulceration; skin and/or muscle necrosis may develop. Injection into the hepatic artery can cause liver and biliary tract disorders such as cholecystitis, cholangitis, and bile duct necrosis.

Mitomycin is contra-indicated in patients with impaired renal function or coagulation disorders. Renal function should be tested before beginning treatment and after each course.

Effects on the bladder. Intravesical instillation of mitomycin after resection of superficial bladder tumours has led to the development of indolent asymptomatic ulcers at the resection site which may persist for months, and must be distinguished from persistent infiltrating bladder cancer.[1,2] Persistent ulceration, inflammation, necrosis, and pain has also occurred, possibly because of mitomycin extravasation at the resection site.[3] Fistula formation has also been described.[4] There are also a few reports[5] of eosinophilic cystitis, in which eosinophilic infiltration of the mucosa and muscle were accompanied by oedema, inflammation, muscle necrosis and fibrosis. Severe bladder contracture is a rare, and often irreversible, complication of intravesical mitomycin;[6] urinary diversion may be required in cases of intolerable urinary frequency.[7] Formation of papillary-like calcifications at the resection site,[8] and calcification of the bladder wall have also been described after the use of mitomycin for superficial transitional cell carcinoma of the bladder.

See also under Effects on the Skin, p. 832.1.

1. Richards B, Tolley D. Benign ulcers after bladder instillation of mitomycin C. *Lancet* 1986; ii: 45.
2. Hetherington JW, Whelan P. Persistent ulcers after bladder instillation of mitomycin C. *Lancet* 1986; i: 324.
3. Cliff AM, *et al.* Perivesical inflammation after early mitomycin C instillation. *BJU Int* 2000; 85: 556–7.
4. Dangle PP, *et al.* Vesicoenteric, vesicovaginal, vesicocutaneous fistula -an unusual complication with intravesical mitomycin. *Can J Urol* 2008; 15: 4269–72.
5. Ülker V, *et al.* Eosinophilic cystitis induced by mitomycin-C. *Int Urol Nephrol* 1996; 28: 755–9.
6. Punga-Maole ML, *et al.* Rétraction vésicale, complication de la chimioprophylaxie du cancer vésical superficiel par mitomycine C endovésicale: a propos d'un cas et revue de la littérature. *Prog Urol* 1995; 5: 580–5.
7. Wajsman Z, *et al.* Severely contracted bladder following intravesical mitomycin C therapy. *J Urol (Baltimore)* 1983; 130: 340–1.
8. Flore AA, *et al.* Papillary-like bladder calcifications following intravesical mitomycin C: a case report. *Minerva Urol Nefrol* 1993; 45: 171–3.

Effects on the eyes. Early complications after the topical use of mitomycin with glaucoma filtering surgery (see Glaucoma, above) include hypotony, shallow anterior chamber, cataract formation, choroidal effusions, hypotonous maculopathy, and suprachoroidal haemorrhage.[1] Late complications include bleb leak, blebitis, and endophthalmitis.[2] Complications from the topical use of mitomycin with or after pterygium surgery (see Pterygium, above) commonly include irritation and photophobia. Other effects include delayed epithelial healing, avascularity of the sclera and cornea, scleral calcification and ulceration, necrotising scleritis, corneal or scleral perforation, iridocyclitis, cataract formation, glaucoma, and symblepharon.[1] Some of these effects may be severe and sight-threatening, and require further surgery.[3] Complications most commonly reported after the use of topical mitomycin in ocular surface neoplasia were hypersensitivity reactions and epiphora (an overflow of tears) secondary to stenosis of the lachrymal punctum.[4]

1. Hardten DR, Samuelson TW. Ocular toxicity of mitomycin-C. *Int Ophthalmol Clin* 1999; 39: 79–90.
2. DeBry PW, *et al.* Incidence of late-onset bleb-related complications following trabeculectomy with mitomycin. *Arch Ophthalmol* 2002; 120: 297–300.
3. Rubinfeld RS, *et al.* Serious complications of topical mitomycin C after pterygium surgery. *Ophthalmology* 1992; 99: 1647–54.
4. Khong JJ, Muecke J. Complications of mitomycin C therapy in 100 eyes with ocular surface neoplasia. *Br J Ophthalmol* 2006; 90: 819–22.

Effects on the kidneys. A syndrome of thrombotic microangiopathy resembling the haemolytic-uraemic syndrome has been seen in patients receiving mitomycin, either alone[1] or more often with other drugs, particularly fluorouracil[2] or tamoxifen.[3,4] The syndrome is characterised by haemolytic anaemia, thrombocytopenia, and progressive renal failure, and may be accompanied by hypertension, pulmonary oedema, and neurological effects including confusion, headache, and seizures.[1,2] Onset is usually delayed, sometimes occurring several months after the end of a course of mitomycin.[1,2]

There is some uncertainty as to whether mitomycin dose is significant, but one study[1] found that all of 25 cases they

reported had received total doses of 70 mg or more, and another[2] reported that 74 of 83 cases had received 60 mg or more.

Symptoms may be exacerbated by blood transfusions.[2] The use of erythropoietin allowed the cessation of blood transfusion, with subsequent haematological improvement and slower progression of chronic renal failure in one case report.[3] Plasma exchange has been suggested as possibly helpful,[1] although only a minority of patients may benefit from this treatment.[2] Extracorporeal protein A immunoadsorption has also been tried.[6] Captopril therapy may also be useful.[7]

1. Cordonnier D, *et al.* La néphrotoxicité de la mitomycine C (à propos de 25 observations): résultats d'une enquête multicentrique organisée par la société de néphrologie. *Nephrologie* 1985; 6: 19–26.
2. Lesesne JB, *et al.* Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol* 1989; 7: 781–9.
3. Montes A, *et al.* A toxic interaction between mitomycin C and tamoxifen causing the haemolytic uraemic syndrome. *Eur J Cancer* 1993; 29A: 1854–7.
4. Ellis PA, *et al.* Haemolytic uraemic syndrome in a patient with lung cancer: further evidence for a toxic interaction between mitomycin-C and tamoxifen. *Clin Oncol (R Coll Radiol)* 1996; 8: 402–3.
5. Catalano C, *et al.* Erythropoietin is beneficial in mitomycin-induced hemolytic-uremic syndrome. *Nephron* 2002; 91: 324–6.
6. Kasper S, *et al.* Protein A immunoadsorption therapy for refractory, mitomycin C-associated thrombotic microangiopathy. *Transfusion* 2007; 47: 1263–7.
7. Schiebe ME, *et al.* Mitomycin C-related hemolytic uremic syndrome in cancer patients. *Anticancer Drugs* 1998; 9: 433–5.

Effects on the liver. Hepatic veno-occlusive disease developed in 6 of 29 patients given intensive mitomycin therapy and autologous bone marrow transplantation.[1] The effect was manifest as abdominal pain, hepatomegaly, and ascites, and liver failure was progressive and fatal in 3. A further patient, who had no symptoms, was found to have veno-occlusive disease at post mortem.

1. Lazarus HM, *et al.* Veno-occlusive disease of the liver after high-dose mitomycin C therapy and autologous bone marrow transplantation. *Cancer* 1982; 49: 1789–95.

Effects on respiratory function. Mitomycin-induced pulmonary toxicity has been reviewed.[1,2] There have been reports of toxicity at total dosages as low as 20 mg/m² of mitomycin,[2] although others report[1] that the average cumulative dose associated with toxicity is 78 mg. Premedication with corticosteroids may reduce the incidence of lung toxicity.[2] Interstitial lung disease associated with intravesical mitomycin has also been described.[3]

See also Effects on the Lungs, p. 729.1. For reference to the respiratory effects of mitomycin used with a vinca alkaloid see Interactions, Antineoplastics, under Vinblastine Sulfate, p. 882.2.

1. Linette DC, *et al.* Mitomycin-induced pulmonary toxicity: case report and review of the literature. *Ann Pharmacother* 1992; 26: 481–4.
2. Okuno SH, Frytak S. Mitomycin lung toxicity: acute and chronic phases. *Am J Clin Oncol* 1997; 20: 282–4.
3. Janeiro Pais JM, *et al.* Mitomicina C endovesical y fibrosis pulmonar. *Actas Urol Esp* 2009; 33: 822–5.

Effects on the skin. Severe eczema of the hands and feet and generalised rash have been reported in patients receiving intravesical mitomycin.[1,2] These symptoms appear to be due to a delayed hypersensitivity (type IV) reaction,[1,2] which is probably also responsible for the bladder irritation and cystitis that may follow intravesical mitomycin[1] (see p. 831.3). Leucocytoclastic vasculitis caused by an immune-complex mediated (type III) reaction and presenting as purpuric papules has also been described.[2]

1. Colver GB, *et al.* Dermatitis due to intravesical mitomycin C: a delayed-type hypersensitivity reaction? *Br J Dermatol* 1990; 122: 217–24.
2. Kunkeler L, *et al.* Type III and type IV hypersensitivity reactions due to mitomycin C. *Contact Dermatitis* 2000; 42: 74–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mitomycin 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 29/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Antineoplastics. Cardiotoxicity developed in 14 of 91 patients who received mitomycin therapy as second-line treatment for breast cancer after the failure of *doxorubicin*-containing regimens, compared with 3 of 89 similar patients whose second-line treatment did not include mitomycin.[1]

For reports of acute bronchospasm after injection of a *vinca alkaloid* in patients pretreated with mitomycin see Vinblastine Sulfate, p. 882.2. For the increased risk of haemolytic-uraemic syndrome that may occur if mitomycin is given with *fluorouracil* or *tamoxifen* see under Effects on the Kidneys, p. 831.3.

1. Buzdar AU, *et al.* Adriamycin and mitomycin C: possible synergistic cardiotoxicity. *Cancer Treat Rep* 1978; 62: 1005–8.

Pharmacokinetics

Mitomycin disappears rapidly from the blood after intravenous injection with an initial (distribution) half-life of 17 minutes. It is widely distributed but does not appear to cross the blood-brain barrier. Mitomycin is metabolised mainly but not exclusively in the liver. The terminal half-life is about 50 minutes. After normal doses about 10% of a dose is excreted unchanged in the urine; small amounts are also present in bile and faeces. With increasing doses metabolic pathways are saturated, and more drug is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Asomutan; Crisofimina; Maximiton; Mitocyna; Mitokebir; Mitonovag; Mitotie; Sintemicina; Vetio; *Braz.*: Baxmicin†; Mitocin; *Fin.*: Mitostat; *Fr.*: Ametycine; *Ger.*: Ametycine; Mitem; Mito-extra; Mito-medac; *India*: Almito; Mitocin; Mitodus; Mitonco; Oncocin; *Mex.*: Mitocin-C†; Mitolem; Mitotie; Mixandex; *Philipp.*: Mytoxid; *Thai.*: Mitocin; Vesimycin; *USA*: Mitosol; Mitozytrex†; Mutamycin†.

Pharmacopoeial Preparations
USP 36: Mitomycin for Injection.

Mitotane *(BAN, USAN, rINN)*

CB-313; Mitotaani; Mitotan; Mitotano; Mitotanum; NSC-38721; *o,p'*DDD; WR-13045; Митотан.

1,1-Dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane.

$C_{14}H_{10}Cl_4$=320.0

CAS — 53-19-0.

ATC — L01XX23.

ATC Vet — QL01XX23.

UNII — 78E4J5IB5J.

Pharmacopoeias. In *US.*

USP 36: (Mitotane). A white crystalline powder with a slight aromatic odour. M.p. is between 75 degrees and 81 degrees. Practically insoluble in water; soluble in alcohol, in ether, in petroleum spirit, and in fixed oils and fats. Store in airtight containers. Protect from light.

Uses and Administration

Mitotane is an oral antineoplastic that directly suppresses the adrenal cortex. It may also modify peripheral steroid metabolism. It is given in the treatment of advanced adrenocortical tumours. Dosing schedules vary. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In the UK, mitotane is given in an initial oral dose of 2 to 3 g daily in patients with adrenocortical tumours, increased at 2-week intervals until plasma mitotane concentrations reach the target range of 14 to 20 micrograms/mL. For rapid control of Cushing's symptoms in these patients, an initial oral dose of 4 to 6 g daily may be necessary, and can be increased as often as every week to achieve the target concentration range. The total daily dose is given in 2 or 3 divided doses with meals containing fat-rich foods. Corticosteroid therapy may also be required for adrenal insufficiency, see Precautions, below. Mitotane plasma concentrations should be measured at frequent intervals (after each dose adjustment) until the target concentration range is reached, usually within 3 to 5 months. Regular monitoring of plasma concentrations should continue once the maintenance dose is established. If severe toxicity occurs, mitotane treatment should be withheld and restarted when plasma concentrations are within the target range. For mild toxicity the dose should be reduced until the maximum tolerated dose is reached. Mitotane treatment may be continued for as long as there is benefit. If there is no benefit after 3 months at an optimal dose, treatment should be stopped. For doses in children, see below.

In the USA, the usual initial oral dosage is 2 to 6 g daily in 3 or 4 divided doses. Doses are usually increased to 9 to 10 g daily, unless adverse effects necessitate dose reduction. The maximum tolerated dose ranges from about 2 to 16 g daily.

Administration in children. Mitotane is used in children and adolescents for the treatment of advanced adrenocortical tumours. In the UK, an initial oral dose of 1.5 to 3.5 g/m² daily can be increased up to a target dose of 4 g/m² daily. The total daily dose is given in 2 or 3 divided doses with meals containing fat-rich foods. Plasma concentrations of mitotane should be monitored as for adults, see above; a sharp increase in mitotane concentration may be seen when 10 micrograms/mL is reached. The dose may be reduced after 2 or 3 months depending on mitotane concentrations or toxicity.

Malignant neoplasms of the adrenal gland. Adrenocortical carcinoma is a rare and aggressive malignancy, and there are few prospective studies of its treatment. Surgery is the treatment of choice and the only curative option for localised disease.[1] Retrospective studies of adjuvant mitotane after resection with curative intent have shown mixed results. Some investigators found that mitotane had no effect on survival[2] or recurrence rate,[3] while others reported significantly improved recurrence-free survival.[4] Nevertheless, mitotane is often suggested as adjuvant therapy because of the high risk of recurrence, although it might be considered unnecessary following complete resection of localised small tumours.[1,5]

Mitotane has been reported to be of benefit in patients undergoing palliative surgery,[2] and is the drug of choice when the tumour cannot be completely removed surgically[1,5] although tumour reduction may be minimal.[3] Response rates range from 13 to 30% in metastatic disease, but most are of limited duration and complete response is rare.[1] It is also used in metastatic disease to control symptoms but adverse effects can limit its use. Mitotane has also been tried with cytotoxic chemotherapy, and various regimens are under investigation.[1]

1. Zini L, *et al.* Contemporary management of adrenocortical carcinoma. *Eur Urol* 2011; 60: 1055–65.
2. Icard P, *et al.* Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg* 2001; 25: 891–7.
3. Grubbs EG, *et al.* Recurrence of adrenal cortical carcinoma following resection: surgery alone can achieve results equal to surgery plus mitotane. *Ann Surg Oncol* 2010; 17: 263–70.
4. Terzolo M, *et al.* Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007; 356: 2372–80.
5. Veytsman I, *et al.* Management of endocrine manifestations and the use of mitotane as a chemotherapeutic agent for adrenocortical carcinoma. *J Clin Oncol* 2009; 27: 4619–29.

Adverse Effects

Almost all patients given mitotane have anorexia, nausea and vomiting, and sometimes diarrhoea, and about 40% suffer some central toxicity with dizziness, vertigo, sedation, lethargy, ataxia, and paraesthesia. Brain damage and impaired function can occur after prolonged use of high doses. Other common adverse effects include leucopenia, thrombocytopenia, anaemia, hypercholesterolaemia, hypertriglyceridaemia, mucositis, gynaecomastia, and headache. Bleeding time may be prolonged, but the mechanism of this effect is unknown. Ocular adverse effects may occur including blurred vision, diplopia, lenticular opacities, maculopathy, and retinopathy. Other adverse effects include hypersensitivity reactions, rashes, fever, myalgia, myasthenia, haemorrhagic cystitis, haematuria, albuminuria, flushing, hypertension, orthostatic hypotension, and hypersalivation. Liver enzymes are commonly increased with mitotane, and there have been reports of auto-immune hepatitis and cholestatic hepatitis. Hypothyroidism has occurred.

Precautions

Mitotane inhibits the adrenal cortex and adrenocortical insufficiency may develop during treatment; corticosteroid therapy is often required. In trauma, infection, or shock the drug should be temporarily withdrawn and corticosteroids should be given systemically. Mitotane should be given with care to patients with renal or hepatic impairment. Before mitotane therapy is begun, all possible tumour tissue from large metastases should be surgically removed, in order to minimise possible infarction or haemorrhage in the tumour. Patients should not drive or operate machinery. Behavioural and neurological assessments should be carried out regularly in patients who have been receiving treatment for 2 years or more, especially when mitotane plasma concentrations exceed 20 micrograms/mL. Plasma concentrations should be monitored to guide dosage; the therapeutic window lies between 14 and 20 micrograms/ml (see also Therapeutic Drug Monitoring, p. 833.1). Fetal adrenal abnormalities have been reported after exposure during pregnancy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mitotane 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 28/09/11)

Interactions

Mitotane can induce hepatic microsomal enzymes such as cytochrome P450 isoenzymes. This may enhance the

metabolism of some other drugs, including coumarin anticoagulants.

Spironolactone. Mitotane in a dose of up to 3 g daily in a 65-year-old patient with Cushing's syndrome appeared to be ineffective and did not produce the usual adverse effects associated with mitotane while the patient was also receiving spironolactone.[1]

1. Wortsman J, Soler NG. Mitotane: spironolactone antagonism in Cushing's syndrome. *JAMA* 1977; 238: 2527.

Pharmacokinetics

Up to 40% of a dose of mitotane is absorbed from the gastrointestinal tract; absorption increases with food. After daily doses of 5 to 15 g, concentrations in the blood of 7 to 90 micrograms/mL of unchanged drug and 29 to 54 micrograms/mL of metabolite have been reported. It is widely distributed and appears to be stored mainly in fatty tissues. It is metabolised in the liver and other tissues and excreted as metabolites in urine and bile. From 10 to 25% of a dose has been recovered in the urine as a water-soluble metabolite. As it is slowly released from storage sites, terminal plasma half-lives ranging from 18 to 159 days have been reported. In most patients mitotane is no longer detected in plasma about 6 to 9 weeks after stopping therapy.

Therapeutic drug monitoring. Monitoring of mitotane and its major metabolite *o,p'*-DDE in 2 patients receiving mitotane in low doses for Cushing's disease found that there is a prolonged lag time in the plasma concentration changes in response to alterations in dosage,[1] presumably because of the lipophilicity of both compounds which leads to accumulation in adipose tissue. A study[2] in adrenal carcinoma found that mitotane is preferentially distributed into the very-low-density lipoprotein (VLDL) fraction of the serum of patients with hypertriglyceridaemia, whereas under normolipidaemic conditions, it is bound to high-density lipoproteins and albumin. Because VLDL is not incorporated into the human adrenal cells, mitotane's lipophilicity has implications for treatment and monitoring in patients with hypertriglyceridaemia. In some studies[3,4] tumour responses were seen only in those patients with a serum concentration of mitotane above 14 micrograms/mL, and a small prospective study[5] found that therapeutic concentrations (defined as between 14 and 20 micrograms/mL) could be reached by sustained low doses (1 to 3 g daily), thus limiting adverse effects.

1. Benecke R, *et al.* Plasma level monitoring of mitotane (o,p'-DDD) and its metabolite (o,p'-DDE) during long-term treatment of Cushing's disease with low doses. *Eur J Clin Pharmacol* 1991; 41: 259–61.
2. Gebhardt DOE, *et al.* The distribution of *o,p'*-DDD (mitotane) among serum lipoproteins in normo-and hypertriglyceridemia. *Cancer Chemother Pharmacol* 1992; 29: 331–4.
3. Haak HR, *et al.* Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. *Br J Cancer* 1994; 69: 947–51.
4. Baudin E, *et al.* Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p'DDD) levels on the treatment of patients with adrenocortical carcinoma. *Cancer* 2001; 92: 1385–92.
5. Terzolo M, *et al.* Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. *J Clin Endocrinol Metab* 2000; 85: 2234–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Lysodren; *Belg.*: Lysodren; *Braz.*: Lisodren; *Canad.*: Lysodren; *Cz.*: Lysodren; *Denm.*: Lysodren; *Fin.*: Lysodren; *Fr.*: Lysodren; *Ger.*: Lysodren†; *Gr.*: Lysodren; *Hong Kong*: Lysodren†; *Hung.*: Lysodren; *Irl.*: Lysodren; *Ital.*: Lysodren; *Neth.*: Lysodren; *Norw.*: Lysodren; *Pol.*: Lysodren; *Port.*: Lysodren; *Spain*: Lysodren; *Switz.*: Lysodren; *UK*: Lysodren; *USA*: Lysodren.

Pharmacopoeial Preparations
USP 36: Mitotane Tablets.

Mitoxantrone Hydrochloride

(BANM, USAN, rINNM)

CL-232315; DHAD; Dihydroxyanthracenedione Dihydrochloride; Hidrocloruro de mitoxantrona; Mitoksantron Hidroklorür; Mitoksantronihydroklorid; Mitoksantrono hidrochloridas; Mitoxantron dihydrochlorid; Mitoxantrona, hidrocloruro de; Mitoxantrone, Chlorhydrate de; Mitoxantronhidroklorid; Mitoxantronhydrochlorid; Mitoxantronhydroklorid; Mitoxantroni Dihydrochloridum; Mitoxantron hydrochloridum; Mitozantrón Hidroklorür; Mitozantrone Hydrochloride; NSC-301739; Митоксантрона Гидрохлорид.

1,4-Dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino] anthraquinone dihydrochloride.

$C_{22}H_{28}N_4O_6.2HCl$=517.4

CAS — 65271-80-9 (mitoxantrone); 70476-82-3 (mitoxantrone hydrochloride).

ATC — L01DB07.

ATC Vet — QL01DB07.

UNII — U6USW86RDQ.

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

Ph. Eur. 8: (Mitoxantrone Hydrochloride). A dark-blue, electrostatic, hygroscopic powder. Sparingly soluble in water; practically insoluble in acetone; slightly soluble in methyl alcohol. Store in airtight containers.

USP 36: (Mitoxantrone Hydrochloride). A dark-blue powder. Sparingly soluble in water; practically insoluble in acetone, in acetonitrile, and in chloroform; slightly soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Mitoxantrone is an anthracenedione antineoplastic structurally related to doxorubicin (p. 782.3). It inhibits topoisomerase II and causes DNA strand breakage, as well as intercalating with DNA. It is cell-cycle non-specific but is most active against cells in the late *S* phase.

It is used in the treatment of metastatic breast cancer (p. 702.1), and of non-Hodgkin's lymphomas (p. 696.3), alone or with other agents. It may also be given to treat adult acute myeloid leukaemias (p. 693.1). Mitoxantrone has also been used in patients with hormone-refractory prostate cancer (p. 712.3), liver cancer (p. 709.3), and ovarian cancer (p. 711.2).

In addition, mitoxantrone is used in the management of secondary progressive or relapsing multiple sclerosis (see below), to reduce neurological disability or the frequency of relapses.

Mitoxantrone is given as the hydrochloride, but doses are expressed in terms of the base; 1.2 mg of the hydrochloride is equivalent to about 1 mg of mitoxantrone. In the treatment of breast cancer, prostate cancer, liver cancer, and lymphomas, a dose equivalent to mitoxantrone 14 mg/m^2 is given initially, then repeated every 3 weeks. It is diluted to at least 50 mL in sodium chloride 0.9% or glucose 5% and injected over at least 3 minutes into a freely-running intravenous infusion of either. Subsequent doses may be adjusted according to the degree of myelosuppression produced. Initial dosage may need to be reduced to 12 mg/m^2 in debilitated patients or those who have had previous chemotherapy. Doses should also probably be reduced when mitoxantrone is given as part of a combination regimen; initial doses should generally be reduced by 2 to 4 mg/m^2 below those recommended for single-agent use.

In the treatment of patients with acute myeloid leukaemia an intravenous dose of 12 mg/m^2 daily for 5 days may be given as monotherapy to induce remission; alternatively 10 to 12 mg/m^2 may be given for 3 days with a 7-day course of cytarabine.

All patients should have cardiac function assessed before starting therapy, including left ventricular ejection fraction (LVEF) evaluation. Regular cardiac examinations are recommended in all patients at increased risk of cardiotoxicity and in those who receive a cumulative dose of mitoxantrone greater than 160 mg/m^2. Regular blood counts should be performed during treatment and courses should not be repeated until blood counts have recovered (see also Bone-marrow Depression, p. 730.3).

In the management of **multiple sclerosis**, the recommended dose is the equivalent of mitoxantrone 12 mg/m^2 by intravenous infusion over 5 to 15 minutes. This dose may be given once every 3 months initially provided that neutrophil counts are above 1500 cells/mm^3 and that LVEF is greater than 50%. Blood counts and liver function should be monitored before each dose. LVEF should be evaluated before beginning mitoxantrone therapy and before all subsequent doses; a total cumulative dose in excess of 140 mg/m^2 should be avoided. LVEF should also be measured if signs or symptoms of heart failure develop.

References.
1. Faulds D, *et al.* Mitoxantrone: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. *Drugs* 1991; 41: 400–49.
2. Fox EJ. Mechanism of action of mitoxantrone. *Neurology* 2004; 63 (suppl): S15–S18.

Multiple sclerosis. Mitoxantrone has produced clinical benefit[1-4] in terms of reduced relapse rate and a slowing of disease progression in patients with multiple sclerosis (p. 996.3). It has been given intravenously in doses of 5 or 12 mg/m^2 every 3 months, or 8 mg/m^2 every month. Patients with progressive relapsing disease may benefit from rapid induction with 12 mg/m^2 monthly for 3 months.[5] Benefit has also been found when used with corticosteroids,[6] although the combination was not compared with mitoxantrone alone. However, cardiotoxicity limits the dose that can be given[7,8] (see Uses and Administration, above). Because of this and other adverse effects, such as possible secondary malignancy or potentially permanent amenorrhoea, some consider the use of mitoxantrone in multiple sclerosis to be unproven[9] and others have cautioned[10] that alternative immunomodulators have less severe toxicities. A systematic review[11] concluded that mitoxantrone was moderately effective in the short-term treatment of multiple sclerosis, but that information on its long-term effects was lacking; use should be limited to patients with worsening relapsing-remitting or secondary progressive disease with evidence of worsening disability.

1. Millefiorini E, *et al.* Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997; 244: 153–9.
2. van de Wyngaert FA, *et al.* A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. *Acta Neurol Belg* 2001; 101: 210–16.
3. Hartung H-P, *et al.* Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002; 360: 2018–25.
4. Jeffery DR, Herndon R. Review of mitoxantrone in the treatment of multiple sclerosis. *Neurology* 2004; 63 (suppl): S19–S24.
5. Rizvi SA, *et al.* Mitoxantrone for multiple sclerosis in clinical practice. *Neurology* 2004; 63 (suppl): S25–S27.
6. Edan G, *et al.* Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997; 62: 112–118.
7. Ghalie RG, *et al.* Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. *Neurology* 2002; 59: 909–13.
8. Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: safety considerations. *Neurology* 2004; 63 (suppl): S28–S32.
9. Chaudhuri A, Behan PO. Mitoxantrone trial in multiple sclerosis. *Lancet* 2003; 361: 1133–4.
10. Marriott JJ, *et al.* The efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; 74: 1463–70.
11. Martinelli Boneschi F, *et al.* Mitoxantrone for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 01/03/06).

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p. 784.1. Mitoxantrone is reported to be better tolerated than doxorubicin. The nadir of the white cell count usually occurs about 10 days after a dose, with recovery by day 21. Elevation in liver enzyme values may occur; there are occasional reports of severe hepatic impairment in patients with leukaemia, in whom doses are generally higher and adverse effects of mitoxantrone may be more frequent and severe.

Transient blue-green coloration of the urine, and occasionally the sclerae, may occur. Blue discoloration of the skin (which can also occur after extravasation) and nails have been reported. Nail dystrophy and onycholysis can occur.

Severe neurotoxicity has resulted from erroneous intrathecal dosage; local or regional neuropathy has followed intra-arterial injection. Care is required in patients with pre-existing heart disease, or who have had prior anthracycline treatment or radiotherapy to the chest, as they are at increased risk of cardiotoxicity; regular cardiac examinations, including left ventricular ejection fraction (LVEF) evaluation, should be performed in these patients from the start of therapy. All patients should be assessed for cardiac signs and symptoms; multiple sclerosis patients with a baseline LVEF below the lower limit of normal should not be treated with mitoxantrone. UK licensed product information states that cardiac monitoring should also be performed in patients without identifiable cardiac risk factors who receive a total cumulative dose of mitoxantrone in excess of 160 mg/m^2; US licensed product information states that the risk of symptomatic congestive heart failure is higher after a cumulative dose of 140 mg/m^2 and that multiple sclerosis patients should not receive a total cumulative dose greater than this. Care is also required in patients with hepatic impairment. Regular blood counts should be performed during treatment. Treatment with mitoxantrone, either alone or with other antineoplastics and/or radiotherapy, has been associated with an increased risk of development of secondary acute myeloid leukaemia.

Alopecia. Two patients receiving therapy with mitoxantrone developed selective alopecia of white but not of dark hair.[1]

1. Arlin ZA, *et al.* Selective alopecia with mitoxantrone. *N Engl J Med* 1984; 310: 1464.

Breast feeding. Mitoxantrone was detected in the breast milk of a woman with acute promyelocytic leukaemia in remission who was given consolidation chemotherapy that included mitoxantrone 6 mg/m^2 on days 1 to 3. Concentrations were 120 nanograms/mL just after the third dose and 18 nanograms/mL 28 days after treatment. Although she breast fed her neonate from 3 weeks after the completion of the course of treatment and no adverse effects were seen, the authors recommended that women treated with mitoxantrone should not breast feed.[1]

1. Azuno Y, *et al.* Mitoxantrone and etoposide in breast milk. *Am J Hematol* 1995; 48: 131–2.

Effects on the heart. Data from over 4000 patients treated with mitoxantrone included 172 reports of cardiac events, including 42 cases of congestive heart failure and 66 of

decreased ejection fraction.[1] Previous anthracycline therapy increased the risk, and congestive heart failure seemed to be more likely in patients exposed to a cumulative mitoxantrone dose of 160 mg/m², or 100 mg/m² in those already given anthracyclines. The risk of symptomatic congestive heart failure in cancer patients has been estimated to be 2.6% for patients receiving a cumulative dose of up to 140 mg/m²; the US manufacturer recommended that patients with multiple sclerosis should not receive a total cumulative dose greater than this.[2] In a further 78 patients,[3] clinical heart failure developed in 2 after cumulative doses of 174 and 243 mg/m². Four of 9 other patients given mitoxantrone in doses above 100 mg/m² showed signs of cardiotoxicity, and a further patient previously given doxorubicin 313 mg/m² had a fall in stress ejection fraction after only 47 mg/m² of mitoxantrone. However, cardiotoxicity has also been seen after lower doses; sinus bradycardia occurred[4] in 2 previously untreated patients after starting continuous infusions of mitoxantrone 10 mg/m², and severe acute heart failure[5] in a patient with multiple sclerosis, 2 months after a second dose of mitoxantrone 12 mg/m² was given. Late cardiotoxicity can also occur; dilated cardiomyopathy, with a left ventricular ejection fraction of 20%, developed[6] in a patient with multiple sclerosis 2 years after a course of mitoxantrone with a cumulative dose of 72 mg/m². For information on the cardiotoxicity of anthracyclines, to which mitoxantrone is structurally related, see under Adverse Effects and Treatment of Doxorubicin, p. 784.1.

1. Crossley RJ. Clinical safety and tolerance of mitoxantrone. *Semin Oncol* 1984; 11: (suppl 1): 54–8.
2. Lammers P (Serono, USA). Novantrone: mitoxantrone for injection concentrate (issued April 2005). Available at: http://www.novantrone.com/assets/pdf/healthcare_professional_letter.pdf (accessed 11/08/09)
3. Stuart-Harris R, *et al.* Cardiotoxicity associated with mitoxantrone. *Lancet* 1984; ii: 219–20.
4. Benekli M, *et al.* Mitoxantrone-Induced bradycardia. *Ann Intern Med* 1997; 126: 409.
5. Dörr J, *et al.* Severe cardiac failure in a patient with multiple sclerosis following low-dose mitoxantrone treatment. *Neurology* 2009; 73: 991–3.
6. Killestein J, *et al.* Severe cardiac failure in a patient with multiple sclerosis following low-dose mitoxantrone treatment. *Neurology* 2010; 74: 934.

Handling and disposal. *Urine and faeces* produced for up to 7 days after a dose of mitoxantrone should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Hypersensitivity. In a report of 3 patients, allergic-type reactions to mitoxantrone included vasculitis, facial oedema and skin rashes, and in one, breathlessness, tachypnoea, cyanosis, and unrecordable pulse and blood pressure.[1] Allergic reactions to the drug appear to be rare.

1. Taylor WB, *et al.* Allergic reactions to mitoxantrone. *Lancet* 1986; i: 1439.

Pregnancy. For a report of a fetal sinusoidal heart rate pattern and neonatal pancytopenia after a woman was given combination chemotherapy including mitoxantrone, see Pregnancy, under Etoposide, p. 791.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mitoxantrone 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 29/09/11)

Interactions

For a report of the effect of ciclosporin in patients receiving mitoxantrone and etoposide, see p. 792.1.

Pharmacokinetics

After intravenous doses mitoxantrone is rapidly and extensively distributed to body tissues, and slowly excreted in urine and bile as unchanged drug and metabolites. The elimination half-life is reported to range from 5 to 18 days. Between 6 and 11% of a dose has been recovered from urine, and 13 to 25% in faeces, within 5 days. It does not appear to cross the blood-brain barrier, but it is distributed into breast milk.

References.

1. Ehninger G, *et al.* Pharmacokinetics and metabolism of mitoxantrone: a review. *Clin Pharmacokinet* 1990; 18: 365–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Batinel†; Micraleve; Mitoxgen; Mitoxmar†; *Austral.*: Novantrone†; Onkotrone; *Austria*: Ebexantron; *Belg.*: Xantrosin; *Braz.*: Evomixan; Misostol; Mitoxal†; *China*: Heng En (恒恩); Mi Xi Ning (米西宁); Novantrone (诺肯林); Ze Kang (泽康); *Cz.*: Onkotrone†; Refador†; *Fin.*: Novantrone; *Fr.*: Elsep; Novantrone; *Ger.*: Haemato-tron†; Novantron; Onkotrone; Ralenova; *Gr.*: Geneladrone; Mitoxan; Novantrone; Zyneva; *Hong Kong*: Novantrone†; Santrone; *Hung.*: Novantrone†; Onkotrone; Refador†; *India*: Mitozan; Oncotron; *Indon.*: Norexan†; *Irl.*: Novantrone†; *Israel*: Novantrone; *Ital.*: Novantrone; Onkotrone; *Mex.*: Formyxan; Mitoxgen; Mitroxone; Neotalem; *Norw.*: Novantrone; *NZ*: Novantrone; Onkotrone; *Philipp.*: Domitrone; Onkotrone†; *Port.*: Mitroxene†; Novantrone†; *Rus.*: Oncotrone (Онкотрон); *S.Afr.*: Novantrone†; *Singapore*: Ebexantron†; *Spain*: Novantrone; Pralifan; *Swed.*: Novantrone; *Switz.*: Novantron; *Thai.*: Neotalem; *Turk.*: Neotalem; Novantrone; Oncocarbin; Oncotron; *UK*: Onkotrone; *USA*: Novantrone†; *Venez.*: Misostol.

Pharmacopoeial Preparations
BP 2014: Mitoxantrone Infusion;
USP 36: Mitoxantrone Injection.

Mogamulizumab *(USAN, rINN)*

AMG-761; KM-8761; KW-0761; Mogamulizumabum; Могамулизумаб.

Immunoglobulin G1, anti-(CC chemokine receptor CCR4) (human-mouse monoclonal KW-0761 heavy chain), disulfide with human-mouse monoclonal KW-0761 κ-chain, dimer.

CAS — 1159266-37-1.
UNII — YI437801BE.

Profile

Mogamulizumab is a humanised monoclonal antibody directed against the CCR4 chemokine receptor. It is used in the treatment of relapsed or refractory adult T-cell leukaemia/lymphoma. It is also under investigation for the treatment of asthma.

References.

1. Ishida T, *et al.* Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol* 2012; 30: 837–42.
2. Tobinai K, *et al.* Targeting chemokine receptor CCR4 in adult T-cell leukemia-lymphoma and other T-cell lymphomas. *Curr Hematol Malig Rep* 2012; 7: 235–40.
3. Subramaniam JM, *et al.* Mogamulizumab: first global approval. *Drugs* 2012; 72: 1293–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Poteligeo.

Motesanib *(USAN, rINN)*

AMG-706; Motésanib; Motesanibum; Мотезаниб.

N-(3,3-Dimethyl-2,3-dihydro-1*H*-indol-6-yl)-2-[(pyridine-4-ylmethyl)amino]pyridine-3-carboxamide.

$C_{22}H_{23}N_5O$=373.5

CAS — 453562-69-1.
UNII — U1JK633AYI.

Motesanib Diphosphate *(USAN, rINN)*

AMG-706; Difosfato de motesanib; Motésanib, Diphosphate de; Motesanibi Diphosphas; Мотезаниба Дифосфат.

Motesanib phosphate (1:2).

$C_{22}H_{23}N_5O,2H_3O_4P$=569.4

CAS — 857876-30-3.
UNII — T6Q3060U91.

Profile

Motesanib is a tyrosine kinase inhibitor that targets the receptors of vascular endothelial growth factor, platelet-derived growth factor, and other growth factors, thereby inhibiting angiogenesis. It is under investigation for the treatment of solid malignancies such as non-squamous non-small cell lung cancer and breast cancer.

Muparfostat

PI-88.

CAS — 185077-23-0.

Profile

Muparfostat is a heparanase inhibitor derived from the yeast *Pichia holstii* that is under investigation for the treatment of malignancies such as liver cancer and advanced melanoma.

Naptumomab Estafenatox *(rINN)*

ABR-217620; Naptumomab Estafénatox; Naptumomabum Estafenatoxum; Наптумомаб Эстафенатокс.

Immunoglobulin fragment, anti-[trophoblast glycoprotein (TPBG, 5T4)] monoclonal 5T4 gamma1 heavy chain fragment fusion protein [*Mus musculus* VH (5T4V14: H41>P, S44>G, I69>T, V113>G)-IGHG1_CH1] - [Glycyl-Glycyl-Prolyl] -superantigen SEA/E-120 (synthetic), non-disulfide linked with monoclonal 5T4 kappa light chain [*Mus musculus* V-KAPPA (5T4V18: F10>S, T45>K, I63>S, F73>L, T77>S, L78>V, L83>A)-IGKC].

CAS — 676258-98-3.
UNII — 93T929W6LC.

Profile

Naptumomab estafenatox is a murine monoclonal antibody conjugated with a bacterial superantigen, a modified variant of staphylococcal enterotoxin A that acts as a target for T-cell activation. The antibody is directed against a tumour-specific antigen 5T4. Naptumomab estafenatox is under investigation for the treatment of renal cell carcinoma.

References.

1. Borghaei H, *et al.* Phase 1 dose escalation, pharmacokinetic and pharmacodynamic study of naptumomab estafenatox alone in patients with advanced cancer and with docetaxel in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2009; 27: 4116–23.
2. Robinson MK, *et al.* Naptumomab estafenatox: a new immunoconjugate. *Expert Opin Biol Ther* 2010; 10: 273–9.
3. Forsberg G, *et al.* Naptumomab estafenatox, an engineered antibody-superantigen fusion protein with low toxicity and reduced antigenicity. *J Immunother* 2010; 33: 492–9.

Nedaplatin *(rINN)*

Nédaplatine; Nedaplatino; Nedaplatinum; NSC-375101O; 254-S; Недаплатин.

cis-Diammine(glycolato-*O*¹,*O*²)platinum.

$C_2H_8N_2O_3Pt$=303.2

CAS — 95734-82-0.
UNII — 8UQ3W6JXAN.

Profile

Nedaplatin is a platinum derivative with general properties similar to those of cisplatin (p. 766.1) although it may be associated with less nephrotoxicity. It is used in the treatment of a variety of malignant neoplasms. It is given by intravenous infusion over 1 hour or more, dissolved in at least 300 mL of an appropriate infusion solution, in doses of 80 to 100 mg/m². The infusion should be followed by infusion of at least 1 litre of fluid to ensure adequate hydration and reduce the risk of renal damage.

References.

1. Ishibashi T, *et al.* Determination of optimal dosage for nedaplatin based on pharmacokinetic and toxicodynamic analysis. *Anticancer Res* 2005; 25: 1273–81.
2. Shirai T, *et al.* Phase II study of the combination of gemcitabine and nedaplatin for advanced non-small-cell lung cancer. *Lung Cancer* 2006; 52: 181–7.
3. Fuwa N, *et al.* Chemoradiation therapy using radiotherapy, systemic chemotherapy with 5-fluorouracil and nedaplatin, and intra-arterial infusion using carboplatin for locally advanced head and neck cancer—Phase II study. *Oral Oncol* 2007; 43: 1014–20.
4. Oshita F, *et al.* Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small cell lung cancer. *Cancer Chemother Pharmacol* 2008; 62: 465–70.
5. Yokoyama Y, *et al.* A phase II multicenter trial of concurrent chemoradiotherapy with weekly nedaplatin in advanced uterine cervical carcinoma: Tohoku Gynecologic Cancer Unit Study. *Oncol Rep* 2008; 19: 1551–6.
6. Yamamoto N, *et al.* A dose-finding and pharmacokinetic study of nedaplatin in elderly patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 2009; 65: 79–88.
7. Hirose T, *et al.* Phase II study of the combination of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer. *Anticancer Res* 2009; 29: 1733–8.
8. Cao W, *et al.* A phase II study of paclitaxel and nedaplatin as first-line chemotherapy in patients with advanced esophageal cancer. *Jpn J Clin Oncol* 2009; 39: 582–7.
9. Shiraishi T, *et al.* Salvage chemotherapy with paclitaxel and gemcitabine plus nedaplatin (TGN) as part of multidisciplinary therapy in patients with heavily pretreated cisplatin-refractory germ cell tumors. *Int J Clin Oncol* 2009; 14: 436–41.
10. Osawa S, *et al.* Prospective study of daily low-dose nedaplatin and continuous 5-fluorouracil infusion combined with radiation for the treatment of esophageal squamous cell carcinoma. *BMC Cancer* 2009; 9: 408.
11. Zhang M-Q, *et al.* Concurrent chemoradiotherapy with paclitaxel and nedaplatin followed by consolidation chemotherapy in locally advanced squamous cell carcinoma of the uterine cervix: preliminary results of a phase II study. *Int J Radiat Oncol Biol Phys* 2010; 78: 821–7.
12. Oshita F, *et al.* Phase II study of nedaplatin and irinotecan with concurrent thoracic radiotherapy in patients with locally advanced non-small-cell lung cancer. *Br J Cancer* 2010; 103: 1325–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ao Xian Da (奥先达); Jepaso (捷佰舒); Lu Bei (鲁贝); Quan Bo (泉铂); *Jpn*: Aqupla.

Nelarabine *(BAN, USAN, rINN)*

506U; 506U78; GW-506U; GW-506U78; MAY; Nelarabin; Nélarabine; Nelarabinum; Nelzarabine; Неларабин.

2-Amino-9-β-D-arabinofuranosyl-6-methoxy-9*H*-purine.

$C_{11}H_{15}N_5O_5$=297.3

CAS — 121032-29-9.
ATC — L01BB07.
ATC Vet — QL01BB07.
UNII — 60158CV180.

Uses and Administration

Nelarabine is a prodrug of ara-G, a purine nucleoside analogue that is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory T-cell acute lymphoblastic leukaemia and lymphoma. A dose of 1.5 g/m² is given undiluted by intravenous infusion over 2 hours in adults, on days 1, 3, and 5 of a 21-day cycle. For doses in children, see below.

Nelarabine should be stopped at the first sign of moderate to severe neurological toxicity. Dosage may be delayed for other toxicities, including haematological toxicity.

References.
1. Gandhi V, *et al.* Evaluation of the combination of nelarabine and fludarabine in leukemias: clinical response, pharmacokinetics, and pharmacodynamics in leukemia cells. *J Clin Oncol* 2001; **19**: 2142–52.
2. Kisor DF. Nelarabine: a nucleoside analog with efficacy in T-cell and other leukemias. *Ann Pharmacother* 2005; **39**: 1056–63.
3. Sanford M, Lyseng-Williamson KA. Nelarabine. *Drugs* 2008; **68**: 439–47.
4. DeAngelo DJ, *et al.* Nelarabine for the treatment of patients with relapsed or refractory T-cell acute lymphoblastic leukemia or lymphoblastic lymphoma. *Hematol Oncol Clin North Am* 2009; **23**: 1121–35.

Administration in children. Nelarabine is given to children for the treatment of relapsed or refractory T-cell acute lymphoblastic leukaemia and lymphoma. It is given undiluted by intravenous infusion over 1 hour, at a dose of 650 mg/m² daily for 5 consecutive days, and repeated every 21 days.

UK licensed product information recommends the above dose for those aged 21 years and younger, and the adult dose (see Uses and Administration, above) in those aged 16 years and older; in studies, for those patients in the age range of 16 to 21 years either dose has been used.

Adverse Effects, Treatment, and Precautions

Neurotoxicity is common with nelarabine and may be dose-limiting. Signs and symptoms include somnolence, confusion, convulsions, ataxia, paraesthesias, and hypoaesthesia. Severe toxicity can manifest as coma, status epilepticus (which may be fatal), craniospinal demyelination, or ascending neuropathy. Risk of neurotoxicity is increased by previous or current intrathecal chemotherapy or previous radiation to the spine or brain. Leucopenia, thrombocytopenia, anaemia, and neutropenia are common, especially in children. Full blood counts should be regularly monitored. Other common adverse events include fatigue, gastrointestinal disorders, respiratory disorders, pyrexia, headache, hypokalaemia, hypoalbuminaemia, hyperbilirubinaemia, and increased liver enzyme values. Fatal cerebral haemorrhage has been reported. Appropriate measures to avoid hyperuricaemia (especially in patients considered at risk for tumour lysis syndrome) include adequate hydration, urinary alkalinisation, and possible prophylaxis with allopurinol.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nelarabine 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 29/09/11)

Pharmacokinetics

In adult patients with leukaemia or lymphoma, nelarabine is rapidly eliminated from the plasma, with a half-life of about 30 minutes; no data are available for paediatric patients although the mean clearance is reported to be about 30% higher in children. Nelarabine is rapidly and extensively demethylated via the enzyme adenosine deaminase to the active metabolite 9-β-D-arabinofuranosylguanine (ara-G; arabinosylguanine; arabinofuranosylguanine; guanine arabinoside); both nelarabine and ara-G are widely distributed throughout the body. Ara-G has an elimination half-life from plasma of about 3 hours. Plasma protein binding is not significant. Nelarabine also undergoes hydrolysis to form methylguanine. Both methylguanine and ara-G undergo further metabolism to guanine, which is deaminated to form xanthine, itself further oxidised to uric acid. Nelarabine and ara-G are partially eliminated by the kidneys; mean apparent clearance is lower in patients with mild to moderate renal impairment.

References.
1. Kisor DF, *et al.* Pharmacokinetics of nelarabine and 9-beta-D-arabinofuranosyl guanine in pediatric and adult patients during a phase I study of nelarabine for the treatment of refractory hematologic malignancies. *J Clin Oncol* 2000; **18**: 995–1003.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Atriance; *Belg.*: Atriance; *Canad.*: Atriance; *Cz.*: Atriance; *Denm.*: Atriance; *Fr.*: Atriance; *Ger.*: Atriance; *Gr.*: Atriance; *Irl.*: Atriance; *Israel*: Atriance; *Ital.*: Atriance; *Jpn*: Arranon; *Neth.*: Atriance; *Norw.*: Atriance; *Pol.*: Atriance; *Port.*: Atriance; *Rus.*: Atriance (Атрианс); *Spain*: Atriance; *Swed.*: Atriance; *Switz.*: Atriance; *UK*: Atriance; *USA*: Arranon.

Neratinib *(USAN, rINN)*

HKI-272; Neratinib; Neratinibum; Нератиниб.
(2*E*)-*N*-[4-({3-Chloro-4-[(pyridine-2-yl)methoxy]phenyl}amino)-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide.
$C_{30}H_{29}ClN_6O_3$=557.1
CAS — 698387-09-6.
UNII — JJH94R3PWB.

Profile

Neratinib is an orally active tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR) family, including HER1, HER2 and HER4. It is under investigation for the treatment of breast cancer and other solid tumours.

References.
1. Wong K-K, *et al.* A phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors. *Clin Cancer Res* 2009; **15**: 2552–8.
2. Bose P, Ozer H. Neratinib: an oral, irreversible dual EGFR/HER2 inhibitor for breast and non-small cell lung cancer. *Expert Opin Invest Drugs* 2009; **18**: 1735–51.
3. Burstein HJ, *et al.* Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol* 2010; **28**: 1301–7.
4. Sequist LV, *et al.* Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 3076–83.

Nilotinib *(BAN, USAN, rINN)*

AMN-107; Nilotinibum; Nilotynib; Нильотиниб.
4-Methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzamide.
$C_{28}H_{22}F_3N_7O$=529.5
CAS — 641571-10-0.
ATC — L01XE08.
ATC Vet — QL01XE08.
UNII — F41401512X.

Nilotinib Hydrochloride *(rINNM)*

Hidrocloruro de nilotinib; Nilotinib, Chlorhydrate de; Nilotinibi Hydrochloridum; Нильотиниба Гидрохлорид.
Nilotinib Hydrochloride Monohydrate.
$C_{28}H_{22}F_3N_7O.HCl.H_2O$=584.0
CAS — 923288-90-8.
ATC — L01XE08.
ATC Vet — QL01XE08.
UNII — K37N7BYX3X (anhydrous nilotinib hydrochloride); 5JHU0N1R6K (nilotinib hydrochloride monohydrate).

Uses and Administration

Nilotinib is a potent inhibitor of BCR-ABL tyrosine kinase. Nilotinib is used for the treatment of adults with Philadelphia chromosome-positive chronic myeloid leukaemia (CML; p. 694.2), both as first-line treatment of chronic phase, and in the treatment of chronic or accelerated phase in those who are resistant to, or intolerant of, previous imatinib-based treatment. Nilotinib is given orally as the hydrochloride, but doses are expressed in terms of the base; 100 mg of nilotinib is equivalent to about 110 mg of nilotinib hydrochloride monohydrate. Doses are given at least 1 hour before or 2 hours after food. Capsules should usually be swallowed whole, but if patients have difficulty swallowing then capsules can be opened and the contents dispersed in one teaspoon of apple sauce; the mixture should be taken immediately (within 15 minutes). *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For first-line treatment of chronic phase CML, nilotinib hydrochloride is given in an oral dose equivalent to nilotinib 300 mg twice daily. In the treatment of patients with chronic or accelerated phase CML resistant to prior treatment or where there has been intolerance to therapy, a dose equivalent to nilotinib 400 mg twice daily is used. If a dose is missed, no catch-up dose is recommended; the next dose should be taken as usual. Treatment may be continued until disease progression. Doses may need to be adjusted or treatment withheld for toxicity, see below. For doses in hepatic impairment, see below.

Nilotinib is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4. Use with strong CYP3A4 inhibitors or inducers should be avoided. If a strong CYP3A4 inhibitor is required, nilotinib treatment should be interrupted. If a strong CYP3A4 inhibitor must be used with nilotinib, US licensed product information suggests reducing the dose of nilotinib as follows:

- In first-line treatment of chronic phase CML, consider a dose reduction to 200 mg once daily
- In the treatment of patients with chronic or accelerated phase CML resistant to prior treatment or where there has been intolerance to therapy, consider a dose reduction to 300 mg once daily

Once the inhibitor is stopped, a washout period should be allowed before nilotinib is increased to the original dose.

Increasing the dose of nilotinib is considered unlikely to compensate for the loss of nilotinib exposure when strong CYP3A4 inducers are used, and their use together is not recommended.

Nilotinib has been investigated for the treatment of gastrointestinal stromal tumours.

References.
1. Weisberg E, *et al.* AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. *Br J Cancer* 2006; **94**: 1765–9.
2. Kantarjian H, *et al.* Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006; **354**: 2542–51.
3. Kantarjian HM, *et al.* Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007; **110**: 3540–6.
4. Plosker GL, Robinson DM. Nilotinib. *Drugs* 2008; **68**: 449–59.
5. Deremer DL, *et al.* Nilotinib: a second-generation tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia. *Clin Ther* 2008; **30**: 1956–75.
6. Breccia M, Alimena G. Nilotinib therapy in chronic myelogenous leukemia: the strength of high selectivity on BCR/ABL. *Curr Drug Targets* 2009; **10**: 530–6.
7. Fava C, *et al.* Development and targeted use of nilotinib in chronic myeloid leukemia. *Drug Des Devel Ther* 2009; **2**: 233–43.
8. Rosti G, *et al.* GIMEMA CML Working Party. Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. *Blood* 2009; **114**: 4933–8.
9. Cortes JE, *et al.* Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol* 2010; **28**: 392–7.
10. Saglio G, *et al.* ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010; **362**: 2251–9.
11. Quintás-Cardama A, *et al.* Nilotinib. *Recent Results Cancer Res* 2010; **184**: 103–17.
12. Breccia M, Alimena G. Nilotinib: a second-generation tyrosine kinase inhibitor for chronic myeloid leukemia. *Leuk Res* 2010; **34**: 129–34.

Administration in hepatic impairment. Exposure to nilotinib is increased in hepatic impairment and US licensed product information recommends a lower initial dose in patients with impairment at baseline. For first-line treatment of chronic phase chronic myeloid leukaemia (CML), those with mild, moderate, or severe impairment (Child-Pugh classes A, B, and C, respectively) are given an initial oral dose equivalent to nilotinib 200 mg twice daily which can be increased up to the usual dose of 300 mg twice daily if tolerated. In the treatment of patients with chronic or accelerated phase CML resistant to prior treatment or where there has been intolerance to therapy, those with mild or moderate impairment are given an initial oral dose equivalent to nilotinib 300 mg twice daily which can be increased up to the usual dose of 400 mg twice daily if tolerated; those with severe impairment are given an initial oral dose equivalent to nilotinib 200 mg twice daily which can be increased up to 300 mg twice daily, and then 400 mg twice daily, as tolerated.

UK licensed product information states that dose adjustments of nilotinib are not necessary in hepatic impairment, although caution is advised.

Dose adjustments may also be required if liver function deteriorates during treatment, see Administration in Toxicity, below.

Administration in toxicity. Nilotinib should be withheld or the dose reduced if haematological toxicity that is not related to the underlying leukemia occurs during treatment of chronic myeloid leukaemia (CML). In chronic phase CML (either when nilotinib is used first-line or when there has been resistance to or intolerance of prior treatment), nilotinib should be withheld when the absolute neutrophil count (ANC) falls to < 1000 cells/mm³ and/or platelets to $< 50\,000$ cells/mm³. If values increase above these levels within 2 weeks, treatment may be resumed using the previous oral dose, but if blood counts remain low for more than 2 weeks, a dose reduction to 400 mg once daily may be required.

Accelerated phase CML in patients that are resistant to or intolerant of prior treatment is managed as for chronic phase in the USA (see above). However, in the UK, nilotinib is withheld when the ANC falls to < 500 cells/mm³ and/or platelets to $< 10\,000$ cells/mm³. If the ANC increases to > 1000 cells/mm³ and/or platelets increase to $> 20\,000$ cells/mm³ within 2 weeks, treatment may be

resumed using the previous dose, but if blood counts remain low for more than 2 weeks, a dose reduction to 400 mg once daily may be required.

Nilotinib treatment may need to be withheld or the dose reduced to 400 mg once daily for increases (grade 3 or above) in serum lipase or amylase, bilirubin, and/or liver enzymes; if withheld, treatment may be restarted at 400 mg once daily when values return to grade 1 or below. Similarly, for other moderate to severe non-haematological toxicity, nilotinib should be withheld, and treatment restarted at 400 mg once daily when toxicity has resolved; if appropriate the dose may be increased back up to the usual recommended dose (see Uses and Administration, p. 835.2).

Nilotinib can prolong the QT interval and US licensed product information recommends withholding treatment for a corrected QT (QTcF) of > 480 milliseconds. If the QTcF interval returns to < 450 milliseconds and to within 20 milliseconds of the baseline value within 2 weeks, nilotinib can be restarted at the previous dose. If the QTcF interval is between 450 and 480 milliseconds after 2 weeks, the dose should be restarted at a lower dose of 400 mg once daily, and treatment stopped if the QTcF increases again to > 480 milliseconds. An ECG should be carried out about 7 days after any dose adjustment.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects of nilotinib are rash, pruritus, fatigue, headache, and gastrointestinal disturbances. Other common adverse effects include fever, alopecia, asthenia, muscle spasms, myalgia, arthralgia, pain including musculoskeletal or chest pain, oedema, folliculitis, papilloma, insomnia, anxiety, dizziness, paraesthesia, conjunctivitis, dry eye, vertigo, flushing, dyspnoea, cough, hyperhidrosis, dry skin, urticaria, and acne. Myelosuppression occurs (commonly thrombocytopenia, neutropenia, and anaemia), but is generally reversible and can be managed by withholding therapy or dose reduction, see Administration in Toxicity, p. 835.3. Complete blood counts should be performed every fortnight for the first 2 months and monthly thereafter. Nilotinib can prolong the QT interval, which may result in ventricular tachycardia (torsade de pointes), causing syncope, seizures, and/or death; treatment may be withheld or the dose reduced (p. 835.3). Nilotinib should not be used in patients at high risk of developing QT prolongation such as those with hypokalaemia or hypomagnesaemia, congenital long QT syndrome, uncontrolled or significant cardiac disease, or those taking other medicines that prolong the QT interval. Taking nilotinib with substances that increase the concentration of nilotinib, such as food or inhibitors of the cytochrome P450 isoenzyme CYP3A4, may increase the risk of QT prolongation, see Interactions, below. ECGs should be obtained at baseline, 1 week after starting nilotinib, and periodically thereafter including after dose adjustments. Other cardiac adverse effects include arrhythmias, palpitations, angina, hypertension, cardiac failure, pericarditis,and myocardial infarction. Sudden death has occurred rarely and may be related to ventricular repolarisation abnormalities. Thrombotic disorders or haemorrhage have been reported.

Tumour lysis syndrome has occurred rarely, and adequate hydration and treatment of elevated uric acid concentrations are recommended before starting nilotinib. Electrolyte abnormalities can occur and electrolytes should be monitored during therapy. Hepatotoxicity has been reported. Pancreatitis can occur and serum lipase should be monitored; caution is recommended in patients with a history of pancreatitis. Other adverse effects that have been reported include pleural or pericardial effusion, interstitial lung disease, mucosal ulceration or inflammation, hypersensitivity, thyroid and/or parathyroid disorders, dyslipidaemia, hyperglycaemia or hypoglycaemia, gout, depression, amnesia, tremor, peripheral neuropathy, chorioretinopathy, tinnitus, visual or hearing impairment, epistaxis, urinary disorders, erectile dysfunction, gynaecomastia, menorrhagia, erythema multiforme, erythema nodosum, palmar-plantar erythrodysesthesia, photosensitivity, and skin changes such as discoloration, hyperpigmentation, exfoliation, hypertrophy, or atrophy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nilotinib 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 27/09/11)

Interactions

Nilotinib is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4, and use with strong inhibitors or inducers of CYP3A4 should be avoided. If strong CYP3A4 inhibitors must be used, dose adjustments may be required (see Uses and Administration, p. 835.2). Grapefruit juice may increase plasma concentrations of nilotinib and should be avoided. St John's wort should also be avoided. *In vitro*, nilotinib is a relatively strong inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and of the uridine diphosphate glucuronosyltransferase isoenzyme UGT1A1; exposure to substrates of these enzymes may be altered by nilotinib. Nilotinib is a substrate for P-glycoprotein and exposure may be affected by drugs that modulate P-glycoprotein. Nilotinib should not be given with drugs that prolong the QT interval.

The solubility of nilotinib is affected by pH, with a reduced solubility at higher pH, and drugs that suppress gastric acid may lead to lower exposure to nilotinib. However, nilotinib absorption was only modestly decreased by esomeprazole despite a marked increase in gastric pH, and nilotinib may be used with esomeprazole or other proton pump inhibitors.

References.

1. Yin OQP, *et al.* Effect of the proton pump inhibitor esomeprazole on the oral absorption and pharmacokinetics of nilotinib. *J Clin Pharmacol* 2010; **50**: 960–7.
2. Tanaka C, *et al.* Effects of rifampin and ketoconazole on the pharmacokinetics of nilotinib in healthy participants. *J Clin Pharmacol* 2011; **51**: 75–83.

Pharmacokinetics

Peak plasma concentrations occur about 3 hours after an oral dose of nilotinib. Bioavailability is about 30% and is increased almost twofold when given with food. Plasma protein binding is about 98%. The apparent elimination half-life is about 17 hours. It is metabolised in the liver via oxidation and hydroxylation, in which cytochrome P450 isoenzyme CYP3A4 plays an important role. Most of an oral dose is eliminated unchanged in the faeces within 7 days.

References.

1. Tanaka C, *et al.* Clinical pharmacokinetics of the BCR-ABL tyrosine kinase inhibitor nilotinib. *Clin Pharmacol Ther* 2010; **87**: 197–203.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tasigna; ***Austral.***: Tasigna; ***Austria***: Tasigna; ***Belg.***: Tasigna; ***Braz.***: Tasigna; ***Canad.***: Tasigna; ***Chile***: Tasigna; ***China***: Tasigna (达希纳); ***Cz.***: Tasigna; ***Denm.***: Tasigna; ***Fr.***: Tasigna; ***Ger.***: Tasigna; ***Gr.***: Tasigna; ***Hong Kong***: Tasigna; ***Hung.***: Tasigna; ***Indon.***: Tasigna; ***Irl.***: Tasigna; ***Israel***: Tasigna; ***Ital.***: Tasigna; ***Malaysia***: Tasigna; ***Neth.***: Tasigna; ***Norw.***: Tasigna; ***NZ***: Tasigna; ***Philipp.***: Tasigna; ***Pol.***: Tasigna; ***Port.***: Tasigna; ***Rus.***: Tasigna (Тасигна); ***Singapore***: Tasigna; ***Spain***: Tasigna; ***Swed.***: Tasigna; ***Switz.***: Tasigna; ***Thai.***: Tasigna; ***Turk.***: Tasigna; ***UK***: Tasigna; ***Ukr.***: Tasigna (Тасигна); ***USA***: Tasigna.

Nilutamide *(BAN, USAN, rINN)*

Nilutamid; Nilutamida; Nilutamidi; Nilutamidum; RU-23908; Нилутамид.

5,5-Dimethyl-3-(α,α,α-trifluoro-4-nitro-*m*-tolyl)-imidazolidine-2,4-dione.

$C_{12}H_{10}F_3N_3O_4$=317.2

CAS — 63612-50-0.

ATC — L02BB02.

ATC Vet — QL02BB02.

UNII — 51G6I88902.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nilutamide). A white or almost white powder. Very slightly soluble in water; freely soluble in acetone; soluble in anhydrous ethanol. Protect from light.

Uses and Administration

Nilutamide is a nonsteroidal anti-androgen that is used similarly to flutamide (p. 798.2) in the treatment of prostatic carcinoma (p. 712.3). It is given orally in a dose of 300 mg daily, usually starting on the same day as orchidectomy or starting treatment with a gonadorelin analogue. Dosage may be reduced to 150 mg daily after 1 month.

References.

1. Dole EJ, Holdsworth MT. Nilutamide: an antiandrogen for the treatment of prostate cancer. *Ann Pharmacother* 1997; **31**: 65–75.
2. Desai A, *et al.* Nilutamide: possible utility as a second-line hormonal agent. *Urology* 2001; **58**: 1016–20.
3. Kassouf W, *et al.* Nilutamide as second line hormone therapy for prostate cancer after androgen ablation fails. *J Urol (Baltimore)* 2003; **169**: 1742–4.
4. Nakabayashi M, *et al.* Efficacy of nilutamide as secondary hormonal therapy in androgen-independent prostate cancer. *BJU Int* 2005; **96**: 783–6.

Adverse Effects and Precautions

As for Flutamide, p. 798.3. Interstitial pneumonitis has occurred in patients receiving nilutamide, and the drug is contra-indicated in those with severe respiratory insufficiency.

Effects on the eyes. Reversible visual disturbances, particularly delayed dark adaptation, have been associated with nilutamide.[1-3] Although some consider such visual disturbances to be mild and generally well tolerated,[4] others suggest that these, together with alcohol intolerance and, more seriously, effects on the lung, mean that other nonsteroidal anti-androgens should be preferred.[5]

1. Harnois C, *et al.* Ocular toxicity of Anandron in patients treated for prostatic cancer. *Br J Ophthalmol* 1986; **70**: 471–3.
2. Brisset JM, *et al.* Ocular toxicity of Anandron. *Br J Ophthalmol* 1987; **71**: 639.
3. Chan P, Odel JG. Delayed dark adaptation caused by nilutamide. *J Neuroophthalmol* 2008; **28**: 158–9.
4. Dijkman GA, *et al.* Comment: clinical experiences of visual disturbances with nilutamide. *Ann Pharmacother* 1997; **31**: 1550–1.
5. Dole EJ, Holdsworth MT. Comment: clinical experiences of visual disturbances with nilutamide. *Ann Pharmacother* 1997; **31**: 1551–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nilutamide 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 05/09/11)

Interactions

Patients receiving nilutamide may exhibit intolerance to alcohol.

Pharmacokinetics

Nilutamide is rapidly and completely absorbed from the gastrointestinal tract. It is extensively metabolised although it may inhibit its own metabolism to some extent after multiple doses. About 60% of an oral dose of nilutamide is eliminated in the urine and less than 10% in the faeces, with an elimination half-life of 41 to 49 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Anandron; ***Braz.***: Anandron; ***Canad.***: Anandron; ***Fr.***: Anandron; ***Gr.***: Anandror; ***Hung.***: Anandron; ***Mex.***: Anandron; ***Neth.***: Anandron; ***Port***: Anandron; ***USA***: Nilandron.

Nimotuzumab *(rINN)*

Cimazumab; h-R3; Nimotutsumabi; Nimótúzúmab; Nimotuzumabas; Nimotuzumabs; Nimotuzumabum; Нимотузумаб. Immunoglobulin G1, anti-(humanized mouse monoclonal hR3 β1 chain anti-human epidermal growth factor receptor), disulfide with humanized mouse monoclonal hR3 κ-chain, dimer.

CAS — 828933-51-3.

Profile

Nimotuzumab is a humanised monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It may be used in some countries for the treatment of glioma and cancers of the head and neck. It is also under investigation for pancreatic cancer, non-small cell lung cancer, oesophageal cancer, and gastric cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: CIMAher; ***Braz.***: Cimaher; ***China***: Taixinsheng (泰欣生); ***India***: Biomab EGFR; ***Indon.***: TheraCIM; ***Philipp.***: Theracim; ***Thai.***: TheraCIM.

Nimustine Hydrochloride *(rINNM)*

ACNU; Hidrocloruro de nimustina; Nimustiinihydrokloridi; Nimustina, hidrocloruro de; Nimustine, Chlorhydrate de; Nimustinhydroklorid; Nimustini Hydrochloridum; NSC-245382; Pimustine Hydrochloride; Нимустина Гидрохлорид.

3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride.

$C_9H_{13}ClN_6O_3$,HCl=309.2

CAS — 42471-28-3 (nimustine); 55661-38-6 (nimustine hydrochloride).

ATC — L01AD06.

ATC Vet — QL01AD06.

UNII — DFR965WKBU.

Profile

Nimustine is a nitrosourea antineoplastic with actions and uses similar to those of carmustine (p. 761.2). It is licensed for use in the treatment of malignant glioma. Nimustine hydrochloride is given in doses of 2 to 3 mg/kg or 90 to

100 mg/m² as a single dose by slow intravenous injection, repeated at intervals of 6 weeks depending on haematological response.

References.
1. Anders K, *et al.* Accelerated radiotherapy with concomitant ACNU/Ara-C for the treatment of malignant glioma. *J Neurooncol* 2000; **48:** 63–73.
2. Kochii M, *et al.* Randomized comparison of intra-arterial versus intravenous infusion of ACNU for newly diagnosed patients with glioblastoma. *J Neurooncol* 2000; **49:** 63–70.
3. Silvani A, *et al.* Intra-arterial ACNU and carboplatin versus intravenous chemotherapy with cisplatin and BCNU in newly diagnosed patients with glioblastoma. *Neurol Sci* 2002; **23:** 219–24.
4. Weller M, *et al.* Neuro-Oncology Working Group 01 trial of nimustine plus teniposide versus nimustine plus cytarabine chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. *J Clin Oncol* 2003; **21:** 3276–84.
5. Watanabe T, *et al.* Human interferon beta, nimustine hydrochloride, and radiation therapy in the treatment of newly diagnosed malignant astrocytomas. *J Neurooncol* 2005; **72:** 57–62.
6. Glas M, *et al.* Nimustine (ACNU) plus teniposide (VM26) in recurrent glioblastoma. *Oncology* 2009; **76:** 184–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Nidran (宁得朗); *Ger.*: ACNU†; *Jpn*: Nidran.

Nolatrexed *(rINN)*

AG-337 (nolatrexed dihydrochloride); Nolatrexedum; Нолатрексед.

2-Amino-6-methyl-5-(4-pyridylthio)-4(3*H*)-quinazolinone.

$C_{14}H_{12}N_4OS$=284.3

CAS — 147149-76-6 (nolatrexed); 152946-68-4 (nolatrexed dihydrochloride).

UNII — K75ZUN743Q.

Profile

Nolatrexed is, like raltitrexed (p. 850.3), a selective inhibitor of thymidylate synthase. It has been investigated as an antimetabolite antineoplastic for the treatment of hepatocellular carcinoma and other solid tumours, although results of single-agent studies have been disappointing.

References.
1. Hughes AN, *et al.* Clinical pharmacokinetic and in vitro combination studies of nolatrexed dihydrochloride (AG337, Thymitaq) and paclitaxel. *Br J Cancer* 2000; **82:** 1519–27.
2. Estlin EJ, *et al.* A phase I study of nolatrexed dihydrochloride in children with advanced cancer. *Br J Cancer* 2001; **84:** 11–18.
3. Pivot X, *et al.* Result of two randomized trials comparing nolatrexed (Thymitaq) versus methotrexate in patients with recurrent head and neck cancer. *Ann Oncol* 2001; **12:** 1595–9.
4. Gish RG, *et al.* Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007; **25:** 3069–75.

Obinutuzumab *(USAN, rINN)*

Afutuzumab; GA-101; huMAB<CD20>; Obinutuzumabum; RG-7159; Ro-5072759; Обинутузумаб.

CAS — 949142-50-1.

UNII — O43472U9X8.

Profile

Obinutuzumab is a humanised anti-CD20 monoclonal antibody that is under investigation for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Gazyva.

Oblimersen Sodium *(USAN, rINNM)*

G-3139; Natrii Oblimersenum; Oblimersen sódico; Oblimersén sódico; Oblimersen Sodique; Натрий Облимерсен.

P-Thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioadenylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioadenylyl-(3′→5′)-thymidine sodium.

$C_{172}H_{204}N_{62}Na_{17}O_{91}P_{17}S_{17}$=6058.3

CAS — 190977-41-4.

UNII — SH55B0RQ9K.

NOTE. The name Genasense has been used as a trade mark for oblimersen sodium.

Profile

Oblimersen sodium is an antisense oligonucleotide that blocks the production of BCL-2, a mitochondrial protein that prevents apoptosis. It is under investigation for the treatment of various malignant neoplasms, including leukaemias and malignant melanoma.

References.
1. Frankel SR. Oblimersen sodium (G3139 Bcl-2 antisense oligonucleotide) therapy in Waldenstrom's macroglobulinemia: a targeted approach to enhance apoptosis. *Semin Oncol* 2003; **30:** 300–304.
2. Büchele T. Proapoptotische Therapie mit Oblimersen (bcl-2-Antisense-Oligonukleotid)—Übersicht über präklinische und klinische Daten. *Onkologie* 2003; **26** (suppl 7): 60–9.
3. Herbst RS, Frankel SR. Oblimersen sodium (Genasense bcl-2 antisense oligonucleotide): a rational therapeutic to enhance apoptosis in therapy of lung cancer. *Clin Cancer Res* 2004; **10** (suppl): 4245s–4248s.
4. Chi KN. Targeting Bcl-2 with oblimersen for patients with hormone refractory prostate cancer. *World J Urol* 2005; **23:** 33–7.
5. O'Brien SM, *et al.* Phase I to II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in patients with advanced chronic lymphocytic leukemia. *J Clin Oncol* 2005; **23:** 7697–7702.
6. Mita MM, *et al.* A phase I pharmacokinetic and biologic correlative study of oblimersen sodium (Genasense, G3139) and irinotecan in patients with metastatic colorectal cancer. *Ann Oncol* 2006; **17:** 313–21.
7. Bedikian AY, *et al.* Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006; **24:** 4738–45.
8. O'Brien S, *et al.* Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol* 2007; **25:** 1114–20. Correction. *ibid.* 2008; **26:** 820.
9. O'Brien S, *et al.* 5-year survival in patients with relapsed or refractory chronic lymphocytic leukemia in a randomized, phase III trial of fludarabine plus cyclophosphamide with or without oblimersen. *J Clin Oncol* 2009; **27:** 5208–12.

Ofatumumab *(BAN, USAN, rINN)*

2F2; GSK-1841157; HuMax-CD20; Ofatumumabum; Офатумумаб.

Immunoglobulin G1, anti-(human CD20 (antigen))(human monoclonal HuMax-CD20 heavy chain), disulfide with human monoclonal HuMax-CD20 κ-chain, dimer.

CAS — 679818-59-8.

ATC — L01XC10.

ATC Vet — QL01XC10.

UNII — M95KG522R0.

Uses and Administration

Ofatumumab is a human anti-CD20 monoclonal antibody that is used in the treatment of refractory chronic lymphocytic leukaemia (p. 693.3) in patients refractory to fludarabine and alemtuzumab. An initial intravenous infusion of ofatumumab 300 mg is given for the first dose, followed after 1 week by 2 g once weekly for a further 7 doses. After a 4- or 5-week interval, 2 g is given every 4 weeks for a further 4 doses. The drug is given via an infusion pump and an in-line 0.2-micrometre filter, and is diluted in 1 litre of sodium chloride 0.9% (giving a concentration of 0.3 mg/mL for the first infusion and 2 mg/mL for subsequent infusions). An initial infusion rate of 12 mL/hour is recommended for the first 2 infusions; this rate can be doubled every 30 minutes until a rate of 200 mL/hour is reached, providing no infusion reactions occur. Subsequent doses may be begun at a rate of 25 mL/hour, and doubled every 30 minutes to a maximum of 400 mL/hour. The infusion rate should be reduced if infusion reactions occur, and premedication with a corticosteroid, analgesic, and an antihistamine is recommended, see Adverse Effects below.

It is also under investigation for non-Hodgkin's lymphoma, rheumatoid arthritis, and multiple sclerosis.

References.
1. Coiffier B, *et al.* Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood* 2008; **111:** 1094–1100.
2. Hagenbeek A, *et al.* First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. *Blood* 2008; **111:** 5486–95.
3. Robak T. Ofatumumab, a human monoclonal antibody for lymphoid malignancies and autoimmune disorders. *Curr Opin Mol Ther* 2008; **10:** 294–309.
4. Castillo J, *et al.* Ofatumumab, a second-generation anti-CD20 monoclonal antibody, for the treatment of lymphoproliferative and autoimmune disorders. *Expert Opin Invest Drugs* 2009; **18:** 491–500.

Adverse Effects, Treatment, and Precautions

As for Rituximab, see p. 854.1. Premedication with an intravenous corticosteroid, an oral analgesic, and an oral or intravenous antihistamine is recommended 30 to 120 minutes before every ofatumumab infusion; the corticosteroid dose may be reduced for later infusions if a severe infusion reaction did not occur with the previous dose. If an infusion-related adverse effect does occur, treatment should be interrupted until the patient is stable. After a mild or moderate reaction, the infusion should be restarted either at half the infusion rate being used at the time of the reaction, or the usual initial rate (12 mL/hour) if this was being used at the time of the reaction. For severe reactions, treatment should either be restarted at 12 mL/hour, regardless of the rate being used before (US recommendation for grade 3 reactions and UK recommendation), or treatment stopped (US recommendation for grade 4 reactions). If restarted, infusion rates can then be increased as usual, according to tolerance (see Uses and Administration, above).

Other adverse effects that have occurred with ofatumumab include agranulocytosis, red cell aplasia, coagulopathy, and hyperhidrosis.

Pharmacokinetics

Peak plasma concentrations of ofatumumab occur at or shortly after the end of the infusion. Ofatumumab is eliminated by proteolytic enzymes and via binding to B-cells. There is a rapid and sustained depletion of CD20 B-cells after the first infusion, leaving a reduced number for binding at subsequent infusions. As a result, clearance and half-life decrease with repeated dosing, and there is increased exposure to ofatumumab, although there is considerable interindividual variation. The mean half-life is reported to be about 1.3 days after the first infusion, and about 14 days after the twelfth.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Arzerra; *Cz.*: Arzerra; *Denm.*: Arzerra; *Fr.*: Arzerra; *Ger.*: Arzerra; *Gr.*: Arzerra; *Irl.*: Arzerra; *Israel*: Arzerra; *Jpn*: Arzerra; *Neth.*: Arzerra; *Norw.*: Arzerra; *Pol.*: Arzerra; *Port.*: Arzerra; *Spain*: Arzerra†; *Swed.*: Arzerra; *Switz.*: Arzerra; *UK*: Arzerra; *USA*: Arzerra.

Olaparib *(rINN)*

AZD-2281; KU-0059436; Olaparibum; Олапариб.

4-[(3-[(4-(Cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one.

$C_{24}H_{23}FN_4O_3$=434.5

CAS — 763113-22-0.

UNII — WOH1JD9AR8.

Profile

Olaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that is under investigation as an antineoplastic for the treatment of breast and ovarian cancer.

References.
1. Fong PC, *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009; **361:** 123–34.
2. Fong PC, *et al.* Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol* 2010; **28:** 2512–19.

Omacetaxine Mepesuccinate *(rINN)*

CGX-635; HHT; Homoharringtonine; Mepesuccinato de omacetaxina; NSC-141633; Omacétaxine, Mépésuccinate d'; Omacetaxini mepesuccinas; Омацетаксина Мепесукцинат.

1-[(1*S*,3a*R*,14b*S*)-2-Methoxy-1,5,6,8,9,14b-hexahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-1-yl] 4-methyl (2*R*)-2-hydroxy-2-(4-hydroxy-4-methylpentyl) butanedioate.

$C_{29}H_{39}NO_9$=545.6

CAS — 26833-87-4.

ATC — L01XX40.

ATC Vet — QL01XX40.

UNII — 6FG804155B.

NOTE. The name Ceflatonin has been used as a trade mark for omacetaxine mepesuccinate.

Pharmacopoeias. In *Chin.*

Uses and Administration

Omacetaxine mepesuccinate is a semisynthetic formulation of homoharringtonine, which is an alkaloid derived from the tree *Cephalotaxus harringtonia*, and related species. It is thought to induce apoptosis by inhibition of protein synthesis.

It is used for the treatment of chronic myeloid leukaemia (p. 694.2) when there is resistance or intolerance to tyrosine kinase inhibitors. The recommended starting dose of omacetaxine mepesuccinate is 1.25 mg/m² twice daily, by subcutaneous injection, for 14 consecutive days of a 28-day cycle. Cycles should be repeated every 28 days until there is a haematological response. The maintenance dose should be 1.25 mg/m² twice daily for 7 consecutive days of a 28-day cycle, repeated as long as there is clinical benefit. Complete blood counts should be performed weekly during induction and initial maintenance therapy, and every two weeks or as needed after initial maintenance cycles; the dose should be adjusted when toxicity occurs (see Administration in Subsequent Cycles, p. 838.1).

Omacetaxine mepesuccinate has also been tried in the treatment of acute leukaemias and other neoplastic disorders. The related compounds harringtonine, isoharringtonine, and deoxyharringtonine have also been investigated.

References.
1. Quintás-Cardama A, Cortes J. Homoharringtonine for the treatment of chronic myelogenous leukemia. *Expert Opin Pharmacother* 2008; 9: 1029–37.
2. Quintás-Cardama A, Cortes J. Omacetaxine mepesuccinate -a semisynthetic formulation of the natural antitumoral alkaloid homoharringtonine, for chronic myelocytic leukemia and other myeloid malignancies. *IDrugs* 2008; 11: 356–72.
3. Li Y-F, *et al.* The effect of homoharringtonine in patients with chronic myeloid leukemia who have failed or responded suboptimally to imatinib therapy. *Leuk Lymphoma* 2009; 50: 1889–91.
4. Quintás-Cardama A, *et al.* Homoharringtonine, omacetaxine mepesuccinate, and chronic myeloid leukemia circa 2009. *Cancer* 2009; 115: 5382–93.
5. Kim TD, *et al.* Omacetaxine mepesuccinate for the treatment of leukemia. *Expert Opin Pharmacother* 2011; 12: 2381–92.

Administration in subsequent cycles. If the absolute neutrophil count (ANC) falls to < 500 cells/mm³ or the platelet count falls to < 50 000 cells/mm³ during treatment with omacetaxine mepesuccinate, then the next cycle should be delayed until the ANC is ≥ 1000 cells/mm³ and the platelet count ≥ 50 000 cells/mm³. The number of dosing days should also be reduced by 2 days for the next cycle.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Omacetaxine mepesuccinate causes myelosuppression, resulting in thrombocytopenia, neutropenia, and anaemia in a significant proportion of patients. Severe thrombocytopenia has resulted in gastrointestinal haemorrhage and cases of fatal cerebral haemorrhage. Other common adverse effects include diarrhoea, nausea, fatigue, asthenia, arthralgia, headache, alopecia, rash, and convulsions. Glucose intolerance and severe hyperglycaemia have been reported. Injection site reactions can occur.

Complete blood counts should be monitored regularly. Blood-glucose should also be monitored, particularly in patients with diabetes or risk factors for diabetes.

Pharmacokinetics

Peak plasma concentrations of omacetaxine mepesuccinate occur about 30 minutes after subcutaneous injection. Plasma protein binding is less than or equal to 50%. Omacetaxine mepesuccinate is hydrolysed by plasma esterases, but the major elimination route is unknown. The mean elimination half-life after subcutaneous use is about 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Chuan Shan Ning (川山宁); Fu Er (扶尔); Gao Rui Te (高瑞特); Hua Pu Le (华普乐); Jin Nuo Xing (金诺星); Sai Lan (赛兰); Wo Ting (沃汀); *USA*: Synribo.

Oregovomab *(USAN, rINN)*

MAb-B43.13; Orégovomab; Oregovomabum; Оревомаб. Immunoglobulin G1, anti-(human CA125 (carbohydrate antigen)) (mouse monoclonal B43.13 γ1-chain), disulfide with mouse monoclonal B43.13 κ-chain, dimer.

CAS — 213327-37-8.

Profile

Oregovomab is a murine monoclonal antibody that binds to CA-125, an antigen that is overexpressed in the majority of ovarian cancer patients, and stimulates an immune response to the tumour cells. It has been investigated for the treatment of ovarian cancer.

Oxaliplatin *(BAN, USAN, rINN)*

JM-83; NSC-266046; L-OHP; Oksaliplatiini; Oksaliplatin; Oksaliplatina; Oxalato-platinum; Oxaliplatina; Oxaliplatine; Oxaliplatino; Oxaliplatinum; RP-54780; SR-96669; Оксалиплатин.

[(1*R*,2*R*)-1,2-Cyclohexanediamine-*N*,*N*'][oxalato(2-)-*O*,*O*']platinum.

$C_8H_{14}N_2O_4Pt$=397.3.

CAS — 61825-94-3.

ATC — L01XA03.

ATC Vet — QL01XA03.

UNII — 04ZR38536J.

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

Ph. Eur. 8: (Oxaliplatin). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol; very slightly soluble in methyl alcohol.

USP 36: (Oxaliplatin). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol; very slightly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Incompatibility. Licensed product information states that oxaliplatin should not be mixed with chloride-containing solutions (including sodium chloride) or alkaline drugs or solutions. In particular, oxaliplatin should not be mixed with fluorouracil or any trometamol salts. While oxaliplatin may be infused through a Y-site with folinic acid (in glucose 5% solution), they may not be mixed in the same infusion bag, and folinic acid must not contain trometamol as an excipient. The infusion line should be flushed with glucose 5% before giving any other medication. Oxaliplatin may degrade on contact with aluminium, and injection equipment containing aluminium should not be used.

Stability. UK licensed product information states that oxaliplatin must be diluted in glucose 5% to give a concentration not less than 200 micrograms/mL. From a microbiological point of view, the infusion preparation should be used immediately; the infusion should not be stored for longer than 24 hours at 2 degrees to 8 degrees unless it has been prepared in controlled and validated aseptic conditions. Chemical and physical stability has been shown for 48 hours at 2 degrees to 8 degrees, and for 24 hours at 25 degrees. US licensed product information states that, after dilution in 250 to 500 mL of glucose 5%, oxaliplatin infusion solutions have a shelf-life of 6 hours at room temperature (20 degrees to 25 degrees) and up to 24 hours when refrigerated (2 degrees to 8 degrees), and that protection from light is not required.

A study[1] found that oxaliplatin solutions at 700 micrograms/mL in polyolefin infusion bags of glucose 5% were chemically stable for at least 30 days at both 3 degrees to 7 degrees and 20 degrees to 24 degrees without regard to light. Another study[2] found that oxaliplatin solutions at 250 micrograms/mL in 5% glucose, in polyolefin bags, were stable at 4 degrees as well as at room temperature (either protected or unprotected from light) for 90 days. Additionally, oxaliplatin solutions diluted to 200 micrograms/mL and 1.3 mg/mL in glucose 5% were found to be stable in PVC, polyethylene, and polypropylene infusion bags for at least 14 days at both 4 degrees and 20 degrees, either protected or unprotected from light.[3]

1. André P, *et al.* Stability of oxaliplatin in infusion bags containing 5% dextrose injection. *Am J Health-Syst Pharm* 2007; 64: 1950–4.
2. Junker A, *et al.* Stability of oxaliplatin solution. *Ann Pharmacother* 2009; 43: 390–1.
3. Elden C, *et al.* Physicochemical stability of oxaliplatin in 5% dextrose injection stored in polyvinyl chloride, polyethylene, and polypropylene infusion bags. *Am J Health-Syst Pharm* 2009; 66: 1929–33.

Uses and Administration

Oxaliplatin is a platinum-containing complex similar to cisplatin (see p. 766.1). It is given with fluorouracil and folinic acid in the treatment of metastatic colorectal cancer and in the adjuvant treatment of stage III (Dukes C) colon cancer (p. 706.3). The recommended dose is 85 mg/m² by intravenous infusion over 2 to 6 hours, dissolved in 250 to 500 mL of glucose 5%. The dose may be repeated at intervals of 2 weeks if toxicity permits, reduced according to tolerance. In the adjuvant setting, oxaliplatin is given for 12 cycles. After persistent neurotoxicity or recovery from severe adverse effects licensed product information recommends an initial reduction to 65 mg/m² in metastatic colorectal cancer, and to 75 mg/m² when given as adjuvant treatment. Oxaliplatin should always be given before fluoropyrimidines.

Oxaliplatin is under investigation for the treatment of ovarian and lung cancer. A liposomal formulation of oxaliplatin is in development.

References.
1. Culy CR, *et al.* Oxaliplatin: a review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000; 60: 895–924.
2. Simpson D, *et al.* Oxaliplatin: a review of its use in combination therapy for advanced metastatic colorectal cancer. *Drugs* 2003; 63: 2127–56.
3. Keam SJ, *et al.* Oxaliplatin: in operable colorectal cancer. *Drugs* 2005; 65: 89–96.
4. Pu S, *et al.* Clinical application of oxaliplatin in epithelial ovarian cancer. *Int J Gynecol Cancer* 2006; 16: 1717–32.
5. Kim GP, Erlichman C. Oxaliplatin in the treatment of colorectal cancer. *Expert Opin Drug Metab Toxicol* 2007; 3: 281–94.
6. Stordal B, *et al.* Oxaliplatin for the treatment of cisplatin-resistant cancer: a systematic review. *Cancer Treat Rev* 2007; 33: 347–57.
7. Cortinovis D, *et al.* Oxaliplatin doublets in non-small cell lung cancer: a literature review. *Lung Cancer* 2008; 60: 325–31.
8. Capdevila J, *et al.* Oxaliplatin-based chemotherapy in the management of colorectal cancer. *Expert Rev Anticancer Ther* 2008; 8: 1223–36.
9. Raez LE, *et al.* Oxaliplatin in first-line therapy for advanced non-small-cell lung cancer. *Clin Lung Cancer* 2010; 11: 18–24.
10. Alcindor T, Beauger N. Oxaliplatin: a review in the era of molecularly targeted therapy. *Curr Oncol* 2011; 18: 18–25.

Administration in the elderly. A review[1] concluded that there are no data to support dose reduction of oxaliplatin based on age alone, other than any dosage adjustment considered necessary for renal impairment (see Administration in Renal Impairment, below).

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in renal impairment. The primary route of platinum elimination is renal, and clearance of platinum is decreased in patients with renal impairment. However, a study determined that increased platinum exposure in patients with renal impairment was not associated with increased oxaliplatin toxicity. Dose reduction was not considered to be necessary in patients with mild to moderate renal impairment (as defined by creatinine clearance of 20 mL/minute or more).[1] UK licensed product information concurs that no dose adjustment is necessary in mild to moderate renal impairment, but contra-indicates the use of oxaliplatin in severe renal impairment (defined as creatinine clearance of less than 30 mL/minute), due to lack of data.

1. Takimoto CH, *et al.* Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute organ dysfunction working group study. *J Clin Oncol* 2003; 21: 2664–72.

Adverse Effects and Precautions

The adverse effects of oxaliplatin are similar to those of cisplatin (p. 767.1) but nausea and vomiting, nephrotoxicity, and myelosuppression, seem to be less marked. Raised liver enzyme values may occur. Neurotoxicity can be dose-limiting. Peripheral neuropathy occurs in 85 to 95% of patients given oxaliplatin; pain, functional impairment, and loss of tendon reflexes may develop. Pulmonary fibrosis, potentially fatal, has also been reported. Extravasation of oxaliplatin can cause local pain and inflammation; complications may sometimes be severe, including necrosis.

Neurological examinations should be carried out at regular intervals during treatment and the dose should be reduced if symptoms are prolonged or severe. Regular blood counts should be performed during treatment and courses should not be repeated until blood counts have recovered (see also Bone-marrow Depression, p. 730.3). Oxaliplatin should not be given to patients with pre-existing sensory neuropathies or myelosuppression, nor to those with severe renal impairment. Renal function and toxicity should be carefully monitored in those with more moderate degrees of renal impairment.

Patients are recommended to use appropriate contraceptive measures during treatment and for 6 months after stopping treatment for men and for 4 months for women.

Effects on the blood. Acute haemolysis, with[1-3] and without[4] anaemia, has been reported with the use of oxaliplatin. The reactions were considered to be immune-mediated. Evan's syndrome (immune-mediated thrombocytopenia and haemolytic anaemia) has also been reported,[7] as has sudden onset of pancytopenia with resultant intracranial haemorrhage.[8]

See also under Hypersensitivity, p. 839.2.

1. Desrame J, *et al.* Oxaliplatin-induced haemolytic anaemia. *Lancet* 1999; 354: 1179–80.
2. Garufi C, *et al.* Immunohemolytic anemia following oxaliplatin administration. *Ann Oncol* 2000; 11: 497.
3. Hofheinz R-D, *et al.* Two potential mechanisms of oxaliplatin-induced haemolytic anaemia in a single patient. *Cancer Chemother Pharmacol* 2004; 53: 276–7.
4. Chen VMY, *et al.* An immediate hemolytic reaction induced by repeated administration of oxaliplatin. *Transfusion* 2004; 44: 838–43.
5. Lai J-I, Wang W-S. Acute hemolysis after receiving oxaliplatin treatment: a case report and literature review. *Pharm World Sci* 2009; 31: 538–41.
6. Koutras AK, *et al.* Oxaliplatin-induced acute-onset thrombocytopenia, hemorrhage and hemolysis: a case report and review of the literature. *Oncology* 2004; 67: 179–82.
7. Earle CC, *et al.* Oxaliplatin-induced Evan's syndrome. *Br J Cancer* 2001; 84: 441.
8. Teng CJ, *et al.* Sudden-onset pancytopenia with intracranial hemorrhage after oxaliplatin treatment: a case report and literature review. *Jpn J Clin Oncol* 2011; 41: 125–9.

Effects on the liver. The development of ascites, portal hypertension, and hepatic lesions in a patient with colorectal cancer was considered to be due to oxaliplatin; metastatic or recurrent cancer had been originally suspected.[1]

1. Tisman G, *et al.* Oxaliplatin toxicity masquerading as recurrent colon cancer. *J Clin Oncol* 2004; 22: 3202–4.

Effects on the nervous system. Neurological toxicity is the principal dose-limiting adverse effect with oxaliplatin.[1-4] The toxicity is biphasic:

- acute paraesthesias or dysaesthesias of the extremities, triggered or exacerbated by cold, are seen in 85 to 95% of patients within hours of infusion, but are normally mild and resolve within hours or days. Some patients also

have distressing laryngopharyngeal symptoms, such as difficulty in breathing or swallowing.
- with increasing cumulative dose, peripheral sensory symptoms increase in duration and intensity. Symptoms are sometimes associated with pain and cramps, and may progress to functional impairment (loss of fine sensorimotor coordination). Dosage reduction may be required, but in clinical practice the onset of functional impairment often occurs after the maximum response to therapy has been attained. Cumulative neurotoxicity is reversible in most cases, and about 80% of patients exhibit symptom regression within 4 to 6 months.

The incidence of neurotoxicity may be higher when oxaliplatin is given with fluorouracil. There is some evidence that more prolonged infusion of oxaliplatin can reduce acute toxicity, particularly laryngopharyngeal symptoms. Antiepileptics such as carbamazepine (see Neuropathic Pain, p. 513.2) or gabapentin have been investigated in the management of oxaliplatin-induced neurotoxicity, although results have been inconclusive.[5] Other drugs that have been tried include amifostine, glutathione, acetylcarnitine, thioctic acid, celecoxib, and ginkgo biloba extract.[5] Initial results have been promising for some of these substances,[5] but, similarly to cisplatin (see p. 767.3), conclusive data are lacking for most interventions. Intravenous calcium gluconate and magnesium chloride infusions have been used to prevent acute oxaliplatin neuropathy with good initial results; similarly, intravenous calcium gluconate and magnesium sulfate have been reported to dramatically improve oxaliplatin-associated neuropathy.[6-8] However, a study designed to evaluate potential reduction of cumulative neurotoxicity associated with oxaliplatin, using calcium and magnesium salts, was terminated after those patients receiving calcium and magnesium reported a significantly lower response to chemotherapy (which consisted of oxaliplatin, folinic acid, fluorouracil, and bevacizumab). Although these results need confirmation, the possibility that calcium and magnesium may reduce the activity of certain drugs in the treatment of colorectal cancer should be considered.[9] Others[10,11] have contended that calcium and magnesium therapy does not affect the antitumour efficacy of oxaliplatin-containing regimens; further studies are planned.

1. Extra JM, *et al.* Pharmacokinetics and safety profile of oxaliplatin. *Semin Oncol* 1998; **25** (suppl 5): 13–22.
2. Culy CR, *et al.* Oxaliplatin: a review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000; **60**: 895–924.
3. Cassidy J, Misset J-L. Oxaliplatin-related side effects: characteristics and management. *Semin Oncol* 2002; **29** (suppl 15): 11–20.
4. Argyriou AA, *et al.* A review on oxaliplatin-induced peripheral nerve damage. *Cancer Treat Rev* 2006; **34**: 368–77.
5. Saif MW, Reardon J. Management of oxaliplatin-induced peripheral neuropathy. *Ther Clin Risk Manag* 2005; **1**: 249–58.
6. Gamelin L, *et al.* Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res* 2004; **10**: 4055–61.
7. Cersosimo RJ. Oxaliplatin-associated neuropathy: a review. *Ann Pharmacother* 2005; **39**: 128–35.
8. Gamelin L, *et al.* Neurotoxicité de l'oxaliplatine. *Bull Cancer* 2006; **93** (suppl 1): S17–S22.
9. Hochster HS, *et al.* Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. *J Clin Oncol* 2007; **25**: 4028–9.
10. Gamelin L, *et al.* Oxaliplatin-related neurotoxicity: interest of calcium-magnesium infusion and no impact on its efficacy. *J Clin Oncol* 2008; **26**: 1188–9.
11. Grothey A, *et al.* Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. *J Clin Oncol* 2011; **29**: 421–7.

GUILLAIN-BARRÉ SYNDROME. A patient with metastatic colon cancer developed Guillain-Barré syndrome after weekly treatment with oxaliplatin-based chemotherapy;[1] he recovered after treatment with intravenous immunoglobulin.

1. Christodoulou C, *et al.* Guillain-Barré syndrome in a patient with metastatic colon cancer receiving oxaliplatin-based chemotherapy. *Anticancer Drugs* 2004; **15**: 997–9.

REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME. Reversible posterior leukoencephalopathy syndrome (RPLS) was diagnosed in a woman given oxaliplatin with bevacizumab, and capecitabine. She tolerated further therapy with bevacizumab and irinotecan with no complications. The authors attributed the RPLS to oxaliplatin.[1]

1. Pinedo DM, *et al.* Reversible posterior leukoencephalopathy syndrome associated with oxaliplatin. *J Clin Oncol* 2007; **25**: 5320–1.

Extravasation. Although oxaliplatin was originally considered to be non-vesicant, there have been reports of extravasation causing inflammation, sclerosis, or, in some cases, severe necrosis.[1-4] Some consider it to be a vesicant drug,[1,2] although others state oxaliplatin extravasation to be less harmful than that of more classic vesicants.[4]

For discussion of the management of extravasation, see under Treatment of the Adverse Effects of Antineoplastics, p. 731.3.

1. Baur M, *et al.* Extravasation of oxaliplatin (Elozatin)–clinical course. *Onkologie* 2000; **23**: 468–71.
2. Poo KF, *et al.* A case report of oxaliplatin extravasation. *Ann Oncol* 2003; **14**: 961–2.
3. Kennedy JG, *et al.* Vesicant characteristics of oxapliplatin [sic] following antecubital extravasation. *Clin Oncol (R Coll Radiol)* 2003; **15**: 237–9.
4. Kretzschmar A, *et al.* Extravasations of oxaliplatin. *J Clin Oncol* 2003; **21**: 4068–9.

Hypersensitivity. Hypersensitivity reactions, including anaphylaxis, have been reported with oxaliplatin,[1-18] usually after several cycles of treatment. Symptoms include hypotension, tachycardia, dyspnoea, burning sensations, pruritus, erythema, sweating, and dizziness.[1,2,7,8] Rashes have also been reported[5,6,12] as have fever and chills.[9,10] While the mechanism of hypersensitivity to oxaliplatin is not clear, it has been suggested that reactions are characterised by development of symptoms during or shortly after the infusion, and are possibly due to a type I IgE-mediated reaction.[7,10] Idiosyncratic or infusional reactions, which are delayed until hours after the infusion,[6,10] are considered to be associated with cytokine release.[7,10] Cases have generally resolved on stopping oxaliplatin and giving appropriate treatment. Acute thrombocytopenia, occurring after the onset of hypersensitivity, has been reported in 2 patients,[15] both of whom were found to have oxaliplatin-dependent IgG platelet antibodies; see also Effects on the Blood, p. 838.3.

Prophylaxis before further oxaliplatin therapy, with corticosteroids and/or antihistamines, has shown variable efficacy.[4-7,9,10] Desensitisation protocols using dilute solutions and longer infusion times have been reported to be successful.[10,11,13,14] For the successful use of cisplatin in a patient hypersensitive to oxaliplatin see p. 768.1.

Intradermal skin testing has been used to identify patients with suspected hypersensitivity to oxaliplatin; however, in some patients with negative skin tests, reactions have occurred upon rechallenge.[6,8]

1. Tourniguand C, *et al.* Severe anaphylactic reactions to oxaliplatin. *Eur J Cancer* 1998; **34**: 1297–8.
2. Médioni J, *et al.* Anaphylaxis after oxaliplatin. *Ann Oncol* 1999; **10**: 610.
3. Larzillière I, *et al.* Anaphylactic reaction to oxaliplatin: a case report. *Am J Gastroenterol* 1999; **94**: 3387–8.
4. Stahl M, *et al.* Reaction after oxaliplatin—prevention with corticosteroids? *Ann Oncol* 2001; **12**: 874.
5. Alliot C, *et al.* Severe anaphylactic reaction to oxaliplatin. *Clin Oncol (R Coll Radiol)* 2001; **13**: 236.
6. Thomas RR, *et al.* Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 2003; **97**: 2301–7.
7. Brandi G, *et al.* Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003; **89**: 477–81.
8. Garufi C, *et al.* Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol* 2003; **14**: 497–8.
9. Lenz G, *et al.* Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. *Anticancer Drugs* 2003; **14**: 731–3.
10. Lim K-H, *et al.* Hypersensitivity reactions to oxaliplatin: a case report and the success of a continuous infusional desensitization schedule. *Anticancer Drugs* 2004; **15**: 605–7.
11. Gammon D, *et al.* Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist* 2004; **9**: 546–9.
12. Ng CVT. Hypersensitivity reactions to oxaliplatin in two Asian patients. *Ann Pharmacother* 2005; **39**: 1114–18.
13. Mis L, *et al.* Successful desensitization to oxaliplatin. *Ann Pharmacother* 2005; **39**: 966–9.
14. Syrigou EI, *et al.* Hypersensitivity reactions to oxaliplatin: a retrospective study and the development of a desensitization protocol. *Clin Colorectal Cancer* 2009; **8**: 106–9.
15. Bautista MA, *et al.* Hypersensitivity reaction and acute immune-mediated thrombocytopenia from oxaliplatin: two case reports and a review of the literature. *J Hematol Oncol* 2010; **3**: 12.
16. Shao Y-Y, *et al.* Characteristics and risk factors of oxaliplatin-related hypersensitivity reactions. *J Formos Med Assoc* 2010; **109**: 362–8.
17. Mori Y, *et al.* Oxaliplatin-free interval as a risk factor for hypersensitivity reaction among colorectal cancer patients treated with POLFOX. *Oncology* 2010; **79**: 136–43.
18. Seki K, *et al.* Risk factors for oxaliplatin-induced hypersensitivity reactions in Japanese patients with advanced colorectal cancer. *Int J Med Sci* 2011; **8**: 210–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxaliplatin 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 26/08/11)

Interactions

For reference to the effect of oxaliplatin on fluorouracil, see Antineoplastics, p. 797.3.

Pharmacokinetics

After intravenous doses, oxaliplatin is widely distributed throughout the body. It binds irreversibly to red blood cells, which can prolong the half-life of the drug. The mean terminal half-life has been variously stated to be 273 hours and 391 hours.

Oxaliplatin is extensively metabolised to both inactive and active compounds and is mainly excreted in the urine.

References.

1. Lévi F, *et al.* Oxaliplatin: pharmacokinetics and chronopharmacological aspects. *Clin Pharmacokinet* 2000; **38**: 1–21.
2. Graham MA, *et al.* Clinical pharmacokinetics of oxaliplatin: a critical review. *Clin Cancer Res* 2000; **6**: 1205–18.
3. Jerremalm E, *et al.* New insights into the biotransformation and pharmacokinetics of oxaliplatin. *J Pharm Sci* 2009; **98**: 3879–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Crisapla; Dabenzol; Dacplat; Goxyral; Kebir; Metaplatin; Mitog; O-Plat; Oxaltic; Platinostyl; Plusplatin; Uxalun; Xaliplat; ***Austral.***: Eloxatin; Oxalatin; ***Austria***: Eloxatin; ***Belg.***: Eloxatin; ***Braz.***: Eloxatin; Ezulen; O-Plat; Oxalibbs; Tevaoxali; Uxalun; ***Canad.***: Eloxatin; ***Chile***: Eloxatin; O-Plat; ***China***: Ai Heng (艾恒); Ai Ke Bo Kang (艾克博康); Ao Zheng Nan (奥正南); Cao Bo (草铂); Chen Ya (辰雅); Duo Ling (多令); Eloxatin (乐沙定); Jia Le Tong Tai (佳乐同泰); Olatin (优铂廷); *Cz.*: Ebeoxal; Eloxatin; Livellin; Oxaliquid; Oxiplat†; Platox; Rezidol; ***Denm.***: Eloxatin; Olatin; Rezidol; ***Fin.***: Eloxatin†; Oxitropic†; ***Fr.***: Eloxatine; ***Ger.***: Axiplatin; Bendaplatin; Croloxat; Eloxatin; Medoxa; Oxaliplan; Riboxatin; ***Gr.***: Axoplan; Eloxatin; Oxaliprol; Oxaltina; Plaxitin; Rectoxal; Rexap; Veraxatin; ***Hong Kong***: Eloxatin; Sindoxplatin; ***Hung.***: Eloxatin; Gessedil; Livellin†; Sinoxal; ***India***: Celdach; Dacotin; Fexoplat; Glenoxal; Kinaplat; Oplatin; Oxamil; Oxiplat; Oxitan; Oxoplan; ***Indon.***: Eloxatin; Rexta; ***Irl.***: Eloxatin; Oxamed†; ***Israel***: Eloxatin; ***Ital.***: Eloxatin; ***Jpn***: Elplat; ***Malaysia***: Eloxatin; ***Mex.***: Eloxatin; Entia; Olipcis; Oxitan; Riptam; ***Neth.***: Eloxatin; Foxantal†; Osigilatin†; Oxalisin; Oxiplasol†; ***Norw.***: Eloxatin; ***NZ***: Eloxatin; Oxaliccord; ***Philipp.***: Eloxatin; Henplatin; Oxalem; Oxitel; Platinox; Zildox; ***Pol.***: Eloxatin; Gessedil; ***Port.***: Eloxatin; Oxalix; ***Rus.***: Eloxatine (Элоксатин); Exorum (Экзорум); Oxatera (Оксатера); Plaksat (Плаксат); Platicad (Платикад); ***S.Afr.***: Eloxatin; Exiplat; Oxaliwin; ***Singapore***: Eloxatin; ***Spain***: Eloxatin; Oxitropic†; ***Swed.***: Eloxatin; ***Switz.***: Eloxatine; ***Thai.***: Eloxatin; Entia; Oxalip; Oxitan; Oxol; Oxplatin; ***Turk.***: Eloxatin; Linoxa; Oxalimedac; Oxalpin; Oxaqual; Oxebewe; Oxerol; Ploxal; ***UK***: Eloxatin†; ***Ukr.***: Eloxatine (Элоксатин); ***USA***: Eloxatin; ***Venez.***: Eloxatin.

Pharmacopoeial Preparations

USP 36: Oxaliplatin for Injection; Oxaliplatin Injection.

Paclitaxel *(BAN, USAN, rINN)*

BMS-181339-01; NSC-125973; Paclitaxelum; Paklitakseeli; Paklitaksel; Paklitaxel; Taxol; Taxol A; Паклитаксел.

(2*S*,5*R*,7*S*,10*R*,13*S*)-10,20-Bis(acetoxy)-2-benzoyloxy-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-13-yl (3*S*)-3-benzoylamino-3-phenyl-o-lactate.

$C_{47}H_{51}NO_{14}$=853.9

CAS — 33069-62-4.

ATC — L01CD01.

ATC Vet — QL01CD01.

UNII — P88XT4IS4D.

NOTE. Paclitaxel was formerly referred to as taxol, but the use of this name is now limited, as Taxol is a trademark.

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

Ph. Eur. 8: (Paclitaxel). Isolated from natural sources or produced by fermentation or by a semisynthetic process. A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Paclitaxel). A white to off-white powder. Insoluble in water; soluble in alcohol. Store in airtight containers at a temperature between 20 degrees and 25 degrees. Protect from light.

Incompatibility. The vehicle for conventional paclitaxel injection, which contains alcohol and polyoxl castor oil, was found to leach the plasticiser diethylhexyl phthalate (DEHP) from some plastic giving sets.[1,2] Consequently, licensed product information recommends the use of non-PVC containers and giving sets; the use of filter devices which incorporate short inlet and/or short outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

Paclitaxel was found to be compatible with doxorubicin for at least 24 hours, but microcrystalline precipitation of paclitaxel occurred after 3 to 5 days.[3] For mention of the incompatibility of paclitaxel and cisplatin see p. 766.1.

1. Trissel LA, *et al.* Compatibility of paclitaxel injection vehicle with intravenous administration and extension sets. *Am J Hosp Pharm* 1994; **51**: 2804–10.
2. Mazzo DJ, *et al.* Compatibility of docetaxel and paclitaxel in intravenous solutions with polyvinyl chloride infusion materials. *Am J Health-Syst Pharm* 1997; **54**: 566–9.
3. Trissel LA, *et al.* Compatibility and stability of paclitaxel combined with doxorubicin hydrochloride in infusion solutions. *Ann Pharmacother* 1998; **32**: 1013–6.

Uses and Administration

Paclitaxel is a taxane originally derived from the bark of the Pacific yew tree *Taxus brevifolia* (Taxaceae), and now obtained semisynthetically from a taxane precursor derived from the needles of the European yew, *Taxus baccata*. Paclitaxel's antineoplastic action arises from induction of microtubule formation and stabilisation of microtubules, thereby disrupting normal cell division in the G_2 and M phases of the cell cycle.

Paclitaxel is used for the primary treatment of advanced ovarian cancer (p. 711.2) with cisplatin or carboplatin, and for secondary treatment, usually after failure of standard platinum-containing therapy. In the treatment of node-positive breast cancer (p. 702.1), paclitaxel is used for adjuvant therapy after anthracycline-containing chemotherapy. In locally advanced or metastatic breast cancer, it is used first-line with an anthracycline, or as a second-line single-agent, usually after failure of anthracycline-based therapy. In patients with locally advanced or metastatic disease who overexpress HER2 (human epidermal growth receptor 2) it may be used with trastuzumab as initial therapy. Paclitaxel is used with cisplatin or carboplatin, for the primary treatment of non-small cell lung cancer (p. 710.2) in patients who are not candidates for potentially curative surgery and/or radiotherapy. In metastatic adenocarcinoma of the pancreas (p. 712.1) it is used first-line with gemcitabine. It may be used for the second-line treatment of AIDS-related Kaposi's sarcoma (p. 718.1), and has been tried in other neoplasms including cancers of the head and neck, and relapsed germ-cell tumours.

The conventional formulation of paclitaxel with polyoxyl castor oil and alcohol is usually given intravenously. It is diluted, usually with sodium chloride 0.9% or glucose 5%, to a final concentration of 0.3 to 1.2 mg/mL, in a non-PVC container and given through an in-line filter (of not greater than 0.22 micrometres). In licensed regimens it is generally given at 3-week intervals although there is increasing evidence that use at smaller intervals of 1 week may be advantageous (see Administration, below). An injectable suspension of albumin-bound paclitaxel nanoparticles (*Abraxane; Celgene, UK and USA;* ABI-007) is also available. It is usually given intravenously over 30 minutes. PVC or non-PVC containers may be used; an in-line filter is not necessary.

The recommended dose of conventional paclitaxel for the primary treatment of **ovarian cancer** is 135 mg/m^2 infused over 24 hours, followed by cisplatin, and repeated at 3-week intervals. Alternatively 175 mg/m^2 may be infused over 3 hours, followed by cisplatin, every 3 weeks. For the secondary treatment of ovarian cancer, the suggested dose as a single agent is 135 or 175 mg/m^2 infused over 3 hours once every 3 weeks.

Paclitaxel has also been given intraperitoneally for the treatment of ovarian cancer.

For **breast cancer**, an intravenous dose of conventional paclitaxel 175 mg/m^2 infused over 3 hours once every 3 weeks is recommended for adjuvant treatment (for 4 courses), for second-line monotherapy, and for first-line treatment with trastuzumab; paclitaxel is given the day after the first dose of trastuzumab, or immediately after subsequent doses if well-tolerated. When used first-line with doxorubicin, paclitaxel 220 mg/m^2 is infused over 3 hours once every 3 weeks; the dose is given 24 hours after doxorubicin.

Albumin-bound paclitaxel nanoparticles are also used for the treatment of refractory or relapsed metastatic breast cancer. The dose is 260 mg/m^2 given intravenously over 30 minutes every 3 weeks.

In **non-small cell lung cancer**, the recommended dose of conventional paclitaxel is 135 mg/m^2 over 24 hours, or 175 mg/m^2 over 3 hours, followed by cisplatin, and repeated at 3-week intervals.

Albumin-bound paclitaxel nanoparticles may also be used with carboplatin as a first-line option for locally advanced or metastatic non-small cell lung cancer. A dose of 100 mg/m^2 is infused intravenously over 30 minutes on days 1, 8, and 15 of a 21-day cycle.

For the first-line treatment of metastatic **pancreatic adenocarcinoma**, albumin-bound paclitaxel nanoparticles are given in a dose of 125 mg/m^2 infused intravenously over 30 to 40 minutes, and followed immediately after by gemcitabine, on days 1, 8, and 15 of a 28-day cycle.

A dose of conventional paclitaxel 135 mg/m^2 over 3 hours once every 3 weeks has been suggested for AIDS-related **Kaposi's sarcoma**. Alternatively, 100 mg/m^2 over 3 hours every 2 weeks may be given, especially in patients with poor performance status.

Regular blood counts should be performed, and dosage should not be given or repeated until the neutrophil and platelet counts are at acceptable levels; see Administration in Subsequent Cycles, below. Pretreatment with corticosteroids, antihistamines, and histamine H_2-antagonists is needed for the conventional formulation of paclitaxel, but not for the albumin-bound nanoparticle formulation.

The dose of paclitaxel may need to be reduced in patients with hepatic impairment (see below).

Various formulations have been developed to avoid the use of polyoxyl castor oil and improve the efficacy and safety of paclitaxel. In addition to the albumin-bound formulation referred to above, formulations in development include paclitaxel linked to docosahexaenoic acid (DHA-paclitaxel) or biodegradable polymers (such as paclitaxel poliglumex, CT-2103), micellar and liposomal formulations, and an oral dosage form. An injectable gel containing a modified-release formulation of paclitaxel is also under investigation, for direct injection into tumours.

Paclitaxel-releasing stents may be used to reduce restenosis after coronary artery stent placement.

References to paclitaxel, and to taxanes as a class.

1. Hayes DF, *et al.* Cancer and Leukemia Group B (CALGB) Investigators. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med* 2007; 357: 1496–1506.
2. Saloustros E, *et al.* Paclitaxel and docetaxel in the treatment of breast cancer. *Expert Opin Pharmacother* 2008; 9: 2603–16.
3. Sakamoto J, *et al.* Paclitaxel chemotherapy for the treatment of gastric cancer. *Gastric Cancer* 2009; 12: 69–78.
4. Fu Y, *et al.* Medicinal chemistry of paclitaxel and its analogues. *Curr Med Chem* 2009; 16: 3966–85.
5. Gaitanis A, Staal S. Liposomal doxorubicin and nab-paclitaxel: nanoparticle cancer chemotherapy in current clinical use. *Methods Mol Biol* 2010; 624: 385–92.
6. Montero AJ, *et al.* Nab-paclitaxel in the treatment of metastatic breast cancer: a comprehensive review. *Expert Rev Clin Pharmacol* 2011; 4: 329–34.
7. Huang TC, Campbell TC. Comparison of weekly versus every 3 weeks paclitaxel in the treatment of advanced solid tumors: a meta-analysis. *Cancer Treat Rev* 2012; 38: 613–17.
8. Socinski MA, *et al.* Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012; 30: 2055–62.
9. Gradishar WJ. Taxanes for the treatment of metastatic breast cancer. *Breast Cancer (Auckl)* 2012; 6: 159–71.
10. Von Hoff DD, *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; 369: 1691–1703.

Administration. Although many of the original studies of conventional paclitaxel employed a 24-hour infusion regimen, the use of *3-hour infusions* has subsequently become widespread. A systematic review[1] noted that although it was difficult to compare efficacy in studies of unlike malignancies there was no conclusive evidence of a difference in efficacy with differing length of infusion; however, there were differences in the adverse effect profile, neutropenia being much less marked with the shorter infusion, although neurotoxic effects were reduced with 24-hour administration. (Note that albumin-bound paclitaxel can be given over 30 minutes, see p. 839.3).

There has also been considerable interest in evaluating the use of conventional paclitaxel in reduced-dose *weekly* schedules.[2-14] Various dosage regimens have been tried: most have found that doses of between 50 and about 100 mg/m^2 weekly, usually by infusion over 1 hour rather than a conventional 3-hour infusion, can be given with relatively modest toxicity. Although higher doses have been tried, neurotoxicity and myelosuppression become problematic and tend to limit dose intensity. Several studies have addressed the use of weekly paclitaxel with other antineoplastics, for example with trastuzumab in breast cancer, estramustine in prostate cancer, and with platinum compounds or gemcitabine in other solid tumours such as those of the ovary or lung. In a randomised controlled study[13] in patients with metastatic breast cancer, weekly paclitaxel (80 mg/m^2) with or without trastuzumab nearly doubled time to progression from 5 to 9 months compared with a 3-weekly regimen, and had better response rates and overall survival. Neuropathy was the main toxicity (see also Effects on the Nervous System, p. 841.3). A meta-analysis[14] of weekly versus 3-weekly taxane regimens in advanced breast cancer found that although the objective response rate was better with a 3-week regimen of paclitaxel, giving the drug weekly produced higher overall survival and was associated with fewer serious adverse effects. There appeared to be little difference between a weekly and a 3-weekly regimen for docetaxel, but it was impossible to come to firm conclusions because of scanty data.

The use of weekly paclitaxel with radiotherapy is also under investigation in the management of lung cancer and glioblastoma multiforme.

For the suggestion that inhibitors of P-glycoprotein (such as ciclosporin) might be used to boost bioavailability and allow the use of *oral* paclitaxel see Immunosuppressants, under Interactions of Docetaxel, p. 782.2.

1. Williams C, *et al.* Short versus long duration infusions of paclitaxel for any advanced adenocarcinoma. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2011 (accessed 29/06/11).
2. Seidman AD, *et al.* Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol* 1998; 16: 3353–61.
3. Fountzilas G, *et al.* Radiation and concomitant weekly administration of paclitaxel in patients with glioblastoma multiforme: a phase II study. *J Neurooncol* 1999; 45: 159–65.
4. Markman M. Weekly paclitaxel in the management of ovarian cancer. *Semin Oncol* 2000; 27 (suppl 7): 37–40.
5. De Pas T, *et al.* Phase I and pharmacologic study of weekly gemcitabine and paclitaxel in chemo-naive patients with advanced non-small-cell lung cancer. *Ann Oncol* 2000; 11: 821–7.
6. Langer CJ, *et al.* Paclitaxel by 1-h infusion in combination with carboplatin in advanced non-small cell lung carcinoma (NSCLC). *Eur J Cancer* 2000; 36: 183–93.
7. Akerley W. Recent developments in weekly paclitaxel therapy in lung cancer. *Curr Oncol Rep* 2001; 3: 165–9.
8. Haas N, *et al.* Phase I trial of weekly paclitaxel plus oral estramustine phosphate in patients with hormone-refractory prostate cancer. *Urology* 2001; 58: 59–64.
9. Seidman AD, *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001; 19: 2587–95.
10. Kouroussis C, *et al.* A dose-finding study of the weekly administration of paclitaxel in patients with advanced solid tumors. *Am J Clin Oncol* 2001; 24: 404–7.
11. Brambilla L, *et al.* Weekly paclitaxel for advanced aggressive classic Kaposi sarcoma: experience in 17 cases. *Br J Dermatol* 2008; 158: 1339–44.
12. Sparano JA, *et al.* Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008; 358: 1663–71. Correction. *ibid.*; 359: 106. Correction. *ibid.* 2009; 360: 1685.
13. Seidman AD, *et al.* Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008; 26: 1642–9.
14. Mauri D, *et al.* Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. *Cancer Treat Rev* 2010; 36: 69–74.

Administration in the elderly. A review[1] stated that data are conflicting regarding the impact of age on paclitaxel clearance. However, studies indicate that both weekly and 3-weekly dosing regimens are feasible in elderly patients, and no dose reduction of paclitaxel is needed on the basis of age alone.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in hepatic impairment. Total bilirubin has been shown to be a good predictor of paclitaxel elimination capacity and of individual susceptibility to paclitaxel-related myelosuppression.[1]

UK licensed product information for the conventional formulation of paclitaxel states that there are inadequate data available to recommend dose adjustment in mild to moderate hepatic impairment. Paclitaxel is not recommended in patients with severe hepatic impairment. US licensed product information makes recommendations for initial dosage adjustment of some paclitaxel regimens in patients with hepatic impairment, according to transaminase and bilirubin concentrations. They suggest the conventional formulation of paclitaxel should not be given if transaminase values are > 10 times the upper limit of normal (ULN), or if bilirubin is > 7.5 mg per 100 mL or 5 times the ULN.

In US licensed product information for the albumin-bound paclitaxel nanoparticle formulation recommendations vary depending on the indication and the degree of hepatic impairment; in patients with aspartate aminotransferase (AST/SGOT) < 10 times ULN and the following bilirubin concentrations:

- bilirubin > ULN to 1.25 times ULN (mild impairment): usual initial dose (see Uses and Administration, p. 839.3)
- 1.26 to 2 times ULN (moderate impairment): an initial dose of 200 mg/m^2 in breast cancer and 75 mg/m^2 in non-small cell lung cancer (NSCLC); not recommended for pancreatic adenocarcinoma
- 2.01 to 5 times ULN (severe impairment): an initial dose of 130 mg/m^2 in breast cancer and 50 mg/m^2 in NSCLC; not recommended for pancreatic adenocarcinoma

Treatment with the albumin-bound formulation is not recommended in any patients with AST/SGOT > 10 times ULN or bilirubin > 5 times ULN. Further dose adjustments in subsequent cycles are based on individual tolerance; in severe impairment, an increase up to 200 mg/m^2 in breast cancer and 75 mg/m^2 in NSCLC can be considered if the initial dose is tolerated.

UK licensed product information for this formulation states that a dose reduction must be considered in patients with bilirubin concentrations more than twice the ULN; patients with bilirubin > 5 times the ULN or with transaminase concentrations > 10 times the ULN should not be treated, due to a lack of data.

1. Joerger M, *et al.* Safety and pharmacology of paclitaxel in patients with impaired liver function: a population pharmacokinetic-pharmacodynamic study. *Br J Clin Pharmacol* 2007; 64: 622–33.

Administration in subsequent cycles. In general, if toxicity occurs paclitaxel doses are withheld until the patient has recovered or symptoms have improved; treatment may be restarted at a reduced dose. If the toxicity is persistent despite dose reductions treatment should be stopped.

Conventional paclitaxel should not be given to patients with baseline neutrophil counts < 1500 cells/mm^3; some manufacturers also contra-indicate use in patients with platelets < 100 000 cells/mm^3. In patients with Kaposi's sarcoma, conventional paclitaxel should not be given if baseline neutrophil counts are < 1000 cells/mm^3 or platelets are < 75 000 cells/mm^3. Subsequent doses should not be given until the neutrophil and platelet counts reach these values or greater. Patients who have severe neutropenia (< 500 cells/mm^3 for a minimum of 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses; for patients with Kaposi's sarcoma, a dose reduction of 25% is recommended.

Albumin-bound paclitaxel should also not be given to patients with baseline neutrophil counts < 1500 cells/mm^3.

- In patients with **breast cancer**, treatment is modified if severe neutropenia or severe sensory neuropathy occur. Doses are reduced in steps of 40 mg/m².
- In patients with **non-small cell lung cancer** treatment is modified for neutropenia, thrombocytopenia, or severe sensory neuropathy. Doses are reduced in steps of 25 mg/m².
- In patients with **pancreatic adenocarcinoma** treatment is modified for neutropenia, thrombocytopenia, severe peripheral neuropathy, grade 2 or 3 cutaneous toxicity, or grade 3 mucositis or diarrhoea. Doses are reduced in steps of 25 mg/m².

Reperfusion and revascularisation procedures. Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p. 1259.2) and various drugs have been tried for its prevention. Coronary stents that elute paclitaxel effectively reduce restenosis and have been widely used, although there is some suggestion that sirolimus-eluting stents may be superior to paclitaxel-eluting stents in terms of clinical outcome and rates of restenosis.[1-3] In a study compared with bare metal stents, paclitaxel-releasing stents reduced the risk of restenosis and the need for repeat revascularisation procedures, although the follow-up rates of death from cardiac causes or myocardial infarction were not significantly reduced at 9 months[4] and 1 year.[5] However, between 9 months and 1 year, major cardiac adverse events were significantly reduced in the paclitaxel-releasing stent group compared with controls.[5] A larger multicentre study[6] in patients with acute myocardial infarction confirmed the reduced risk of restenosis and recurrent ischaemia with paclitaxel-releasing as against bare-metal stents; no evidence of differences in mortality or stent thrombosis was seen at 1 year of follow-up. A review[7] of various stent designs concluded that safety of paclitaxel-releasing stents was independent of design, dose-density, or presence or absence of a polymer carrier system; however, those without a polymer carrier were unable to show a positive effect on clinical outcome in patients with de novo coronary lesions. However, in a paclitaxel-releasing stent system, failure of the stent-delivery balloon to deflate has been associated with serious injuries and 1 fatality.[8] The risk of late stent thrombosis may also be increased with drug eluting stents,[9] although the evidence is controversial,[10] and their role in complex interventions is not yet established.[11,12]

Positive effects on restenosis have also been reported[13] with use of a paclitaxel-coated angioplasty balloon.

1. Windecker S, *et al.* Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005; 353: 653–62.
2. Dibra A, *et al.* Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; 353: 663–70.
3. Hofma SH, *et al.* One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; 91: 1176–80.
4. Stone GW, *et al.* A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; 350: 221–31.
5. Stone GW, *et al.* One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004; 109: 1942–7.
6. Stone GW, *et al.* HORIZONS-AMI Trial Investigators. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med* 2009; 360: 1946–59.
7. Silber S. Paclitaxel-eluting stents: are they all equal? An analysis of six randomized controlled trials in de novo lesions of 3,319 patients. *J Interv Cardiol* 2003; 16: 485–90.
8. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. *N Engl J Med* 2004; 351: 1593–5.
9. Stone GW, *et al.* Safety and efficacy of sirolimus-and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; 356: 998–1008.
10. Mauri L, *et al.* Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; 356: 1020–9.
11. Beohar N, *et al.* Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007; 297: 1992–2000.
12. Win HK, *et al.* Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 2007; 297: 2001–9.
13. Scheller B, *et al.* Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006; 355: 2113–24.

Adverse Effects, Treatment, and Precautions

Paclitaxel is available as two formulations: a conventional formulation and an albumin-bound form. The two formulations are not interchangeable and one cannot be substituted for the other. While adverse effects are similar, the frequency of these effects can vary between formulations.

Conventional paclitaxel commonly produces severe dose-limiting myelosuppression, mainly neutropenia. The nadir of the white cell count usually occurs after about 11 days, with recovery usually by day 15 to 21 after a dose. Neutropenia may be less frequent when infusions are given over 3 rather than 24 hours. Blood counts should be monitored frequently.

Peripheral neuropathy can also be severe, and occasionally dose-limiting. Neurotoxicity appears to be more frequent and more severe when infusions are given over 3 hours rather than 24 hours. Hypersensitivity reactions, with flushing, rash, chills, dyspnoea, hypotension (or hypertension), chest pain, back pain, tachycardia, generalised urticaria, and angioedema may occur; anaphylaxis has been reported. All patients should be given initial premedication with corticosteroids, antihistamines, and histamine H_2-antagonists. Mild hypersensitivity reactions do not require interruption of therapy, but serious reactions (which may be fatal, and can occur despite premedication) require treatment to be stopped; patients who have serious reactions should not be re-treated with paclitaxel. Conventional paclitaxel is formulated in polyoxyl castor oil and it should be avoided in patients hypersensitive to this substance.

Cardiac disorders include bradycardia, arrhythmias, myocardial infarction, and heart failure; severe cardiac conduction disorders occur rarely and require continuous cardiac monitoring.

Common adverse effects include alopecia, arthralgia and myalgia, gastrointestinal disturbances, transient mild nail and skin changes, and elevation of liver enzyme values. Infections are also common, and fatalities have been reported. Injection site reactions and mucositis may occur more frequently with the 24-hour infusion than the 3-hour infusion. Manifestations include localised oedema, pain, erythema, and induration; extravasation may result in tissue damage.

Rare adverse events include febrile neutropenia, motor or autonomic neuropathy (which can result in paralytic ileus and orthostatic hypotension), seizures, encephalopathy, dizziness, headache, ataxia, severe thrombotic events, optic nerve and/or visual disturbances (especially at high doses), ototoxicity, bowel obstruction or perforation, pancreatitis, interstitial pneumonia, and pseudomembranous colitis. There are reports of hepatic necrosis and hepatic encephalopathy, some of which have been fatal. Increases in bilirubin and blood creatinine have been reported. Severe skin disorders include Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, and exfoliative dermatitis.

Albumin-bound paclitaxel also causes myelosuppression, mainly neutropenia which is rapidly reversible and dose-dependent. Febrile neutropenia is common. Sensory neuropathy occurs frequently, but is usually mild and does not generally require dose modification. Hypersensitivity is uncommon, and premedication is not required. Patients who have a severe hypersensitivity reaction to paclitaxel should not be given the drug again. Tachycardia and arrhythmias occur commonly; bradycardia, cardiac arrest, congestive heart failure, and left ventricular dysfunction are rare, but cardiac monitoring may be required, especially if patients have underlying cardiac disease or previous exposure to anthracyclines.

As with conventional paclitaxel, adverse effects such as alopecia, arthralgia, myalgia, gastrointestinal disturbances, nail and skin disorders, infections, and increases in liver enzyme values are common. Other common adverse effects include anorexia, hypokalaemia, stomatitis, flushing, hypertension, oedema (including lymphoedema), dyspnoea, epistaxis, cough, rhinitis, rhinorrhoea, fatigue, eye disorders, vertigo, and pain. Headache, ataxia, dizziness, dysgeusia, insomnia or somnolence, depression, and anxiety are also common.

Rare adverse effects include hypotension, thrombotic events, injection site reactions, and interstitial pneumonia. Other uncommon adverse effects include glucose and electrolyte disturbances, increases in bilirubin and blood creatinine, and urinary disorders. There have been rare reports of stroke and transient ischaemic attacks, cranial nerve palsies, and vocal cord paresis.

Both conventional and albumin-bound paclitaxel should be used with caution in patients with hepatic impairment (see Administration in Hepatic Impairment, p. 840.3).

Alcohol intoxication. Acute alcohol intoxication resulting from high-dose paclitaxel infusion has been reported;[1] it was calculated that the dose used (348 mg/m²) supplied 50 mL of alcohol, or the equivalent of about 3 drinks (half a bottle of wine).

1. Wilson DB, *et al.* Paclitaxel formulation as a cause of ethanol intoxication. *Ann Pharmacother* 1997; 31: 873–5.

Effects on the eyes. Optic neuritis has occurred with paclitaxel. There is a report of glaucoma possibly related to the use of docetaxel and paclitaxel in a patient also receiving corticosteroids.[1]

1. Fabre-Guillevin E, *et al.* Taxane-induced glaucoma. *Lancet* 1999; 354: 1181–2.

Effects on the heart. Infusion of paclitaxel has been associated with sinus bradycardia, atrial arrhythmias, ventricular tachycardia, heart block, myocardial infarction, and sudden death.[1,2] Symptoms of heart failure have been reported.[3] In another report sudden death 7 days after paclitaxel treatment raised the question of whether paclitaxel might have had a delayed effect.[4] There is some evidence of cellular damage to the myocardium of a patient with paclitaxel-associated cardiac symptoms.[3] Licensed product information notes that severe cardiovascular events have been seen more frequently after the use of paclitaxel in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.

1. Rowinsky EK, *et al.* Cardiac disturbances during the administration of taxol. *J Clin Oncol* 1991; 9: 1704–12.
2. Arbuck SG, *et al.* A reassessment of cardiac toxicity associated with Taxol. *J Natl Cancer Inst Monogr* 1993; 15: 117–30.
3. Jekunen A, *et al.* Paclitaxel-induced myocardial damage detected by electron microscopy. *Lancet* 1994; 343: 727–8.
4. Alagaratnam TT. Sudden death 7 days after paclitaxel infusion for breast cancer. *Lancet* 1993; 342: 1232–3.

Effects on the musculoskeletal system. For discussion of paclitaxel-induced arthralgia and myalgia (also referred to as paclitaxel-acute pain syndrome), and its association with neuropathic pain, see Effects on the Nervous System, below.

Effects on the nervous system. Neurotoxicity, usually manifesting as cumulative sensory peripheral neuropathy, is the most important non-haematological toxicity associated with use of paclitaxel, particularly when given in weekly dose-dense regimens,[1] where it is often dose-limiting (see also Administration, p. 840.2). The risk appears to be greater in older patients, those with diabetes, and those with co-existing alcohol abuse. Motor neuropathy is much less common than sensory symptoms, which may include numbness, paraesthesia, and burning sensations in a symmetric glove-and-stocking pattern that usually affects the lower limbs first. Orthostatic hypotension, arrhythmias, and ileus have sometimes been reported as possible signs of autonomic neuropathy. Although mild sensory neuropathy is generally reversible within a few months, more severe cases may persist much longer. Treatment options are lacking and close monitoring of patients to avoid the development of severe symptoms is important.[1]

Paclitaxel-acute pain syndrome (also called paclitaxel-induced arthralgia and myalgia), has been described as a diffuse aching discomfort that is most often felt in the legs, hips, and lower back. Symptoms usually develop over 1 to 4 days of treatment and resolve over a similar timeframe. It has been noted that the intensity of pain felt with the first paclitaxel infusion appeared to predict the later severity of sensory-predominant peripheral neuropathy (particularly shooting or burning pain) that gradually developed over a 12-week course of therapy, supporting the hypothesis that paclitaxel-acute pain syndrome is a form of neurotoxicity.[2,3] Gabapentin has been reported to be of benefit in the management of taxane-induced arthralgia and myalgia.[4,5]

Acute encephalopathy, manifesting between 5 hours and 16 days after infusion, has also been reported rarely in patients given paclitaxel.[6] Symptoms have included disorientation, mood disorders, language disorders, delirium, hallucinations, and coma.

1. Mielke S, *et al.* Peripheral neuropathy: a persisting challenge in paclitaxel-based regimes. *Eur J Cancer* 2006; 42: 24–30.
2. Loprinzi CL, *et al.* Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. *J Clin Oncol* 2011; 29: 1472–8.
3. Reeves BN, *et al.* Further data supporting that paclitaxel-associated acute pain syndrome is associated with development of peripheral neuropathy: North Central Cancer Treatment Group trial N08C1. *Cancer* 2012; 118: 5171–8.
4. van Deventer H, Bernard S. Use of gabapentin to treat taxane-induced myalgias. *J Clin Oncol* 1999; 17: 434–5.
5. Nguyen VH, Lawrence HJ. Use of gabapentin in the prevention of taxane-induced arthralgias and myalgias. *J Clin Oncol* 2004; 22: 1767–9.
6. Lachkar S, *et al.* Encéphalopathie aiguë après injection de paclitaxel. *Rev Mal Respir* 2006; 23: 73–7.

Effects on the respiratory system. Acute bilateral interstitial pneumonitis has been reported rarely in patients receiving paclitaxel, despite premedication with corticosteroids and histamine antagonists.[1] Symptoms resolved on treatment with parenteral corticosteroids.

1. Khan A, *et al.* Paclitaxel-induced acute bilateral pneumonitis. *Ann Pharmacother* 1997; 31: 1471–4.

Effects on the skin, hair, and nails. Nail changes, noted as pigmentation or discoloration of the nail-bed, may occur with paclitaxel. Onycholysis (separation of the nail from the nail-bed) has also been reported.[1] Discoloration and onycholysis can also occur after docetaxel use, and there are reports of subungual hyperkeratosis and haemorrhage.[2-4]

Localised oedema evolving into skin sclerosis, mimicking systemic sclerosis, has been reported after taxane use.[5,6] In most patients, the sclerosis developed mainly on the extremities, and especially the lower extremities. Joint contracture may occur. The total cumulative dose of the taxane may contribute to the onset.[5]

Severe and irreversible alopecia has been reported after use of docetaxel or paclitaxel in patients with breast cancer.[7]

1. Flory SM, *et al.* Onycholysis associated with weekly administration of paclitaxel. *Ann Pharmacother* 1999; 33: 584–5.
2. Wasner G, *et al.* Clinical picture: nail changes secondary to docetaxel. *Lancet* 2001; 357: 910.
3. Pavithran K, Doval DC. Nail changes due to docetaxel. *Br J Dermatol* 2002; 146: 709–10.
4. Leonard GD, Zujewski JA. Docetaxel-related skin, nail, and vascular toxicity. *Ann Pharmacother* 2003; 37: 148.

5. Itoh M, *et al.* Taxane-induced scleroderma. *Br J Dermatol* 2007; 156: 363–7.
6. Takahashi T, *et al.* A case of taxane-induced scleroderma: a different expression profile of Fli1 proteins in dermal fibroblasts and microvascular endothelial cells compared with systemic sclerosis. *Br J Dermatol* 2011; 164: 1393–5.
7. Prevezas C, *et al.* Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 2009; 160: 883–5.

Hypersensitivity. Despite premedication with corticosteroids, antihistamines, and H_2-antagonists, hypersensitivity reactions are common in patients given conventional paclitaxel; up to about 40% of patients may have a mild reaction and about 2% a severe reaction. Fatalities have been reported. There are rare reports of delayed hypersensitivity reactions with paclitaxel; necrotic ulceration has occurred, without evidence of extravasation.[1] Some consider the cause to be the polyoxyl castor oil diluent for paclitaxel, and docetaxel has been suggested as a suitable alternative.[2] However, hypersensitivity reactions have also occurred with docetaxel and taxane cross-reactivity has been reported.[3,4] Although the manufacturers of both drugs consider further use to be contra-indicated after a severe reaction, strategies for continuation of treatment and desensitisation have been described.[5,6]

Hypersensitivity reactions to paclitaxel-eluting stents have also been reported;[7] however, the incidence is low, and some consider the polymer coating of the stent to be the likely cause.[8]

1. Beri R, *et al.* Severe dermatologic reactions at multiple sites after paclitaxel administration. *Ann Pharmacother* 2004; 38: 238–41.
2. Bernstein BJ. Docetaxel as an alternative to paclitaxel after acute hypersensitivity reactions. *Ann Pharmacother* 2000; 34: 1332–5.
3. Denman JP, *et al.* Hypersensitivity reaction (HSR) to docetaxel after a previous HSR to paclitaxel. *J Clin Oncol* 2002; 20: 2760–1.
4. Karacan Ö, *et al.* Acute interstitial pneumopathy associated with docetaxel hypersensitivity. *Onkologie* 2004; 27: 563–5.
5. Markman M, *et al.* Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol* 2000; 18: 102–5.
6. Feldweg AM, *et al.* Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* 2005; 96: 824–9.
7. Nebeker JR, *et al.* Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006; 47: 175–81.
8. Azarbal B, Currier JW. Allergic reactions after the implantation of drug-eluting stents: Is it the pill or the polymer? *J Am Coll Cardiol* 2006; 47: 182–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paclitaxel 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 05/09/11)

Pregnancy. Paclitaxel has been shown to be embryotoxic and fetotoxic in *animal* studies, but, although the use of potentially teratogenic drugs would normally be avoided during pregnancy, the risk to the mother of inadequate treatment may outweigh whatever risks exist of abnormality in the fetus. A retrospective study[1] of 15 women who were given taxane chemotherapy for breast and ovarian cancer during the second and third trimesters of pregnancy found no differences in birth-weight, gestational age at delivery, rate of growth restriction, congenital anomalies and incidence of maternal and neonatal neutropenia for taxanes when compared with conventional chemotherapy. A systematic review[2] of taxane use for ovarian cancer during 12 pregnancies (11 for paclitaxel and 1 for docetaxel) found that in 92% of cases a healthy child was born; in 6 out of 8 cases with survival data, the mother was alive and disease free at the end of follow-up (median 20 months, and ranging from 9.75 to 45 months). The authors concluded that taxanes may be valuable for treatment of ovarian cancer during the second and third trimesters, but use in early pregnancy is associated with an increased risk of abortion or congenital abnormalities.

Oligohydramnios has been reported[3] with paclitaxel in a pregnant woman with breast cancer. From 24 weeks of gestation the patient received four cycles of doxorubicin and cyclophosphamide and was then started on a weekly regimen of paclitaxel; growth factor support was given throughout chemotherapy. Oligohydramnios was noted after the fourth week of paclitaxel. A healthy infant was delivered at 36 weeks of gestation.

1. Cardonick E, *et al.* Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. *Ann Oncol* 2012; 23: 3016–23.
2. Zagouri F, *et al.* Taxanes for ovarian cancer during pregnancy: a systematic review. *Oncology* 2012; 83: 234–8.
3. Shieh MP, Mehta RS. Oligohydramnios associated with administration of weekly paclitaxel for triple-negative breast cancer during pregnancy. *Ann Oncol* 2011; 22: 2151–2.

Sickle-cell disease. A patient with previously undiagnosed sickle-cell disease had a painful crisis after being given conventional paclitaxel as part of a chemotherapy regimen for breast cancer.[1] It was unclear if the reaction was due to paclitaxel or its vehicle, and whether an alternative taxane or albumin-bound paclitaxel would cause a similar effect.

1. Wilson NM, *et al.* Paclitaxel-induced sickle cell crisis. *Am J Health-Syst Pharm* 2008; 65: 1333–6.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Pretreatment with cisplatin may reduce the clearance of paclitaxel, resulting in increased toxicity, and when both drugs are given, paclitaxel should be given first.

Paclitaxel is metabolised by the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. No clinically relevant interactions with other CYP2C8 substrates are likely. While use with ketoconazole (a potent inhibitor of CYP3A4) does not affect paclitaxel elimination, data are limited on use with other CYP3A4 inhibitors or inducers, and caution is advised when paclitaxel is used with these drugs.

Antineoplastics. For reference to enhanced cardiotoxicity when paclitaxel was given with *doxorubicin*, see p. 785.2. For the pharmacokinetic changes reported when paclitaxel was given with *gemcitabine*, see p. 802.1.

Pretreatment with *fluorouracil* has been reported to inhibit paclitaxel's cytotoxic action, possibly by preventing tumour cells from entering the G_2-M phases of the cell cycle.[1] The effect also occurred when the 2 drugs were given simultaneously, suggesting that combination therapy might not be appropriate.

Valspodar inhibits P-glycoprotein, and a pharmacokinetic study[2] found that it decreased clearance of paclitaxel and prolonged the terminal half-life, increasing exposure to paclitaxel and myelosuppressive effects. The authors suggested that the dose of paclitaxel may need to be reduced by about 60%.

Variable effects on paclitaxel pharmacokinetics have been seen when it has been given with *carboplatin* plus *sorafenib*; see under Interactions of Sorafenib, p. 858.2.

1. Johnson KR, *et al.* 5-Fluorouracil interferes with paclitaxel cytotoxicity against human solid tumor cells. *Clin Cancer Res* 1997; 3: 1739–45.
2. Advani R, *et al.* A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance. *Clin Cancer Res* 2001; 7: 1221–9.

Antiretrovirals. In a patient given various antiretrovirals during paclitaxel treatment for Kaposi's sarcoma, pharmacokinetic parameters of paclitaxel were not significantly different when compared with historical controls.[1] The first course of therapy combined paclitaxel with *lamivudine, stavudine,* and the HIV-protease inhibitors *ritonavir* and *saquinavir*. In subsequent courses, paclitaxel was given with *nevirapine,* and the final course consisted of paclitaxel given with ritonavir and *indinavir*.

However, licensed product information for paclitaxel states that studies suggest that systemic clearance of paclitaxel was significantly lower in the presence of *nelfinavir* and ritonavir, but not indinavir, and that paclitaxel should be given with caution to patients taking HIV-protease inhibitors. HIV-protease inhibitors are metabolised by the cytochrome P450 isoenzyme CYP3A4, but are also reported to inhibit CYP3A activity. This may lead to increased adverse effects when given with taxanes; the combination of *delavirdine* and saquinavir has been reported to cause serious mucositis, severe myalgia, alopecia, and leucopenia when given with paclitaxel.[2] In other case reports, one patient tolerated *lopinavir*, ritonavir, delavirdine, and *didanosine* without complications until the addition of paclitaxel caused fatal toxicity. In another patient taking indinavir, ritonavir, stavudine, and lamivudine, the addition of paclitaxel caused profound cytopenia and total body alopecia; further courses of paclitaxel were given at a reduced dose with no sequelae.[3]

1. Nannan Panday VR, *et al.* Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma—drug-drug interactions with protease inhibitors and a nonnucleoside reverse transcriptase inhibitor: a case report study. *Cancer Chemother Pharmacol* 1999; 43: 516–19.
2. Schwartz JD, *et al.* Potential interaction of antiretroviral therapy with paclitaxel in patients with AIDS-related Kaposi's sarcoma. *AIDS* 1999; 13: 283–4.
3. Bundow D, Aboulafia DM. Potential drug interaction with paclitaxel and highly active antiretroviral therapy in two patients with AIDS-associated Kaposi sarcoma. *Am J Clin Oncol* 2004; 27: 81–4.

Immunosuppressants. For the effect of ciclosporin on the oral absorption of paclitaxel, see Immunosuppressants, under Interactions of Docetaxel, p. 782.2.

For the effects of *valspodar* (an analogue of ciclosporin) on paclitaxel, see Antineoplastics, above.

Pharmacokinetics

Intravenous paclitaxel exhibits a biphasic decline in plasma concentrations, with a mean terminal half-life of anywhere between about 3 and 50 hours. The pharmacokinetics are non-linear. The steady-state volume of distribution is reported to range from 200 to 700 litres/m², indicating extensive extravascular distribution, tissue binding, or both. Paclitaxel is 89% or more bound to plasma protein *in vitro*. The elimination of paclitaxel has not been fully elucidated; only about 1 to 12% of a dose is reported to be excreted in urine, as unchanged drug, indicating extensive non-renal clearance. Paclitaxel is metabolised in the liver, with the major metabolic pathway apparently mediated by the cytochrome P450 isoenzyme CYP2C8, although CYP3A4 may play a minor role. Metabolites are excreted in the faeces via the bile, the primary metabolite being 6α-hydroxypaclitaxel.

The clearance and volume of distribution of albumin-bound paclitaxel nanoparticles are reported to be markedly greater (by about 45 and 55% respectively) than those from conventional formulations. In addition, the fraction of free (unbound) paclitaxel in the blood has been reported to be higher than with conventional paclitaxel.

References.
1. Sonnichsen DS, Relling MV. Clinical pharmacokinetics of paclitaxel. *Clin Pharmacokinet* 1994; 27: 256–69.
2. Walle T, *et al.* Taxol metabolism and disposition in cancer patients. *Drug Metab Dispos* 1995; 23: 506–12.
3. Sonnichsen DS, *et al.* Variability in human cytochrome P450 paclitaxel metabolism. *J Pharmacol Exp Ther* 1995; 275: 566–75.
4. Henningsson A, *et al.* Mechanism-based pharmacokinetic model for paclitaxel. *J Clin Oncol* 2001; 19: 4065–73.
5. Gerritsen-van Schieveen P, Royer B. Suivi Thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Niveau de preuve du suivi thérapeutique pharmacologique du paclitaxel. *Therapie* 2010; 65: 195–200.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Asotax; Clitaxel; Dalys; Drifen; Erioxal; Paclikebir; Pacliteva; Paklitaxfil; Panataxel; Tarvexol; Taxocris; Taxol; Taycovit; ***Austral.***: Abraxane; Anzatax; Taxol; ***Austria***: Ebetaxel; Taxol; ***Belg.***: Paclitaxin; Paxene†; Taxol; ***Braz.***: Biopaxel; Evotaxel; Ontax; Onxel; Paclitax; Pantium; Parexel; Tarvexol; Taxilan; Taxol; Tevapacli; ***Cana.***: Abraxane; Taxol; ***Chile***: Britaxol; Oncoplaxel†; Praxel; Taxodiol; ***China***: Anzatax (安素泰); Li Pu Su (力扑素); Medaxol (紫舒); Taxol (泰素); Te Su (特素); ***Cz.***: Abraxane; Anzatax; Brevitax; Egilitax; Eucol; OncoTax; Onxol†; Paclimedac; Pacline; Paxene†; Taxol; ***Denm.***: Abraxane; Cantaxel†; Paclimedac; Taxli; ***Fin.***: Paclitaxin; Taxol†; ***Fr.***: Abraxane; Paxene†; Taxol; ***Ger.***: Abraxane; Axitaxel; Bendatax; celltaxel; NeoTaxan†; Paclit; Ribotax; Taxol†; Taxomedac; ***Gr.***: Abraxane; Biotaxel; Cedol; Oncotaxen; Ovapac; Pacline; Paclit; Paclitaxin; Paclitol; Paclixel; Pataxel; Paxene; Paxital; Ribotal; Taxogen; Taxol; Taxoprol; Xenius; ***Hong Kong***: Anzatax; Ebetaxel; Intaxel†; Sindaxel; Taxol; ***Hung.***: Genexol; Intaxel†; Paxene†; Taxol†; ***Indi.***: Abraxane; Altaxel; Betaxel; Cansure; Cantaxel; Celtax; Cytrax; Dutaxel; Intaxel; Mitotax; Nanoxel; Napro-Tax; Neotaxl; Oncotaxel; Paclicad; Pacliron; Paclitax; Paclitec; Paclitrust; Petaxel; ***Indon.***: Anzatax; Ebetaxel; Paxus; Sindaxel; Taxol†; ***Irl.***: Abraxane; Cantaxel; Ebetaxel; Palat; Paxene†; Taxol†; ***Israel***: Biotax†; Ebetaxel; Medixel; Paclavenir; ***Ital.***: Anzatax; Taxol; ***Jpn***: Taxol; ***Malaysia***: Anzatax; Formoxol; Mitotax; Taxol; ***Mex.***: Aclixel†; Acoexcel; Asotax; BrisTaxol; Cryoxet; Daburex; Ifaxol†; Paclisan; Praxel; ***Neth.***: Abraxane; Paclitaxin; Paxene†; Taxol; ***Norw.***: Abraxane; ***NZ***: Abraxane; Anzatax; Taxol; ***Philipp.***: Intaxel; Nanoxel; Napro-Tax; Paclitaxin; Palitax; Paxol; Taxol†; Unitaxel; ***Pol.***: Abraxane; Poltaxel†; Sindaxel; Taxol; ***Port.***: Abraxane; Paxene†; Taxobine; Taxol; ***Rus.***: Abitaxel (Абитаксел); Intaxel (Интаксел); Mitotax (Митотакс); Paclitax (Паклитакс); Paclitera (Паклитера); Paxene (Паксен); Sindaxel (Синдаксел); Taxacad (Таксакад); Taxol (Таксол); ***S.Afr.***: Anzatax; Biolyse; Ebetaxel; Paxitas; Paxitas; Taxol; ***Singapore***: Aclipak; Anzatax; Ebetaxel; Genexol; Mitotax; Paclitaxin; Taxol; ***Spain***: Abraxane; Paxene†; Taxol; ***Swed.***: Abraxane; Paxene†; Taxol†; ***Switz.***: Taxol; ***Thai.***: Anzatax; Genetaxyl; Inoxel; Intaxel; Oncotaxel†; Paclitaxin; Paxoll; Praxel; Sindaxel; Taxol; ***Turk.***: Anzatax; Ebetaxel; Taksen; Taxol; Vitax; ***UK***: Abraxane; Paxene†; ***Ukr.***: Mitotax (Митотакс); ***USA***: Abraxane; Onxol†; Taxol†; ***Venez.***: Clitaxel; Intaxel; Paclitax.

Pharmacopoeial Preparations

USP 36: Paclitaxel Injection.

Palifosfamide *(USAN, rINN)*

IPM; Palifosfamida; Palifosfamidum; ZIO-201; Палифосфамид.

N,N'-Bis(2-chloroethyl)phosphorodiamidic acid.

$C_4H_{11}Cl_2N_2O_2P$=221.0

CAS — 31645-39-3.

UNII — 6A4U6NN813.

Profile

Palifosfamide is an active metabolite of ifosfamide (p. 806.1) that is under investigation for the treatment of soft-tissue sarcoma.

Panitumumab *(BAN, USAN, rINN)*

ABX-EGF; E7.6.3; Panitumumabum; rHuMAb-EGFr; Панитумумаб.

Immunoglobulin, anti-(human epidermal growth factor receptor) (human monoclonal ABX-EGF heavy chain), disulfide with human monoclonal ABX-EGF light chain, dimer.

CAS — 339177-26-3.
ATC — L01XC08.
ATC Vet — QL01XC08.
UNII — 6A901E312A.

Stability. Panitumumab was physically stable when stored for 14 days at 4 degrees in either PVC infusion bags at a concentration of 2.5 mg/mL in sodium chloride 0.9%, or the opened original glass vial at a concentration of 20 mg/mL.[1]

1. Ikesue H, *et al.* Stability of cetuximab and panitumumab in glass vials and polyvinyl chloride bags. *Am J Health-Syst Pharm* 2010; 67: 223–6.

Uses and Administration

Panitumumab is a recombinant human monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). Like cetuximab (p. 762.3), panitumumab can therefore affect cell growth regulation and angiogenesis in patients with wild-type (non-mutated) *RAS* (rat sarcoma) oncogene but it is ineffective in patients who have *RAS* gene mutations. It is used in the treatment of EGFR-expressing, *RAS* wild type, metastatic colorectal cancer (p. 706.3) either with fluoropyrimidine-containing chemotherapy as first- or second-line therapy, or as monotherapy in patients with disease progression after fluoropyrimidine-, oxaliplatin-, or irinotecan-containing regimens.

The recommended dose is 6 mg/kg given as an intravenous infusion every 14 days. Doses up to and including 1 g are given in 100 mL sodium chloride 0.9% over 60 minutes whereas doses above 1 g are diluted in 150 mL and given over 90 minutes; the final concentration of the infusion should not exceed 10 mg/mL. The infusion should be given via an infusion pump using a low-protein-binding 0.2 or 0.22 micrometre in-line filter. It may be given through a peripheral line or indwelling catheter; the line should be flushed with sodium chloride 0.9% before and after giving panitumumab. The infusion rate should be reduced by 50% in patients who have a mild to moderate infusion reaction, and stopped immediately and permanently if a severe reaction occurs.

Panitumumab should be withheld if severe dermatological toxicity develops, and permanently stopped if toxicity does not improve within 1 month. If toxicity improves after withholding no more than 2 doses of panitumumab, treatment may be restarted, either at the same dose or at a reduced dose; recommendations for dose modifications vary between countries.

References.

1. Gibson TB, *et al.* Randomized phase III trial results of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, in metastatic colorectal cancer. *Clin Colorectal Cancer* 2006; 6: 29–31.
2. Saif MW, Cohenuram M. Role of panitumumab in the management of metastatic colorectal cancer. *Clin Colorectal Cancer* 2006; 6: 118–24.
3. Saadeh CE, Lee HS. Panitumumab: a fully human monoclonal antibody with activity in metastatic colorectal cancer. *Ann Pharmacother* 2007; 41: 606–13.
4. Giusti RM, *et al.* FDA drug approval summary: panitumumab (Vectibix™). *Oncologist* 2007; 12: 577–83.
5. Peeters M, *et al.* Review article: panitumumab—a fully human anti-EGFR monoclonal antibody for treatment of metastatic colorectal cancer. *Aliment Pharmacol Ther* 2008; 28: 269–81.
6. Hecht JR, *et al.* A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 2009; 27: 672–80.
7. Peeters M, *et al.* Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy. *Cancer* 2009; 115: 1544–54.
8. Keating GM. Panitumumab: a review of its use in metastatic colorectal cancer. *Drugs* 2010; 70: 1059–78.

Adverse Effects, Treatment, and Precautions

As for Cetuximab, p. 763.1, although the use of premedication for prevention of infusion reactions with panitumumab has not been standardised. The infusion rate should be reduced by 50% in patients who have mild to moderate infusion reactions and this lower rate should be maintained for subsequent infusions. If a severe reaction occurs, the drug should be stopped immediately and permanently. Fatal angioedema has been reported. In patients who developed skin reactions, infectious complications including abscesses and sepsis, also in some cases fatal, have been reported. Fatigue is very common, as is paronychia; the latter may be severe enough to require stoppage of therapy. Panitumumab should not be used in patients with interstitial pneumonitis or pulmonary fibrosis, and therapy should be permanently stopped in patients who develop interstitial lung disease, pneumonitis, or lung infiltrates; fatalities have been reported. Eye disorders are common and include conjunctivitis, ocular hyperaemia, increased lachrymation, dry eye, eye pruritus, and eyelash growth. There are rare reports of keratitis and ulcerative keratitis with panitumumab, and therapy should be interrupted or stopped if this occurs; contact lens use is a risk factor for development of keratitis and ulceration.

Wild-type *RAS* (rat sarcoma oncogene) status should be confirmed before starting treatment as panitumumab is ineffective in patients who have *RAS* mutations. Panitumumab should not be used with some chemotherapy regimens; for details of the adverse effects associated with such combinations, see Interactions, below.

Effects on the skin, hair, and nails. For reference to cutaneous adverse effects of epidermal growth factor receptor inhibitors, including panitumumab, see under Cetuximab, p. 763.2.

Hypersensitivity. Although infusion reactions and hypersensitivity have been reported with panitumumab (see above) there is evidence from a limited number of patients that there is no cross-sensitivity between panitumumab and cetuximab,[1-4] and that therefore the former can be used in those with severe reactions to the latter. Successful use of cetuximab in those with reactions to panitumumab has also been reported.[5] Despite this, fatal hypersensitivity reactions have occurred after panitumumab; one was in a patient who had previously reacted to cetuximab.[6]

1. Cartwright TH, Genther R. Successful administration of panitumumab alone after severe infusion reaction to cetuximab in a patient with metastatic colorectal cancer. *Clin Colorectal Cancer* 2008; 7: 202–3.
2. Saif MW, *et al.* Successful re-challenge with panitumumab in patients who developed hypersensitivity reactions to cetuximab: report of three cases and review of literature. *Cancer Chemother Pharmacol* 2009; 63: 1017–22.
3. Langerak A, *et al.* Panitumumab monotherapy in patients with metastatic colorectal cancer and cetuximab infusion reactions: a series of four case reports. *Clin Colorectal Cancer* 2009; 8: 49–54.
4. Nielsen DL, *et al.* Six cases of treatment with panitumumab in patients with severe hypersensitivity reactions to cetuximab. *Ann Oncol* 2009; 20: 798.
5. Saif MW, *et al.* Successful desensitization with cetuximab after an infusion reaction to panitumumab in patients with metastatic colorectal cancer. *Cancer Chemother Pharmacol* 2009; 63: 107–12.
6. MHRA/CHM. Panitumumab (Vectibix): serious hypersensitivity reactions. *Drug Safety Update* 2010; 3(10): 8–9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON081866&RevisionSelectionMethod=LatestReleased (accessed 26/05/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies panitumumab 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 29/09/11)

Interactions

Panitumumab should not be used with some chemotherapy regimens. A high incidence of severe diarrhoea occurred in patients given panitumumab with fluorouracil, folinic acid, and irinotecan (the IFL regimen, see Table I, Common Chemotherapy Regimens for Malignant Disease, p. 719). Increased toxicity and risk of death occurred when panitumumab was given with bevacizumab. A reduced survival-time was reported in patients with tumours expressing *RAS* gene mutations or with unknown *RAS* status who were given panitumumab with oxaliplatin-based chemotherapy for metastatic colorectal cancer.

Pharmacokinetics

The pharmacokinetics of panitumumab are reported to be non-linear. Steady-state concentrations were reached by the third infusion with the recommended dose regimen. The elimination half-life was about 7.5 days.

References.

1. Ma P, *et al.* Population pharmacokinetic analysis of panitumumab in patients with advanced solid tumors. *J Clin Pharmacol* 2009; 49: 1142–56.
2. Yang B-B, *et al.* Pharmacokinetic and pharmacodynamic perspectives on the clinical drug development of panitumumab. *Clin Pharmacokinet* 2010; 49: 729–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Vectibix; *Austria*: Vectibix; *Belg.*: Vectibix; *Braz.*: Vectibix; *Canad.*: Vectibix; *Cz.*: Vectibix; *Denm.*: Vectibix; *Fr.*: Vectibix; *Ger.*: Vectibix; *Gr.*: Vectibix; *Hung.*: Vectibix; *Irl.*: Vectibix; *Israel*: Vectibix; *Ital.*: Vectibix; *Jpn*: Vectibix; *Norw.*: Vectibix; *Pol.*: Vectibix; *Port.*: Vectibix; *Rus.*: Vectibix (Вектибикс); *Spain*: Vectibix; *Swed.*: Vectibix; *Switz.*: Vectibix; *UK*: Vectibix; *USA*: Vectibix.

Panobinostat *(USAN, rINN)*

LBH-589; Panobinostatum; Панобиностат.

(2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]prop-2-enamide.

$C_{21}H_{23}N_3O_2$=349.4

CAS — 404950-80-7.
UNII — 9647FM7Y3Z.

Profile

Panobinostat is a histone deacetylase inhibitor that is under investigation as an antineoplastic for the treatment of malignancies such as cutaneous T-cell lymphoma.

Patupilone *(rINN)*

EPO-906; Epothilone B; Patupilona; Patupilonum; Патупильон.

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-{(1*E*)-1-(2-methyl-1,3-thiazol-4-yl)prop-1-en-2-yl}-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

$C_{27}H_{41}NO_5S$=507.7

CAS — 152044-54-7.
UNII — UEC0H0URSE.

Profile

Patupilone is a metabolite isolated from the bacterium *Sorangium cellulosum*, with microtubule stabilising activity similar to that of the taxanes. It is under investigation as an antineoplastic for the treatment of malignancies such as ovarian cancer.

References.

1. Rubin EH, *et al.* Phase I dose-finding study of weekly single-agent patupilone in patients with advanced solid tumors. *J Clin Oncol* 2005; 23: 9120–9.
2. Forster M, *et al.* A phase Ib and pharmacokinetic trial of patupilone combined with carboplatin in patients with advanced cancer. *Clin Cancer Res* 2007; 13: 4178–84.
3. Schelman W, *et al.* A phase I trial of gemcitabine in combination with patupilone in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 2008; 62: 727–33.
4. Hussain A, *et al.* Phase II trial of weekly patupilone in patients with castration-resistant prostate cancer. *Ann Oncol* 2009; 20: 492–7.
5. ten Bokkel Huinink WW, *et al.* Safety and efficacy of patupilone in patients with advanced ovarian, primary fallopian, or primary peritoneal cancer: a phase I, open-label, dose-escalation study. *J Clin Oncol* 2009; 27: 3097–3103.

Pazopanib Hydrochloride

(BANM, USAN, rINNM)

GW-786034B; Hidrocloruro de pazopanib; Pazopanib, Chlorhydrate de; Pazopanibi Hydrochloridum; Пазопаниба Гидрохлорид.

5-{[4-[(2,3-Dimethyl-2*H*-indazol-6-yl)methylamino]pyrimidin-2-yl]amino}-2-methylbenzenesulfonamide hydrochloride.

$C_{21}H_{23}N_7O_2S.HCl$=474.0

CAS — 444731-52-6 (pazopanib); 635702-64-6 (pazopanib hydrochloride).
ATC — L01XE11.
ATC Vet — QL01XE11.
UNII — 33Y9ANM545.

Uses and Administration

Pazopanib hydrochloride is an inhibitor of multiple tyrosine kinases including those associated with the vascular epidermal growth factor receptor (VEGFR). It is used in the treatment of advanced renal cell carcinoma (p. 708.3). It may also be used in advanced soft-tissue sarcoma (p. 718.2), although efficacy in adipocytic soft-tissue sarcoma or gastrointestinal stromal tumours has not been shown.

Doses are expressed in terms of the base; 1 mg pazopanib is equivalent to about 1.08 mg pazopanib hydrochloride. The recommended oral dose of pazopanib is 800 mg once daily at least 1 hour before or 2 hours after food. Dose modifications should be in steps of 200 mg, although US licensed product information allows for an initial dose reduction to 400 mg once daily if needed in patients with renal cell carcinoma. The daily dose should not exceed 800 mg. Tablets should be swallowed whole and not crushed. If a daily dose is missed and it is less than 12 hours until the next dose, the missed dose should be omitted and the next daily dose taken as usual. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

If a potent cytochrome P450 isoenzyme CYP3A4 inhibitor must also be used, US licensed product information recommends that the pazopanib dose should be reduced to 400 mg once daily; the dose may be reduced further if adverse effects occur.

For dose adjustments in hepatic impairment or if hepatotoxicity occurs, see p. 844.1.

Pazopanib eye drops are under investigation for the treatment of age-related macular degeneration.

References.
1. Sonpavde G, *et al.* Pazopanib, a potent orally administered small-molecule multitargeted tyrosine kinase inhibitor for renal cell carcinoma. *Expert Opin Invest Drugs* 2008; 17: 253–61.
2. Sloan B, Scheinfeld NS. Pazopanib, a VEGF receptor tyrosine kinase inhibitor for cancer therapy. *Curr Opin Investig Drugs* 2008; 9: 1324–35.
3. Sleijfer S, *et al.* Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol* 2009; 27: 3126–32.
4. Sternberg CN, *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010; 28: 1061–8.
5. Kelsner SV, Shah SR. Pazopanib: the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma. *Drugs* 2011; 71: 443–54.
6. NICE. Pazopanib for the first-line treatment of advanced renal cell carcinoma. Technology Appraisal Guidance 215 (issued February 2011). Available at: http://www.nice.org.uk/nicemedia/live/13346/53185/53185.pdf (accessed 30/04/12)

Administration in hepatic impairment. Patients with mild hepatic impairment, defined as either normal bilirubin and any degree of alanine aminotransferase (ALT) elevation or an elevation of bilirubin up to 1.5 times the upper limit of normal (ULN) regardless of the ALT value, have been shown to have similar pazopanib pharmacokinetics to patients with normal hepatic function, and therefore can be given the usual initial recommended dose of pazopanib (see Uses and Administration, p. 843.3). Clearance of pazopanib is reduced by about 50% in patients with moderate hepatic impairment, and patients with pre-existing moderate impairment (defined as an elevation of bilirubin > 1.5 to 3 times the ULN, regardless of ALT values) should be given a lower initial oral dose of pazopanib 200 mg once daily. Due to poor tolerability, pazopanib is not recommended in those with pre-existing severe impairment, defined as total bilirubin > 3 times the ULN.

Hepatotoxicity may occur during pazopanib treatment at the usual recommended dose, and liver function should be monitored before and during treatment, see Adverse Effects and Precautions, below. The following adjustments are recommended, according to increases in ALT and bilirubin concentrations:

- For isolated ALT increases of between 3 and 8 times the ULN, the current pazopanib dose may be continued, with weekly monitoring of liver function until ALT returns to grade 1 or baseline.
- For isolated ALT increases of > 8 times the ULN, treatment should be withheld until ALT returns to grade 1 or baseline. If the benefit of continued treatment is thought to outweigh the risk of hepatotoxicity, pazopanib can be restarted at a dose of no more than 400 mg once daily, and liver function monitored weekly for 8 weeks. If ALT increases of > 3 times the ULN recur, pazopanib should be stopped permanently.
- For ALT increases of > 3 times the ULN with bilirubin increases of > 2 times the ULN, pazopanib should be stopped permanently. Liver function should be monitored until toxicity has resolved.

Patients with Gilbert's syndrome (mild unconjugated hyperbilirubinaemia), and an increase in ALT > 3 times the ULN, should be managed according to the above recommendations.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects with pazopanib include diarrhoea and other gastrointestinal disturbances, headache, hair colour changes, fatigue, asthenia, anorexia, dysgeusia, and abdominal pain. Hypertension has also occurred commonly and hypertensive crisis may develop; patients should be monitored and treated with antihypertensives as required. If hypertension persists despite treatment, the dose of pazopanib may be reduced; pazopanib should be stopped for severe hypertension despite treatment and dose reduction. QT prolongation and torsade de pointes have occurred, and caution is required in those with cardiac disease or a history of QT prolongation, those taking antiarrhythmics, or those taking other medicines that prolong the QT interval. ECGs and electrolytes should be monitored before starting pazopanib and periodically during treatment. Pazopanib has been associated with cardiac dysfunction such as a reduction in left ventricular ejection fraction and congestive heart failure in some patients. Arterial thrombotic adverse effects have been reported, including myocardial infarction, angina, ischaemic stroke, and transient ischaemic attacks; fatalities have occurred. Caution is required in patients with risk factors for thrombosis, and use is not recommended in those who have suffered an event in the previous 6 months. Cases of venous thrombosis and pulmonary embolism have also occurred. Haemorrhagic adverse effects including fatal haemorrhages have also been reported with pazopanib, and use is not recommended in those who have suffered haemoptysis, cerebral haemorrhage, or significant gastrointestinal haemorrhage in the previous 6 months.

Use of pazopanib is not recommended in those with pre-existing severe hepatic impairment. Hepatotoxicity, manifested as raised serum transaminases and bilirubin, has been reported during treatment and can be severe; fatalities have occurred. Liver function should be monitored before starting treatment, at least once every 4 weeks for the first 4 months, and periodically thereafter. Treatment may need to be stopped or the dose reduced for severe hepatotoxicity, see Administration in Hepatic Impairment, above.

Hypothyroidism has been reported with pazopanib and monitoring of thyroid function is recommended. Monitoring for proteinuria is also recommended, before and during treatment, and pazopanib should be stopped permanently if severe proteinuria develops.

Other common adverse effects include alopecia, chest pain, oedema, palmar-plantar erythrodysesthesia, rash, skin depigmentation, and changes in electrolyte and glucose concentrations. Pazopanib has been associated with gastrointestinal perforation and fistula, including some fatalities. Thrombocytopenia, neutropenia, leucopenia, dizziness, paraesthesia, hot flushes, epistaxis, dysphonia, erythema, pruritus, dry skin, hyperhidrosis, myalgia, muscle spasms, mucosal inflammation, and increased blood creatinine have also commonly occurred. Less commonly reported effects include bradycardia, pancreatitis, peritonitis, photosensitivity reactions, and skin exfoliation. Reversible posterior leukoencephalopathy syndrome, which presents with visual and neurological disturbances, has been reported.

Vascular endothelial growth factor receptor inhibitors such as pazopanib may impair healing, and it is recommended that treatment is stopped at least 7 days before surgery; pazopanib should be stopped permanently if wound dehiscence develops.

Interactions

Pazopanib is metabolised by cytochrome P450 isoenzymes, mainly CYP3A4, and inhibitors or inducers of CYP3A4 may affect exposure to pazopanib. Pazopanib is also a substrate for P-glycoprotein (PgP) and breast cancer resistance protein (BCRP) and use with potent PgP or BCRP inhibitors or inducers may alter exposure and distribution of pazopanib.

Use of pazopanib eye drops with ketoconazole (a potent CYP3A4 inhibitor and a PgP inhibitor) increased exposure to pazopanib. Use of lapatinib (a substrate for and weak inhibitor of CYP3A4 and PgP, and a potent inhibitor of BCRP) also substantially increased exposure to pazopanib. Combination of pazopanib with strong CYP3A4, PgP, or BCRP inhibitors should therefore be avoided. If use together cannot be avoided, US licensed product information states that a dose reduction of pazopanib can be considered, see Uses and Administration, p. 843.3. Grapefruit juice inhibits CYP3A4 activity and it should be avoided during treatment with pazopanib.

Combination of pazopanib with strong CYP3A4, PgP, or BCRP inducers is also not recommended.

In vitro, pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 and may affect exposure to substrates of these enzymes. It is also an inhibitor of glucuronidation by the enzyme UGT1A1, and inhibits the organic anion transporting polypeptide (OATP) 1B1.

Concomitant use of pazopanib with simvastatin increases the incidence of elevations of alanine aminotransferase. In such cases the dose of pazopanib should be adjusted (see Administration in Hepatic Impairment, above), and consideration given to stopping simvastatin. The effect of pazopanib use with other statins is unknown.

Pharmacokinetics

Peak plasma concentrations occur about 2 to 4 hours after an oral dose of pazopanib. Absorption and bioavailability are increased when tablets are crushed and systemic exposure is increased when given with food. Pazopanib is highly protein bound (> 99%) and is a substrate for P-glycoprotein and breast cancer resistant protein (BCRP). Metabolism occurs via cytochrome P450 isoenzymes, mainly CYP3A4, with a minor contribution from CYP1A2 and CYP2C8. Elimination is mostly via the faeces with less than 4% in the urine. Pazopanib has a mean half-life of about 31 hours after an oral dose.

References.
1. Di Gion P, *et al.* Clinical pharmacokinetics of tyrosine kinase inhibitors: focus on pyrimidines, pyridines and pyrroles. *Clin Pharmacokinet* 2011; 50: 551–603.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Votrient; *Austria*: Votrient; *Belg.*: Votrient; *Canad.*: Votrient; *Cz.*: Votrient; *Denm.*: Votrient; *Fr.*: Votrient; *Ger.*: Votrient; *Gr.*: Votrient; *Irl.*: Votrient; *Israel*: Votrient; *Jpn*: Votrient; *Neth.*: Votrient *Norw.*: Votrient; *NZ*: Votrient; *Pol.*: Votrient; *Port.*: Votrient *Singapore*: Votrient; *Spain*: Votrient; *Swed.*: Votrient; *Switz.* Votrient; *Thai.*: Votrient; *Turk.*: Votrient; *UK*: Votrient; *Ukr.* Votrient (Вотриент); *USA*: Votrient.

Pemetrexed Disodium

(BANM, USAN, rINNM)

LY-231514 (pemetrexed or pemetrexed disodium); MTA; Multi-targeted Antifolate; Pemetreksed Disodyum; Pemetrexed disódico; Pémétrexed Disodique; Pemetrexedum Dinatricum; Динатрий Пеметрексед.

Disodium *N*-[*p*-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamate.

$C_{20}H_{19}N_5Na_2O_6$=471.4

CAS — 137281-23-3 (pemetrexed); 150399-23-8 (pemetrexed disodium); 357166-29-1 (pemetrexed disodium heptahydrate).

ATC — L01BA04.

ATC Vet — QL01BA04.

UNII — 2PKU919BA9 (pemetrexed disodium); 9T47E4OM16 (pemetrexed disodium heptahydrate).

NOTE. In practice, pemetrexed is given as the disodium heptahydrate ($C_{20}H_{19}N_5Na_2O_6.7H_2O$ = 597.5).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pemetrexed Disodium Heptahydrate). A white or almost white powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane. pH of a 5.6% solution in water is 7.5 to 8.4.

Incompatibility. Licensed product information states that pemetrexed is physically incompatible with diluents containing calcium, including Ringer's solution and lactated Ringer's solution. A study[1] found pemetrexed disodium 20 mg/mL to be physically incompatible with 24 drugs resulting in precipitation or colour change during simulated Y-site administration. These drugs include amphotericin B, some cephalosporin and cephamycin antibacterials, chlorpromazine hydrochloride, ciprofloxacin, dobutamine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, gemcitabine hydrochloride, gentamicin sulfate, irinotecan hydrochloride, metronidazole, minocycline hydrochloride, mitoxantrone hydrochloride, nalbuphine hydrochloride, ondansetron hydrochloride, prochlorperazine edisilate, tobramycin sulfate, and topotecan hydrochloride.

1. Trissel LA, *et al.* Physical compatibility of pemetrexed disodium with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2004; 61: 2289–93.

Stability. Licensed product information states that pemetrexed is chemically and physically stable, once reconstituted and diluted, for 24 hours either refrigerated at 2 degrees to 8 degrees or at 25 degrees; from a microbiological point of view, solutions should be used immediately, unless prepared under controlled and validated aseptic conditions.

Pemetrexed, reconstituted in polypropylene syringes with sodium chloride 0.9% to a concentration of 25 mg/mL, was found to be both chemically and physically stable for 2 days when stored at room temperature, and for 31 days when refrigerated.[1] Although pemetrexed solutions of 2, 10, and 20 mg/mL in glucose 5% and sodium chloride 0.9% in PVC bags were chemically stable for 90 days when frozen at -20 degrees, microparticulates formed, possibly related to the PVC containers. Pemetrexed solutions should therefore not be frozen.[2]

1. Zhang Y, Trissel LA. Physical and chemical stability of pemetrexed solutions in plastic syringes. *Ann Pharmacother* 2005; 39: 2026–8.
2. Zhang Y, Trissel LA. Physical instability of frozen pemetrexed solutions in PVC bags. *Ann Pharmacother* 2006; 40: 1289–92.

Uses and Administration

Pemetrexed is mainly a thymidylate synthase inhibitor like raltitrexed (p. 850.3), but it also inhibits other folate-dependent enzymes involved in purine synthesis such as dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. It is used as second-line monotherapy or first-line with cisplatin in the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (p. 710.2); it is also used as maintenance monotherapy in patients whose disease has not progressed after platinum-based first-line chemotherapy. Pemetrexed is also used with cisplatin in the first-line treatment of unresectable malignant pleural mesothelioma (p. 711.2).

Pemetrexed is given as the disodium heptahydrate but doses are expressed in terms of the base: pemetrexed disodium heptahydrate 1.4 g is equivalent to about 1 g of pemetrexed. A dose of pemetrexed 500 mg/m² is given by intravenous infusion over 10 minutes. The dose may be repeated in 21-day cycles, and should be adjusted according to toxicity. In combination therapy, cisplatin (at a dose of

75 mg/m² infused over 2 hours) is given about 30 minutes after the end of pemetrexed infusion. Doses may need to be modified according to toxicity, see Administration in Subsequent Cycles, below. For further information on use in renal impairment, see below.

Pretreatment with oral dexamethasone 4 mg twice daily for 3 days is recommended, starting the day before pemetrexed. At least 5 doses of oral folic acid (350 micrograms to 1 mg) should be taken during the 7 days before the first dose of pemetrexed; dosing should continue throughout pemetrexed therapy, and for 21 days after the last pemetrexed dose. Patients should also receive an intramuscular injection of vitamin B_{12} 1 mg in the week before the first pemetrexed dose, and once every 3 cycles thereafter; subsequent injections may be given on the same day as pemetrexed.

Pemetrexed is under investigation as an antifolate antimetabolite in the treatment of colon, pancreatic, breast, and head and neck cancer.

References.
1. Hochster HS. The role of pemetrexed in the treatment of gastrointestinal malignancy. *Clin Colorectal Cancer* 2004; 4: 190–5.
2. Rollins KD, Lindley C. Pemetrexed: a multitargeted antifolate. *Clin Ther* 2005; 27: 1343–82.
3. Martin M. Clinical experience with pemetrexed in breast cancer. *Semin Oncol* 2006; 33 (suppl 2): S15–S18.
4. Dundar Y, *et al.* Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation. *Health Technol Assess* 2007; 11: 1–90.
5. Green J, *et al.* Pemetrexed disodium in combination with cisplatin versus other cytotoxic agents or supportive care for the treatment of malignant pleural mesothelioma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 24/08/07).
6. Longo-Sorbello GS, *et al.* Role of pemetrexed in non-small cell lung cancer. *Cancer Invest* 2007; 25: 59–66.
7. Meriggi F, *et al.* The potential role of pemetrexed in gastrointestinal cancer. *Chemotherapy* 2008; 54: 1–8.
8. Baldwin CM, Perry CM. Pemetrexed: a review of its use in the management of advanced non-squamous non-small cell lung cancer. *Drugs* 2009; 69: 2279–2302.
9. Tomao F, *et al.* Emerging role of pemetrexed in ovarian cancer. *Expert Rev Anticancer Ther* 2009; 9: 1727–35.

Administration in the elderly. A retrospective analysis found pemetrexed to be effective as a second-line therapy in non-small cell lung cancer patients aged 70 years or older, with a more favourable toxicity profile than docetaxel.[1]

UK licensed product information states that there are no data to suggest that patients aged 65 years or older are at increased risk of adverse effects compared with younger patients; no dose reductions are recommended on the basis of age alone.

1. Weiss GJ, *et al.* Elderly patients benefit from second-line cytotoxic chemotherapy: a subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2006; 24: 4405–11.

Administration in renal impairment. A pharmacokinetic study[1] found that pemetrexed clearance decreased with declining renal function. Although systemic exposure increased in these patients, this was not associated with an increase in drug-related dose-limiting toxicities for patients with a GFR of 40 mL/minute or more and receiving vitamin supplementation (folic acid and vitamin B_{12} supplementation appears to reduce toxicity without altering pemetrexed pharmacokinetics). Patients with a GFR of 80 mL/minute or more tolerated a dose of pemetrexed 600 mg/m², given intravenously every 3 weeks, whereas patients with a GFR of 40 to 79 mL/minute tolerated 500 mg/m² every 3 weeks. One patient with a GFR of 19 mL/minute died as a result of treatment-related toxicity and accrual into this group was stopped. As a result, no data were available for patients with a GFR below 40 mL/minute.

Licensed product information states that no dose adjustment is necessary in patients with a creatinine clearance (CC) of 45 mL/minute or more. Use in patients with a CC of less than 45 mL/minute is not recommended due to lack of data. Caution is advised when giving pemetrexed with NSAIDs in patients whose CC is less than 80 mL/minute (see Interactions, below).

1. Mita AC, *et al.* Phase I and pharmacokinetic study of pemetrexed administered every 3 weeks to advanced cancer patients with normal and impaired renal function. *J Clin Oncol* 2006; 24: 552–62.

Administration in subsequent cycles. Complete blood counts should be performed in all patients given pemetrexed. Patients should not begin a new cycle unless:
- the absolute neutrophil count (ANC) is ⩾ 1500 cells/mm³
- the platelet count is ⩾ 100 000 cells/mm³
- creatinine clearance is ⩾ 45 mL/min (see also Administration in Renal Impairment, above)

Dose adjustments at the start of a subsequent cycle should be based on nadir haematological counts or maximum non-haematological toxicity from the preceding cycle of therapy. Treatment should be delayed to allow sufficient time for recovery. Upon recovery, patients are treated according to the following recommendations, which are suitable for pemetrexed monotherapy or use with cisplatin.

For **haematological** toxicities:
- nadir ANC < 500 cells/mm³ and nadir platelets ⩾ 50 000 cells/mm³; 75% of previous dose (pemetrexed and cisplatin)
- nadir platelets < 50 000 cells/mm³ without bleeding, regardless of nadir ANC; 75% of previous dose (pemetrexed and cisplatin)
- nadir platelets < 50 000 cells/mm³ with bleeding, regardless of nadir ANC; 50% of previous dose (pemetrexed and cisplatin)

If **non-haematological** toxicities (excluding neurotoxicity) are severe, treatment should be withheld until resolution, and treatment resumed according to the following recommendations:
- any grade 3 or 4 toxicities except mucositis; 75% of previous dose (pemetrexed and cisplatin)
- any diarrhoea requiring hospitalisation, or grade 3 or 4 diarrhoea; 75% of previous dose (pemetrexed and cisplatin)
- grade 3 or 4 mucositis; 50% of previous pemetrexed dose and 100% of previous cisplatin dose

Patients should stop therapy if **neurotoxicity** is severe (grade 3 or 4); otherwise doses are adjusted as follows:
- grade 0 to 1; 100% of previous dose (pemetrexed and cisplatin)
- grade 2; 100% of previous pemetrexed dose and 50% of previous cisplatin dose

Pemetrexed should be stopped if patients have any severe haematological or non-haematological toxicities after 2 dose reductions.

Adverse Effects, Treatment, and Precautions

As for Raltitrexed, p. 851.1. Neutropenia and febrile neutropenia are common and myelosuppression may be dose-limiting.

Pemetrexed may also cause fatigue, stomatitis, pharyngitis, oesophagitis, chest pain, and neuropathy. Rare cases of hepatitis, colitis, and interstitial pneumonitis have occurred; fatalities have been reported. Bullous skin conditions have been reported, including Stevens-Johnson syndrome and toxic epidermal necrolysis, which in some cases were fatal. Serious renal events, including acute renal failure, have been reported with pemetrexed when it was used either alone or with other cytotoxic drugs; most patients had underlying risk factors such as dehydration, hypertension, or diabetes. Cardiovascular events, including myocardial infarction and cerebrovascular events, have occurred rarely, usually when pemetrexed was used with other cytotoxic drugs and in patients with cardiovascular risk factors. Arrhythmias have been reported. Cases of radiation pneumonitis or oesophagitis, and radiation recall have been reported in patients treated with radiotherapy. Hypersensitivity reactions may occur. Cases of peripheral ischaemia leading to extremity necrosis have been reported. The effect of pleural effusions or ascites on pemetrexed is unknown; in those patients with significant third-space fluid, draining of any effusions before treatment with pemetrexed should be considered.

Complete blood cell counts should be monitored, and folate and vitamin B_{12} are given as prophylaxis against haematological and gastrointestinal toxicity during pemetrexed therapy. Pretreatment with a corticosteroid, such as oral dexamethasone, reduces the incidence and severity of skin reactions. (For dosing details, see Uses and Administration, p. 844.3.) Gastrointestinal toxicity may be severe, leading to dehydration, and antiemetics and appropriate hydration should be given before and after treatment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pemetrexed 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 29/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

High doses of NSAIDs and aspirin may decrease pemetrexed elimination. In patients with mild to moderate renal impairment (creatinine clearance 45 to 79 mL/minute) high doses of NSAIDs and aspirin should be avoided from 2 days before until 2 days after pemetrexed use, and NSAIDs that have longer half-lives, such as piroxicam, should be avoided from 5 days before until 2 days after pemetrexed.

Analgesics. Enteric-coated *aspirin* 325 mg given orally every 6 hours for a total of 9 doses before pemetrexed, did not affect the pharmacokinetic profile of pemetrexed in an interaction study; the authors considered no dose adjustment necessary when moderate doses of aspirin were given with pemetrexed. However, this result could not be extrapolated to high-dose aspirin regimens, as the interaction might be dependent on salicylate concentrations. In contrast, oral *ibuprofen* 400 mg every 6 hours for a total of 9 doses before pemetrexed significantly reduced systemic pemetrexed clearance. Despite an increase in pemetrexed exposure, no increase in toxicity was seen. Dose adjustments were not considered necessary in patients with normal renal function (defined as creatinine clearance of 80 mL/minute or greater). However, in patients with pre-existing reduced pemetrexed clearance due to renal impairment, giving ibuprofen may result in further increases in pemetrexed exposure; the authors advised caution when using these 2 drugs together in patients with a creatinine clearance of less than 80 mL/minute.[1] For licensed product information regarding the use of aspirin and NSAIDs with pemetrexed, see above.

1. Sweeney CJ, *et al.* Two drug interaction studies evaluating the pharmacokinetics and toxicity of pemetrexed when coadministered with aspirin or ibuprofen in patients with advanced cancer. *Clin Cancer Res* 2006; 12: 536–42.

Pharmacokinetics

Pemetrexed has a plasma elimination half-life of 3.5 hours in patients with normal renal function. *In-vitro* data indicate that pemetrexed is about 81% bound to plasma proteins. It undergoes limited hepatic metabolism, and about 70 to 90% of a dose is eliminated unchanged in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alimta; Enzastar; Trexam; ***Austral.***: Alimta; ***Austria***: Alimta; ***Belg.***: Alimta; ***Braz.***: Alimta; ***Canad.***: Alimta; ***Chile***: Alimta; ***China***: Alimta (力比泰); Jepale (捷佰立); Pu Lai Le (普来乐); Yiluoze (怡罗泽); ***Cz.***: Alimta; ***Denm.***: Alimta; ***Fin.***: Alimta; ***Fr.***: Alimta; ***Ger.***: Alimta; ***Gr.***: Alimta; ***Hong Kong***: Alimta; ***Hung.***: Alimta; ***India***: Alimta; Pamifect; ***Irl.***: Alimta; ***Israel***: Alimta; ***Ital.***: Alimta; ***Malaysia***: Alimta; ***Mex.***: Alimta; ***Neth.***: Alimta; ***Norw.***: Alimta; ***NZ***: Alimta; ***Philipp.***: Alimta; ***Pol.***: Alimta; ***Port.***: Alimta; ***Rus.***: Alimta (Алимта); ***S.Afr.***: Alimta; ***Singapore***: Alimta; ***Spain***: Alimta; ***Swed.***: Alimta; ***Switz.***: Alimta; ***Thal.***: Alimta; ***Turk.***: Alimta; Pemtrex; ***UK***: Alimta; ***Ukr.***: Alimta (Алимта); ***USA***: Alimta.

Pentostatin *(BAN, USAN, rINN)*

CI-825; Co-vidarabine; Covidarabine; Deoxycoformycin; NSC-218321; PD-81565; Pentostatina; Pentostatine; Pentostatinum; 2'-Deoxycoformycin; YK-176; Пентостатин.

(*R*)-3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol; 1,2-Dideoxy-1-[(*R*)-3,6,7,8-tetrahydro-8-hydroxyimidazo[4,5-*d*][1,3]diazepin-3-yl]-D-*erythro*-pentofuranose.

$C_{11}H_{16}N_4O_4$=268.3

CAS — 53910-25-1.

ATC — L01XX08.

ATC Vet — QL01XX08.

UNII — 395575MZO7.

Uses and Administration

Pentostatin is a potent inhibitor of the enzyme adenosine deaminase and probably exerts its cytotoxic actions through the interruption of normal purine metabolism and DNA synthesis. Lymphocytes are particularly sensitive to its actions.

Pentostatin is used as a single agent in the treatment of hairy-cell leukaemia (p. 694.3), in usual doses of 4 mg/m² every other week. The dose is given as an intravenous bolus injection, or as an infusion over 20 to 30 minutes. Hydration with 500 mL to 1 litre of glucose 5% in sodium chloride 0.18 or 0.9%, or equivalent, is recommended beforehand; a further 500 mL of the hydration solution should be infused once the drug has been given.

Pentostatin has been tried in cutaneous T-cell lymphomas (see Mycosis Fungoides, p. 698.3). It is also under investigation in some other lymphoid malignancies, including chronic lymphocytic leukaemia (p. 693.3), and for the management of chronic graft-versus-host disease following haematopoietic stem cell transplantation (p. 1937.1).

References.
1. Grever MR, *et al.* Pentostatin in the treatment of hairy-cell leukemia. *Best Pract Res Clin Haematol* 2003; 16: 91–9.
2. Drapkin R, *et al.* Results of a phase II multicenter trial of pentostatin and rituximab in patients with low grade B-cell non-Hodgkin's lymphoma: an effective and minimally toxic regimen. *Clin Lymphoma* 2003; 4: 169–75.
3. Tsimberidou AM, *et al.* Phase II study of pentostatin in advanced T-cell lymphoid malignancies: update of an MD Anderson Cancer Center series. *Cancer* 2004; 100: 342–9.

4. Tsiara SN, *et al.* Treatment of resistant/relapsing chronic lymphocytic leukemia with a combination regimen containing deoxycoformycin and rituximab. *Acta Haematol (Basel)* 2004; 111: 185–8.
5. Dillman RO. Pentostatin (Nipent™) in the treatment of chronic lymphocyte leukemia and hairy cell leukemia. *Expert Rev Anticancer Ther* 2004; 4: 27–36.
6. Higman M, *et al.* Pentostatin—pharmacology, immunology, and clinical effects in graft-versus-host disease. *Expert Opin Pharmacother* 2004; 5: 2605–13.
7. Ho AD, Hensel M. Pentostatin and purine analogs for indolent lymphoid malignancies. *Future Oncol* 2006; 2: 169–83.
8. Grever MR. Pentostatin: impact on outcome in hairy cell leukemia. *Hematol Oncol Clin North Am* 2006; 20: 1099–1108.
9. Sauter C, *et al.* Pentostatin in chronic lymphocytic leukemia. *Expert Opin Drug Metab Toxicol* 2008; 4: 1217–22.
10. Lamanna N, Kay NE. Pentostatin treatment combinations in chronic lymphocytic leukemia. *Clin Adv Hematol Oncol* 2009; 7: 386–92.

Adverse Effects and Precautions

The most common adverse effects in patients given pentostatin include myelosuppression (and in particular suppression of the CD4+ lymphocyte subset), headache, abdominal pain, fever and chills, gastrointestinal disturbances (notably diarrhoea and nausea and vomiting), hypersensitivity reactions, and hepatotoxicity. Central neurotoxicity may manifest as tiredness, anxiety, depression, sleep disturbances, and paraesthesias: treatment should be withheld or stopped in such patients. Impaired renal function and pulmonary toxicity (cough, dyspnoea, and pneumonia) may occur. Severe toxicity in early studies, affecting mainly the CNS, kidneys, liver, and lungs, was associated with the use of doses higher than those currently recommended and produced some fatalities.

Other adverse effects reported with pentostatin include dry skin and rashes (sometimes severe and worsening with continued treatment), pruritus, conjunctivitis, alopecia, arthralgia and myalgia, peripheral oedema, thrombophlebitis, and cardiovascular disorders including arrhythmias, angina pectoris, and heart failure.

Pentostatin should not be given to patients with impaired renal function, or in active infection. It is teratogenic in *animals* and potentially genotoxic: it is therefore contra-indicated in pregnancy and men given pentostatin should not father children for 6 months after therapy.

Interactions

Pentostatin should not be given with fludarabine, as the combination may increase pulmonary toxicity. A similar increase in toxicity is expected when pentostatin is used with vidarabine.

Use of pentostatin with carmustine, etoposide and high-dose cyclophosphamide, has produced acute pulmonary oedema and hypotension, leading to death. Pentostatin should therefore not be given with high-dose cyclophosphamide.

Allopurinol. Fatal acute necrotising arteritis developed in a patient given pentostatin and allopurinol.[1] Although the hypersensitivity vasculitis may have been due to allopurinol alone there is circumstantial evidence to suggest that pentostatin may predispose patients to drug hypersensitivity and it may be wise to avoid this combination, and to observe pentostatin-treated patients closely for allergic manifestations.

1. Steinmetz JC, *et al.* Hypersensitivity vasculitis associated with 2-deoxycoformycin and allopurinol therapy. *Am J Med* 1989; 86: 498–9.

Pharmacokinetics

After intravenous injection, pentostatin has an elimination half-life of about 6 hours. About 90% of a dose is excreted in the urine as unchanged drug and metabolites. Pentostatin crosses the blood-brain barrier and can be measured in the CSF.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Nipent; *Fr.*: Nipent; *Ger.*: Nipent; *Gr.*: Nipent; *Irl.*: Nipent; *Ital.*: Nipent; *Neth.*: Nipent; *Port.*: Nipent; *Spain*: Nipent; *UK*: Nipent; *USA*: Nipent.

Peplomycin Sulfate *(USAN, rINNM)*

NK-631; Pepleomycin Sulphate; Peplomicina, sulfato de; Peplomycin Sulphate; Péplomycine, Sulfate de; Peplomycini Sulfas; Sulfato de peplomicina; Пепломицина Сульфат.

N^1-[3-[(*S*)-(α-Methylbenzyl)amino]propyl]bleomycinamide sulphate.

$C_{61}H_{88}N_{18}O_{21}S_2.H_2SO_4$=1571.7

CAS — 68247-85-8 *(peplomycin)*; 70384-29-1 *(peplomycin sulfate)*.

UNII — 6A668951HW.

Pharmacopoeias. In *Jpn*.

Profile

Peplomycin is an antineoplastic derived from bleomycin (p. 749.3) and with similar properties. It has been given as the sulfate in the treatment of a variety of malignant neoplasms, including lymphomas and tumours of the head and neck, breast, cervix, lung, oesophagus, prostate, and skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Pepleo.

Peretinoin *(rINN)*

Ácido poliprénico; Acyclic Retinoid; E-5166; NIK-333; Peretinoína; Péritinoïne; Peretinoinum; Polyprenic Acid; Polyprenoic Acid; Полипреноевая Кислота; Перетиноин.

(*all-E*)-3,7,11,15-Tetramethyl-2,4,6,10,14-hexadecapentaenoic acid.

$C_{20}H_{30}O_2$=302.5

CAS — 81485-25-8.

UNII — 11ALM7A4RV.

Profile

Peretinoin is a retinoid that has been tried in psoriasis and keratoderma and is being studied in the treatment of liver cancers.

References.
1. Muto Y, *et al.* Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. *N Engl J Med* 1996; 334: 1561–7.
2. Muto Y, *et al.* Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. *N Engl J Med* 1999; 340: 1046–7.
3. Takai K, *et al.* Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma: updated analysis of the long-term follow-up data. *Intervirology* 2005; 48: 39–45.

Perifosine *(rINN)*

D-21266; KRX-0401; Perifosina; Périfosine; Perifosinum; Перифозин.

4-Hydroxy-1,1-dimethylpiperidinium hydroxide octadecyl hydrogen phosphate inner salt.

$C_{25}H_{52}NO_4P$=461.7

CAS — 157716-52-4.

UNII — 2GWV496552.

Profile

Perifosine is an oral alkylphospholipid compound that is structurally related to miltefosine (p. 829.3); it has similarities to the phospholipid components of the cell membrane and exerts its antineoplastic action by disruption of cell-membrane functions. It is under investigation for the treatment of multiple myeloma and advanced metastatic colorectal cancer.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.
1. Ghobrial IM, *et al.* Clinical and translational studies of a phase II trial of the novel oral Akt inhibitor perifosine in relapsed or relapsed/refractory Waldenstrom's macroglobulinemia. *Clin Cancer Res* 2010; 16: 1033–41.
2. Unger C, *et al.* First-time-in-man and pharmacokinetic study of weekly oral perifosine in patients with solid tumours. *Eur J Cancer* 2010; 46: 920–5.

Pertuzumab *(BAN, USAN, rINN)*

2C4; Pertuzumabum; R-1273; rhuMAb-2C4; Пертузумаб.

Immunoglobulin G1, anti-(human v (receptor)) (human-mouse monoclonal 2C4 heavy chain), disulfide with human-mouse monoclonal 2C4 κ-chain, dimer.

CAS — 380610-27-5.

ATC — L01XC13.

ATC Vet — QL01XC13.

UNII — K16AIQ8CTM.

NOTE. The name Omnitarg has been used as a trade mark for pertuzumab.

Uses and Administration

Pertuzumab is a humanised monoclonal antibody and a human epidermal growth factor receptor (HER) dimerisation inhibitor. It inhibits HER2 heterodimerisation with other HER family receptors, thereby preventing the activation of HER signalling pathways. Pertuzumab is used with trastuzumab and docetaxel in the treatment of HER2-positive metastatic breast cancer (p. 702.1), in patients who have not been given anti-HER2 therapy or chemotherapy.

The initial dose of pertuzumab is 840 mg given by intravenous infusion over 60 minutes. This is followed by a dose of 420 mg given by infusion over 30 to 60 minutes once every 3 weeks. If a dose is delayed or missed then treatment should be resumed as soon as possible, but if the time between doses is 6 weeks or more then pertuzumab should be restarted at 840 mg followed by 420 mg once every 3 weeks.

Pertuzumab should be withheld or stopped if trastuzumab is withheld or stopped. Pertuzumab and trastuzumab should be withheld for at least 3 weeks if there is a drop in left ventricular ejection fraction (LVEF) to less than 40%, or if LVEF is 40 to 45% with a 10% or greater absolute decrease below pretreatment values. Pertuzumab may be restarted if the LVEF has recovered to more than 45%, or to 40 to 45% associated with less than a 10% absolute decrease below pretreatment values. If the LVEF has not improved, or has declined further, after about 3 weeks then stopping pertuzumab and trastuzumab permanently should be strongly considered.

Pertuzumab is under investigation in the treatment of HER2-positive gastric cancer.

References.
1. Baselga J, *et al.* CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366: 109–19.
2. Keating GM. Pertuzumab: in the first-line treatment of HER2-positive metastatic breast cancer. *Drugs* 2012; 72: 353–60.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Hypersensitivity and infusion reactions have been reported in patients given pertuzumab. Patients should be monitored for 60 minutes after the first dose, and for 30 minutes after subsequent doses. Other adverse effects reported in patients given pertuzumab (with trastuzumab and docetaxel) include diarrhoea, nausea, neutropenia, fatigue, rash, and peripheral neuropathy. Decreases in left ventricular ejection fraction (LVEF) have occurred in patients who have been given drugs that block HER2 activity, including pertuzumab; LVEF should be assessed before starting pertuzumab and regularly during treatment (see also Uses and Administration, above).

Licensed product information warns against the use of pertuzumab during pregnancy, based on reports of oligohydramnios, delayed fetal kidney development, and embryo-fetal death in *animal* studies.

References.
1. Drucker AM, *et al.* Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. *Breast Cancer Res Treat* 2012; 133: 347–54.

Effects on the heart. Pertuzumab is anticipated to have adverse cardiac effects because of its inhibition of human epidermal growth factor receptor 2 dimerisation, which has a role in cardiac myocyte homoeostasis. Cardiac safety data from 598 patients in phase 2 studies of pertuzumab have been pooled and analysed.[1] Pertuzumab had been given as monotherapy and in combination regimens with non-anthracycline cytotoxics, trastuzumab, or erlotinib, for various malignancies including metastatic breast cancer. In 331 patients given monotherapy there were 13 cases (6.9%) of asymptomatic left ventricular systolic dysfunction and 1 case (1.4%) of symptomatic heart failure. The incidence of cardiac dysfunction was not significantly different when pertuzumab was given in combination therapy. The median time to these effects was about cycle 4.

However, these studies included patients with a lifetime exposure to anthracyclines up to doxorubicin 360 mg/m^2 or equivalent and excluded those with cardiac comorbidities, which probably contributed to the low rates of cardiac events. In addition, where patients had a history of anthracycline treatment, it had generally been given several months or years before pertuzumab therapy. The effects of regimens containing pertuzumab and anthracyclines is under investigation.

See Effects on the Heart under Trastuzumab (p. 876.3) and Doxorubicin (p. 784.1, for anthracyclines) for further information about the cardiotoxicity of these other drugs.

1. Lenihan D, *et al.* Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. *Ann Oncol* 2012; 23: 791–800.

Pharmacokinetics

Pertuzumab has a half-life of about 18 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Israel*: Perjeta; *Jpn*: Perjeta; *Switz.*: Perjeta; *UK*: Perjeta; *USA*: Perjeta.

Picoplatin *(BAN, USAN, rINN)*

AMD-473; NX-473; Picoplatine; Picoplatino; Picoplatinum; ZD-0473; Пикоплатин.

cis-Amminedichloro(2-methylpyridine)platinum(II).

$C_6H_{10}Cl_2N_2Pt$=376.1

CAS — 181630-15-9.

UNII — B5TAN0L720.

Profile

Picoplatin is a platinum derivative that is under investigation as an intravenous antineoplastic for the treatment of small-cell lung cancer, and other solid tumours such as colorectal, ovarian, and prostate cancer. An oral dosage form is also being developed.

References.

1. Kelland L. Broadening the clinical use of platinum drug-based chemotherapy with new analogues: satraplatin and picoplatin. *Expert Opin Invest Drugs* 2007; 16: 1009–21.
2. Eckardt JR, *et al.* Phase II study of picoplatin as second-line therapy for patients with small-cell lung cancer. *J Clin Oncol* 2009; 27: 2046–51.

Pipobroman *(USAN, pINN)*

A-8103; NSC-25154; Pipobromán; Pipobromanum; Пипоброман.

1,4-Bis[3-bromopropionyl)piperazine.

$C_{10}H_{16}Br_2N_2O_2$=356.1

CAS — 54-91-1.

ATC — L01AX02.

ATC Vet — QL01AX02.

UNII — 6Q99RDT97R.

Profile

Pipobroman is an antineoplastic which appears to act by alkylation. It may be used in the treatment of polycythaemia vera (p. 695.2), in patients requiring myelosuppressive therapy, and in refractory chronic myeloid leukaemia (p. 694.2).

The usual initial dose for polycythaemia vera is 1 mg/kg daily, given orally, and increased to 3 mg/kg, if necessary, according to response. Maintenance dosage is 100 to 200 micrograms/kg daily. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The main adverse effect is moderate bone-marrow depression, which may develop 4 weeks or more from starting treatment. Anaemia may be marked at higher doses and is usually accompanied by leucopenia. Thrombocytopenia and haemolysis have occurred. In the initial stages of treatment, white cell and platelet counts should be determined on alternate days and complete blood counts once or twice weekly. Dosage should be stopped if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p. 730.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Vercyte; *Gr.*: Vercite; *Ital.*: Vercite.

Pirarubicin *(rINN)*

Pirarubicina; Pirarubicine; Pirarubicinum; 1609-RB; Tepirubicin; THP-ADM; THP-doxorubicin; Пирарубицин.

(8*S*,10*S*)-10-[[3-Amino-2,3,6-trideoxy-4-*O*-(2*R*-tetrahydro-2*H*-pyran-2-yl)-α-L-*lyxo*-hexopyranosyl]oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione.

$C_{32}H_{37}NO_{12}$=627.6

CAS — 72496-41-4.

ATC — L01DB08.

ATC Vet — QL01DB08.

UNII — D58G680W0G.

Pharmacopoeias. In *Jpn*.

Profile

Pirarubicin is an antineoplastic anthracycline antibiotic that is a structural analogue of doxorubicin (p. 782.3), and has similar properties. It is used in the management of breast cancer and has also been tried in other solid neoplasms, acute leukaemias and lymphomas.

Pirarubicin is formulated as the hydrochloride but doses are in terms of the base. A usual dose of 25 to 50 mg/m² every 3 to 4 weeks has been recommended in breast cancer, but other dosage regimens have been used. Doses may be given by intravenous injection over 5 to 10 minutes into a rapidly-flowing intravenous infusion of glucose 5%. Patients should undergo regular blood counts and monitoring of cardiac function: at cumulative doses above 600 mg/m² ventricular ejection fraction should be checked before each course. Pirarubicin has also been given by the intra-arterial and intravesical routes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Theprubicine†; *Jpn*: Therarubicin.

Pixantrone *(BAN, USAN, rINN)*

BBR-2778; Pixantrona; Pixantronum; Пиксантрон.

6,9-Bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5,10-dione.

$C_{17}H_{19}N_5O_2$=325.4

CAS — 144510-96-3.

ATC — L01DB11.

ATC Vet — QL01DB11.

UNII — F5SXN2KNMR.

Pixantrone Maleate *(BANM, rINNM)*

BBR-2778 (pixantrone or pixantrone maleate); Maleato de pixantrona; Pixantrone Dimaleate (USAN); Pixantrone, Maléate de; Pixantroni Maleas; Пиксантрона Малеат.

6,9-bis[(2-Aminoethyl)amino]benzo[g]isoquinoline-5,10-dione (2*Z*)-but-2-endioate (1:2).

$C_{17}H_{19}N_5O_2.2C_4H_4O_4$=557.5

CAS — 144675-97-8.

ATC — L01DB11.

ATC Vet — QL01DB11.

UNII — P0R64C4CR9.

Profile

Pixantrone is an aza-anthracenedione anthracycline derivative that is structurally similar to mitoxantrone (p. 833.1). However, it lacks the 5,8-dihydroxy substitution groups thought to be responsible for mitoxantrone-induced cardiotoxicity. It is a weak inhibitor of topoisomerase II that directly alkylates DNA to form stable DNA adducts and cross-strand breaks.

Pixantrone is given as monotherapy for the treatment of patients with relapsed or refractory aggressive non-Hodgkin's B-cell lymphomas (p. 696.3).

Pixantrone is given as the dimaleate, but doses are expressed in terms of the base; 1.7 mg of the dimaleate is equivalent to about 1 mg of pixantrone. It is given in a dose equivalent to pixantrone 50 mg/m² on days 1, 8, and 15 of each 28-day cycle, for up to 6 cycles. It is diluted to 250 mL in sodium chloride 0.9% and given by slow intravenous infusion over at least 60 minutes.

Doses may need to be delayed or adjusted according to the degree of toxicity produced.

References.

1. Engert A, *et al.* EXTEND PIX301: a phase III randomized trial of pixantrone versus other chemotherapeutic agents as third-line monotherapy in patients with relapsed, aggressive non-Hodgkin's lymphoma. *Clin Lymphoma Myeloma* 2006; 7: 152–4.
2. El-Helw LM, Hancock BW. Pixantrone: a novel aza-anthracenedione in the treatment of non-Hodgkin's lymphomas. *Expert Opin Invest Drugs* 2007; 16: 1683–91.
3. El-Helw LM, Hancock BW. Pixantrone: a promising drug in the treatment of non-Hodgkin lymphomas. *Future Oncol* 2009; 5: 445–53.
4. Mukherji D, Pettengell R. Pixantrone maleate for non-Hodgkin's lymphoma. *Drugs Today* 2009; 45: 797–805.
5. Cabanillas F. Pixantrone: a new agent for relapsed aggressive lymphomas. *Lancet Oncol* 2012; 13: 654–6.
6. Pettengell R, *et al.* Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. *Lancet Oncol* 2012; 13: 696–706. Correction, *ibid.*: e285.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Pixuvri; *Neth.*: Pixuvri; *Norw.*: Pixuvri; *Spain*: Pixuvri; *UK*: Pixuvri.

Plevitrexed *(BAN, rINN)*

BGC-9331; plevitredex; Plévitrexed; Plevitrexedum; ZD-9331; Плевитрексед.

(2*S*)-2-[(4-[[(2,7-Dimethyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl](prop-2-ynyl)amino]-2-fluorobenzoyl)amino]-4-(1*H*-tetrazol-5-yl)butanoic acid.

$C_{26}H_{25}FN_8O_4$=532.5

CAS — 153537-73-6.

UNII — L9P2881C3H.

Profile

Plevitrexed is a thymidylate synthase inhibitor that is under investigation for the treatment of stomach and ovarian cancers.

Plitidepsin *(BAN, rINN)*

Aplidine; Dehydrodidemnin B; Plitidepsina; Plitidepsine; Plitidepsinum; Плитидепсин.

3,6-Anhydro(*N*-[(2*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-3-hydroxy-4-[(*N*-(2-oxopropanoyl)-L-prolyl-*N*-methyl-D-leucyl-L-threonyl]amino)-5-methylheptanoyloxy]-2,5-dimethyl-3-oxohexanoyl]-L-leucyl-L-prolyl-*N*,*O*-dimethyl-L-tyrosine).

$C_{57}H_{87}N_7O_{15}$=1110.4

CAS — 137219-37-5.

UNII — Y76ID234HW.

NOTE. The name Aplidin has been used as a trade mark for plitidepsin.

Profile

Plitidepsin is an antineoplastic isolated from the marine tunicate *Aplidium albicans*. It is under investigation in the treatment of acute lymphoblastic leukaemia, multiple myeloma, and solid tumours.

References.

1. Muñoz-Alonso MJ, *et al.* The mechanism of action of plitidepsin. *Curr Opin Investig Drugs* 2009; 10: 536–42.
2. Eisen T, *et al.* Phase II study of weekly plitidepsin as second-line therapy for small cell lung cancer. *Lung Cancer* 2009; 64: 60–5.
3. Schöffski P, *et al.* Phase II randomized study of Plitidepsin (Aplidin), alone or in association with L-carnitine, in patients with unresectable advanced renal cell carcinoma. *Mar Drugs* 2009; 7: 57–70.
4. Eisen T, *et al.* Phase II study of biweekly plitidepsin as second-line therapy in patients with advanced malignant melanoma. *Melanoma Res* 2009; 19: 185–92.
5. Dumez H, *et al.* Phase II study of biweekly plitidepsin as second-line therapy for advanced or metastatic transitional cell carcinoma of the urothelium. *Mar Drugs* 2009; 7: 451–63.
6. Baudin E, *et al.* Phase II study of plitidepsin 3-hour infusion every 2 weeks in patients with unresectable advanced medullary thyroid carcinoma. *Am J Clin Oncol* 2010; 33: 83–8.
7. Le Tourneau C, *et al.* Reports of clinical benefit of plitidepsin (Aplidine), a new marine-derived anticancer agent, in patients with advanced medullary thyroid carcinoma. *Am J Clin Oncol* 2010; 33: 132–6.
8. Mateos MV, *et al.* Phase II clinical and pharmacokinetic study of plitidepsin 3-hour infusion every two weeks alone or with dexamethasone in relapsed and refractory multiple myeloma. *Clin Cancer Res* 2010; 16: 3260–9.

Pomalidomide *(USAN, rINN)*

CC-4047; IMiD-3; Pomalidomid; Pomalidomida; Pomalidomidum; Помалидомид.

4-Amino-2-[(3*RS*)-2,6-dioxopiperidin-3-yl]-1*H*-isoindole-1,3(2*H*)-dione.

$C_{13}H_{11}N_3O_4$=273.2

CAS — 19171-19-8.

UNII — D2UX06XLB5.

NOTE. IMiD-3 has also been used as a synonym for lenalidomide (p. 816.1).

Uses and Administration

Pomalidomide is a derivative of thalidomide (p. 867.3) that has immunomodulatory and antiangiogenic properties. It is used with dexamethasone or as monotherapy for the treatment of multiple myeloma (p. 699.2) in patients who have been treated with at least 2 other therapies including lenalidomide and bortezomib, and whose disease has progressed within 60 days of completing the last therapy. A usual oral dose of pomalidomide is 4 mg once daily taken on an empty stomach, for 21 days of a 28-day cycle. The dose may need to be modified if toxicities occur, see Administration in Subsequent Cycles, p. 848.1. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Pomalidomide is also under investigation in myelofibrosis.

References.

1. Lacy MQ, *et al.* Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). *Leukemia* 2010; 24: 1934–9.
2. Begna KH, *et al.* A phase-2 trial of low-dose pomalidomide in myelofibrosis. *Leukemia* 2011; 25: 301–4.
3. Lacy MQ, Tefferi A. Pomalidomide therapy for multiple myeloma and myelofibrosis: an update. *Leuk Lymphoma* 2011; 52: 560–6.
4. Lacy MQ, *et al.* Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood* 2011; 118: 2970–5.
5. Schey S, Ramasamy K. Pomalidomide therapy for myeloma. *Expert Opin Invest Drugs* 2011; 20: 691–700.
6. Leleu X, *et al.* Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. *Blood* 2013; 121: 1968–75.
7. Elkinson S, McCormack PL. Pomalidomide: first global approval. *Drugs* 2013; 73: 595–604.

Administration in subsequent cycles. The usual oral dose of pomalidomide may need to be modified if toxicity occurs.

If haematological toxicity occurs, the absolute neutrophil count (ANC) must be at least 500 cells/mm³ and the platelet count must be at least 50 000 cells/mm³ before a dose of pomalidomide is given. The following dose modifications are required when values fall below these concentrations.

- For ANC < 500 cells/mm³, ANC < 1000 cells/mm³ with fever ≥ 38.5 degrees, or platelets < 25 000 cells/mm³: pomalidomide should be withheld until values recover and then resumed at a dose of 3 mg once daily.
- For each subsequent fall (ANC < 500 cells/mm³ or platelets < 25 000 cells/mm³): pomalidomide should be withheld until values recover and then resumed at a daily dose 1 mg less than the previous dose. If toxicities occur at a dose of 1 mg once daily, treatment should be stopped.

If other grade 3 or 4 toxicities occur, pomalidomide should be withheld until values recover to at least grade 2 and then resumed at a daily dose 1 mg less than the previous dose. If toxicities occur at a dose of 1 mg once daily, treatment should be stopped.

Adverse Effects and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Because of its potential teratogenicity, pomalidomide use is restricted in women of child-bearing potential and similar precautions to thalidomide are required, see p. 869.2.

Pomalidomide is associated with haematological toxicity, particularly neutropenia, anaemia, and thrombocytopenia. Full blood counts should be monitored weekly for the first 8 weeks of treatment and then monthly thereafter; dose adjustments may be required, see Administration in Subsequent Cycles, above. Venous thromboembolism has occurred during pomalidomide treatment, and prophylactic measures should be considered in those at increased risk.

Neuropathy, including peripheral neuropathy, has been reported with pomalidomide. Dizziness, confusion, anxiety, insomnia, and headache have occurred.

Other common adverse effects include fatigue, pyrexia, chills, gastrointestinal disorders, anorexia, changes in body weight, muscle spasm or weakness, arthralgia, pain including bone and muscle pain, dyspnoea, cough, epistaxis, hyperhidrosis, rash, dry skin, pruritus, electrolyte disturbances, hyperglycaemia, increases in blood creatinine, and renal failure. Vertigo, increases in bilirubin and hepatic enzymes, and interstitial lung disease have also occurred.

Licensed product information recommends that pomalidomide should be avoided in patients with serum creatinine greater than 3 mg/dL, or with serum bilirubin greater than 2 mg/dL and aspartate aminotransferase or alanine aminotransferase greater than 3 times the upper limit of normal, due to a lack of data in such patients.

There have been reports of acute myeloid leukaemia in patients treated with pomalidomide.

Effects on the lungs. For reports of respiratory toxicity associated with pomalidomide, see under Thalidomide, p. 870.1.

Interactions

Pomalidomide is mainly metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4; potent inhibitors or inducers of these isoenzymes may affect exposure to pomalidomide. Tobacco smoking may reduce pomalidomide exposure due to induction of CYP1A2.

Pomalidomide is a substrate of P-glycoprotein and other drugs that inhibit or induce P-glycoprotein may affect its exposure.

Pharmacokinetics

Maximum serum concentrations of pomalidomide occur 2 to 3 hours after an oral dose. Plasma protein binding ranges from 12 to 44%. Pomalidomide is distributed into the semen. It is mainly metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2 and CYP3A4, with CYP2C19 and CYP2D6 playing a minor role. Pomalidomide is excreted via the kidneys with a plasma half-life of about 9.5 hours in healthy adults and 7.5 hours in those with multiple myeloma. About 73% of a dose was eliminated in the urine and 15% in the faeces, mainly as metabolites with a small portion as unchanged drug.

References.
1. Hoffmann M, *et al.* Absorption, metabolism and excretion of [^{14}C] pomalidomide in humans following oral administration. *Cancer Chemother Pharmacol* 2013; 71: 489–501.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Imnovid; *USA*: Pomalyst.

Ponatinib *(USAN, rINN)*

AP-24534; Ponatinibum; Понатиниб.

3-[2-(Imidazo[1,2-*b*]pyridazin-3-yl)ethynyl]-4-methyl-*N*-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]benzamide.

$C_{29}H_{27}F_3N_6O$=532.6

CAS — 943319-70-8.

UNII — 4340891KFS.

Ponatinib Hydrochloride *(USAN, rINNM)*

Hidrocloruro de ponatinib; Ponatinib, Chlorhydrate de; Ponatinibi Hydrochloridum; Понатиниба Гидрохлорид.

$C_{29}H_{27}F_3N_6O$,HCl=569.0

CAS — 1114544-31-8.

UNII — 96R6PU3D8J.

Uses and Administration

Ponatinib is a BCR-ABL tyrosine kinase inhibitor that is used for the treatment of chronic, accelerated, or blast phase chronic myeloid leukaemia, or Philadelphia chromosome-positive acute lymphoblastic leukaemia, that is resistant to, or in patients who are intolerant of, prior tyrosine kinase inhibitor therapy. An oral dose of 45 mg once daily is used and continued until disease progression is noted. Treatment may need to be modified if toxicities occur (see Administration in Subsequent Cycles, below).

If ponatinib is used with a potent cytochrome P450 isoenzyme CYP3A inhibitor, a reduced oral dose of 30 mg once daily is recommended.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.
1. Cortes JE, *et al.* Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med* 2012; 367: 2075–88.

Administration in subsequent cycles. The oral dose of ponatinib may need to be modified if toxicity occurs during treatment for chronic myeloid leukaemia, or Philadelphia chromosome-positive acute lymphoblastic leukaemia.

If myelosuppression occurs with the absolute neutrophil count (ANC) falling below 1000 cells/mm³ or platelets falling below 50 000 cells/mm³, interrupt ponatinib until the ANC recovers to at least 1500 cells/mm³ and platelets recover to at least 75 000 cells/mm³. When restarting, the dose should be adjusted as follows:

- for the first occurrence, resume ponatinib at the usual dose of 45 mg once daily
- for the second occurrence, resume ponatinib at a reduced dose of 30 mg once daily
- for the third occurrence, resume ponatinib at a further reduced dose of 15 mg once daily

Treatment modifications for other toxicities are as follows:

- if hepatotoxicity occurs with liver transaminases increased to > 3 times the upper limit of normal (ULN), interrupt ponatinib until transaminases have recovered to < 3 times the ULN
- for asymptomatic grade 1 or 2 increases in serum lipase, consider interruption or dose reduction of ponatinib
- for asymptomatic grade 3 or 4 increases in serum lipase (> 2 times the ULN) or asymptomatic grade 2 pancreatitis, interrupt ponatinib until lipase has recovered to < 1.5 times the ULN
- for symptomatic grade 3 pancreatitis, interrupt ponatinib until symptoms have completely resolved and lipase has recovered to < 1.5 times the ULN
- for grade 4 pancreatitis, stop ponatinib treatment

When restarting therapy, the dose should be adjusted as follows:

- when toxicity occurs on a dose of 45 mg once daily, resume ponatinib at a reduced dose of 30 mg once daily
- when toxicity occurs on a dose of 30 mg once daily, resume ponatinib at a further reduced dose of 15 mg once daily
- when toxicity occurs on a dose of 15 mg once daily, stop ponatinib treatment

Adverse Effects, Treatment, and Precautions

The most common adverse effects with ponatinib are gastrointestinal disorders such as constipation and nausea, hypertension, rash, dry skin, abdominal pain, fatigue, headache, arthralgia, and pyrexia. Other commonly reported effects include arterial ischaemia, heart failure, peripheral oedema, myelosuppression, infections, peripheral neuropathy, dizziness, cough, dyspnoea, myalgia, muscle spasm, pain including back pain and bone pain, mucositis, anorexia, and insomnia. Abnormalities associated with ponatinib treatment include increased liver and pancreatic enzyme values, increased bilirubin, decreased albumin, increased creatinine, increased triglycerides, and electrolyte and blood glucose abnormalities.

Severe myelosuppression has occurred in nearly half of patients treated with ponatinib. Thrombocytopenia, neutropenia, leucopenia, anaemia, and lymphopenia have been seen. Blood counts should be measured every 2 weeks for the first 3 months and then monthly or as clinically indicated, and the dose adjusted as necessary, see Administration in Subsequent Cycles, above.

Arterial thrombotic events have included cardiovascular, cerebrovascular, and peripheral thrombosis, including myocardial infarction and stroke. Most of the patients who developed arterial thrombosis had one or more cardiovascular risk factors. Ponatinib should be interrupted or stopped if such events occur. Venous thromboembolism including deep-vein thrombosis and pulmonary embolism has also occurred, and may require dose modification or treatment to be stopped. Serious bleeding events have been reported, particularly cerebral or gastrointestinal haemorrhage, and were most often seen in patients with severe thrombocytopenia; treatment should be interrupted if bleeding occurs.

Cardiovascular adverse effects include cardiac arrhythmias such as bradyarrhythmias and supraventricular tachyarrhythmias, congestive heart failure or left ventricular dysfunction, and hypertension sometimes leading to hypertensive crisis. Blood pressure should be monitored, and treatment may need to be stopped for severe heart failure. Fluid retention has been seen, particularly peripheral oedema, and pleural or pericardial effusion.

Hepatotoxicity and acute liver failure have occurred and liver function tests should be checked at baseline and at least monthly thereafter; treatment should be adjusted as necessary. Ponatinib is metabolised in the liver and use should be avoided in those with moderate to severe hepatic impairment due to the risk of increased exposure. Pancreatitis has been reported; lipase concentrations may be increased and should be monitored every 2 weeks for the first 2 months and then monthly thereafter or as needed, and treatment modified as necessary.

Hyperuricaemia has occurred, and tumour lysis syndrome has developed occasionally. Ponatinib could compromise wound healing, and gastrointestinal perforation has occurred over a month after abdominal surgery was carried out. Treatment should be stopped at least 1 week before major surgery, and reintroduced once wound healing is deemed adequate.

Interactions

In vitro studies have suggested that ponatinib is a substrate for the cytochrome P450 isoenzyme family CYP3A. Exposure to ponatinib was increased when given with the potent CYP3A4 inhibitor ketoconazole, and ponatinib dose adjustments are required when used with a potent CYP3A inhibitor; for further details, see Uses and Administration, above. Potent inducers of the CYP3A family should be avoided where possible during ponatinib treatment due to the risk of reduced efficacy.

An increase in gastric pH may reduce the bioavailability of, and exposure to, ponatinib and caution is advised with drugs that increase gastric pH such as proton pump inhibitors, histamine H_2-antagonists, or antacids.

Pharmacokinetics

Peak plasma concentrations of ponatinib are seen within 6 hours of an oral dose. Solubility is pH dependent, with higher pH resulting in lower solubility. It is more than 99% bound to plasma proteins *in vitro*, and is a weak substrate for, and an inhibitor of, P-glycoprotein and breast cancer resistance protein (BCRP or ABCG2). Ponatinib is metabolised by the cytochrome P450 isoenzymes CYP3A4 and to a lesser extent CYP3A5, CYP2C8, and CYP2D6, as well as by esterases and amidases. The elimination half-life ranged from 12 to 66 hours (mean 24 hours) once steady state was achieved. Ponatinib is excreted mainly in the faeces (nearly 90%), with a small amount in the urine (about 5%).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Iclusig; *USA*: Iclusig.

Porfimer Sodium *(BAN, USAN, rINN)*

CL-184116; Dihaematoporphyrin Ether; Éter de dihematoporfirina; Porfimeerinatrium; Porfimère Sodique; Porfimera-

trium; Porfímero sódico; Porfimerum Natricum; Порфимер Натрий.
CAS — 87806-31-3.
ATC — L01XD01.
ATC Vet — QL01XD01.
UNII — Y3834SIK5F.

Uses and Administration

Porfimer sodium is a haematoporphyrin derivative that reportedly accumulates in malignant tissue on injection. It is then activated by laser light to release oxygen radicals within malignant cells, producing cytotoxicity. Porfimer sodium is used as a photosensitiser in the photodynamic therapy of endobronchial non-small cell lung cancer (p. 710.2), oesophageal cancer (p. 705.3), and superficial bladder cancer (p. 700.2). It is also used for the treatment of dysplasia associated with Barrett's oesophagus (see Gastro-oesophageal Reflux Disease, p. 1810.2).

Porfimer sodium should be reconstituted with glucose 5% or sodium chloride 0.9% to a final concentration of 2.5 mg/mL. It is given by slow intravenous injection at a dose of 2 mg/kg. This is followed, 40 to 50 hours later, by activation using a laser tuned to a wavelength of 630 nanometres and delivered to the area of the tumour using a fibre optic guide. Residual tumour may subsequently be debrided surgically. A second laser treatment may be given 96 to 120 hours after the original injection. A maximum of 3 courses of photodynamic therapy may be used, with each injection separated by a minimum of 30 days for oesophageal and endobronchial tumours, and a minimum of 90 days for dysplasia in Barrett's oesophagus. However, in the treatment of superficial bladder cancer, only one dose of drug and light is given due to an increased risk of bladder contracture, and no surgical debridement is performed.

For further information about use in hepatic or renal impairment, see below.

Administration in hepatic impairment. US licensed product information states that hepatic impairment could prolong the elimination of porfimer, and that patients with mild to severe hepatic impairment should be warned that the precautions for photosensitivity (see below) may need to be followed for longer than 90 days. EU licensed product information recommends similar warnings for those with mild to moderate impairment; use is contra-indicated in severe hepatic impairment.

Administration in renal impairment. EU licensed product information for some porfimer products (*Photofrin, Axcan*) states that, because excretion of porfimer is mainly via the faecal route, no special precautions are necessary in patients with renal impairment. However, EU licensed product information for other porfimer products (*Photo-Barr*, Axcan) contra-indicates use in severe renal impairment, as it has not been evaluated. US licensed product information (*Photofrin, Axcan*) states that renal impairment could prolong the elimination of porfimer, and that patients with severe renal impairment should be warned that the precautions for photosensitivity (see below) may need to be followed for longer than 90 days.

Photodynamic therapy. Photodynamic therapy (PDT) probably has the greatest potential of the various forms of light-activated treatment.[1] Photosensitising drugs are given intravenously, orally, or topically, and are selectively retained by tumour cells. When exposed to the correct wavelength of light the drug produces toxic oxygen radicals that destroy cell membranes and thereby kill the tumour cells. Vascular damage and immune-mediated injury may also occur.[2-4] Tumour cells must have an adequate supply of oxygen to be sensitive to PDT,[2] and as light penetration is usually limited, early or superficial malignant lesions respond best to therapy.[1,2] Photodynamic therapy has been tried in skin, gastrointestinal, head and neck, bladder, gynaecological, pancreatic, pulmonary, and various intraperitoneal malignancies[2,3,5-12] It is also used for the treatment of Barrett's oesophagus[12-14] and for the treatment of age-related macular degeneration (p. 880.2); it has been tried for other ocular disorders.[15] There is also an interesting report of cytotoxicity against leukaemic cells *in vitro* when exposure to porfimer sodium was combined with ultrasound.[6]

The main adverse effect of photosensitisers such as porfimer is photosensitivity lasting 4 to 8 weeks; patients should be advised to avoid sunlight during this period and therapy is best delayed until the darker winter months if possible.[1] Newer photosensitisers are being developed to show increased tissue penetration and less prolonged photosensitivity.[3] The natural haem precursor 5-aminolevulinic acid (p. 740.1) has the advantage that photosensitivity lasts only a few hours.

1. Bown SG. New techniques in laser therapy. *BMJ* 1998; 316: 754–7.
2. Hsi RA, *et al.* Photodynamic therapy in the treatment of cancer: current state of the art. *Drugs* 1999; 57: 725–34.
3. Ost D, *et al.* Photodynamic therapy in lung cancer. *Oncology* 2000; 14: 379–86.
4. Brown SB, Ibbotson SH. Photodynamic therapy and cancer. *BMJ* 2009; 339: b2459.
5. Wilson JHP, *et al.* Photodynamic therapy for gastrointestinal tumors. *Scand J Gastroenterol* 1991; 26 (suppl 188): 20–5.
6. Tachibana K, *et al.* Eliminating adult T-cell leukaemia cells with ultrasound. *Lancet* 1997; 349: 325.
7. Walther MM. The role of photodynamic therapy in the treatment of recurrent superficial bladder cancer. *Urol Clin North Am* 2000; 27: 163–70.
8. Metz JM, Friedberg JS. Endobronchial photodynamic therapy for the treatment of lung cancer. *Chest Surg Clin North Am* 2001; 11: 829–39.
9. Biel MA. Photodynamic therapy in head and neck cancer. *Curr Oncol Rep* 2002; 4: 87–96.
10. Moghissi K. Role of bronchoscopic photodynamic therapy in lung cancer management. *Curr Opin Pulm Med* 2004; 10: 256–60.
11. Bown SG, *et al.* Photodynamic therapy for cancer of the pancreas. *Gut* 2002; 50: 549–57.
12. Brown SB, *et al.* The present and future role of photodynamic therapy in cancer treatment. *Lancet Oncol* 2004; 5: 497–508.
13. Wolfsen HC, *et al.* Photodynamic therapy for dysplastic Barrett esophagus and early esophageal adenocarcinoma. *Mayo Clin Proc* 2002; 77: 1176–81.
14. Kelty CJ, *et al.* Photodynamic therapy for Barrett's esophagus: a review. *Dis Esophagus* 2002; 15: 137–44.
15. Sivaprasad S, Hykin P. The role of photodynamic therapy in ophthalmology. *Br J Hosp Med* 2006; 67: 647–50.

Adverse Effects and Precautions

Photosensitivity occurs in all patients treated with porfimer sodium. This effect is likely to be prolonged, and patients should avoid sunlight or bright indoor light for at least 30 days. Some patients may remain photosensitive for longer, and may need to follow these precautions for at least 90 days. However, exposure to ambient indoor light is encouraged, as it allows gradual inactivation of any remaining drug. Other reported adverse effects include local inflammation and pain, including chest, back, or abdominal pain, respiratory insufficiency or distress (including dyspnoea), dehydration, dysphagia, constipation, nausea and vomiting, fever, tachycardia, atrial fibrillation, pleural effusion, and anaemia due to tumour bleeding. Pneumonia, bronchitis, anxiety, insomnia, cardiac failure, and peripheral or generalised oedema have also been reported. Photodynamic therapy with porfimer sodium is contra-indicated in patients with porphyria, oesophageal or gastric varices, large oesophageal ulcers, oesophageal fistulas, erosion of major blood vessels, or severe acute respiratory distress. Sufficient time should be allowed between photodynamic therapy and radiotherapy to allow inflammatory reactions from either treatment to subside.

Porphyria. Licensed product information states that the use of porfimer sodium is contra-indicated in patients with porphyria.

Interactions

Use of porfimer sodium with other drugs causing photosensitivity should be avoided as the reaction may be increased.

Pharmacokinetics

Porfimer sodium is distributed and eliminated slowly after intravenous injection, with plasma elimination half-life reported to be between 11 and 28 days. *In vitro* studies indicate that plasma protein binding is about 90%. Excretion occurs mainly via the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Photofrin; *Canad.*: Photofrin; *Cz.*: PhotoBarr; *Fr.*: Photobarr†; Photofrin; *Ger.*: Photofrin†; *Gr.*: Photofrin; *Hung.*: Photobarr; Photofrin; *Irl.*: Photobarr; Photofrin; *Israel*: Photofrin†; *Mex.*: Photofrin; *Neth.*: Photobarr†; *Pol.*: PhotoBarr; *Port.*: Photobarr; Photofrin; *UK*: Photofrin; *USA*: Photofrin.

Porfiromycin *(BAN, USAN, rINN)*

Methyl Mitomycin; NSC-56410; Porfiromicina; Porfiromycine; Porfiromycinum; U-14743; Порфиромицин.
6-Amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-1,5-dimethylazirino[2',3':3,4]pyrrolo[1,2-*a*]indole-4,7-dione carbamate ester.
$C_{16}H_{20}N_4O_5$=348.4
CAS — 801-52-5.
UNII — H1WK901OA6.

Profile

Porfiromycin is an antibiotic antineoplastic structurally related to mitomycin (p. 830.3). It is under investigation for the treatment of malignant neoplasms of the cervix, and the head and neck.

References.
1. Haffty BG, *et al.* Bioreductive alkylating agent porfiromycin in combination with radiation therapy for the management of squamous cell carcinoma of the head and neck. *Radiat Oncol Invest* 1997; 5: 235–45.
2. Haffty BG, *et al.* Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: final results of a randomized clinical trial. *Int J Radiat Oncol Biol Phys* 2005; 61: 119–28.

Pralatrexate *(USAN, rINN)*

PDX; Pralatrexato; Pralatrexatum; Пралатрексат.
(2*S*)-2-[(4-{(1*RS*)-1-[(2,4-Diaminopteridin-6-yl)methyl]but-3-ynyl}benzoyl)amino]pentanedioic acid.
$C_{23}H_{23}N_7O_5$=477.5
CAS — 146464-95-1.
ATC — L01BA05.
ATC Vet — QL01BA05.
UNII — A8Q8I19Q20.

Uses and Administration

Pralatrexate is an antineoplastic that acts as an antimetabolite of folic acid; it competitively inhibits the enzyme dihydrofolate reductase. Pralatrexate is used for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. It is given as an intravenous bolus over 3 to 5 minutes into a free-flowing infusion of sodium chloride 0.9%. The recommended dose is 30 mg/m² once weekly for 6 weeks, in 7-week cycles.

Patients are also given oral folic acid 1 to 1.25 mg daily, which should be started up to 10 days before starting pralatrexate, and continued until 30 days after the last dose. In addition, an intramuscular dose of vitamin B_{12} 1 mg, is given no more than 10 weeks before starting pralatrexate, and every 8 to 10 weeks thereafter; doses may be given on the same day as pralatrexate.

Doses of pralatrexate are modified according to toxicity (see Administration in Subsequent Cycles, below); once the dose is reduced, it should not be increased again.

Pralatrexate is also under investigation for diffuse large B-cell lymphoma, follicular lymphoma, and non-papillary transitional cell carcinoma of the urinary bladder.

References.
1. O'Connor OA, *et al.* Pralatrexate, a novel class of antifol with high affinity for the reduced folate carrier-type 1, produces marked complete and durable remissions in a diversity of chemotherapy refractory cases of T-cell lymphoma. *Br J Haematol* 2007; 139: 425–8.
2. Mould DR, *et al.* A population pharmacokinetic and pharmacodynamic evaluation of pralatrexate in patients with relapsed or refractory non-Hodgkin's or Hodgkin's lymphoma. *Clin Pharmacol Ther* 2009; 86: 190–6.
3. O'Connor OA, *et al.* Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. *J Clin Oncol* 2009; 27: 4357–64.
4. Rueda A, *et al.* Pralatrexate, a new hope for aggressive T-cell lymphomas? *Clin Transl Oncol* 2009; 11: 215–20.
5. Zain J, O'Connor O. Pralatrexate: basic understanding and clinical development. *Expert Opin Pharmacother* 2010; 11: 1705–14.

Administration in subsequent cycles. Before any dose of pralatrexate is given, the following conditions are required:
- mucositis must be grade 1 or less
- platelet count should be at least 100 000 cells/mm³ for the first dose, and 50 000 cells/mm³ for all subsequent doses
- absolute neutrophil count (ANC) should be at least 1000 cells/mm³

Doses are omitted or reduced according to toxicity, as outlined below. Once the dose is reduced, it is not increased again.

For **mucositis**, according to grade on the day of treatment, and upon recovery to grade 1 or better, respectively:
- grade 2: omit dose, restart at previous dose
- grade 2 recurrence, or grade 3: omit dose, reduce next dose to 20 mg/m²
- grade 4: stop therapy

For **haematological toxicity**, according to blood count on the day of treatment, duration, and dose upon restarting:
- platelets < 50 000 cells/mm³:
  for 1 week: omit dose, restart at previous dose
  for 2 weeks: omit dose, reduce next dose to 20 mg/m²
  for 3 weeks: stop therapy
- ANC 500 to 1000 cells/mm³ and no fever for 1 week: omit dose, restart at previous dose
- ANC 500 to 1000 cells/mm³ with fever, or ANC < 500 cells/mm³:
  for 1 week: omit dose, give colony-stimulating factor (CSF) support, and restart with previous dose (with CSF support)
  for 2 weeks, or recurrence: omit dose, give CSF support, and reduce next dose to 20 mg/m² (with CSF support)
  for 3 weeks or at second recurrence: stop therapy

For all **other** toxicities, based on grade on day of treatment, and upon recovery to grade 2 or less:

- grade 3: omit dose, restart with 20 mg/m²
- grade 4: stop therapy

Adverse Effects, Treatment, and Precautions

As for Methotrexate, p. 825.1, p. 826.3, and p. 827.1. Patients treated with pralatrexate are also given folic acid and vitamin B_{12} (see Uses and Administration, p. 849.3) to reduce treatment-related haematological toxicity and mucositis.

Interactions

As for Methotrexate, p. 827.3.

Pharmacokinetics

Pralatrexate exposure and peak plasma concentrations have been reported to increase proportionally with dose. Pralatrexate is about 67% bound to plasma proteins. The terminal elimination half-life is about 12 to 18 hours after a single intravenous dose. It is excreted in the urine and clearance decreases with decreasing creatinine clearance.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Israel*: Difolta; *USA*: Folotyn.

Prednimustine *(USAN, rINN)*

Leo-1031; NSC-134087; Prednimustiini; Prednimustin; Prednimustina; Prednimustinum; Преднимустин.

11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(4-[4-[bis(2-chloroethyl)amino]phenyl]butyrate).

$C_{35}H_{45}Cl_2NO_6$=646.6

CAS — 29069-24-7.

ATC — L01AA08.

ATC Vet — QL01AA08.

UNII — 9403SIO2S8.

Profile

Prednimustine is the prednisolone ester of chlorambucil, (p. 764.1) and has been given orally in the treatment of various malignant diseases.

Procarbazine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de procarbazina; Ibenzmethyzin Hydrochloride; NSC-77213; Procarbazina, hidrocloruro de; Procarbazine, Chlorhydrate de; Procarbazini Hydrochloridum; Ro-4-6467/1; Прокарбазина Гидрохлорид.

N-Isopropyl-α-(2-methylhydrazino)-*p*-toluamide hydrochloride.

$C_{12}H_{19}N_3O.HCl$=257.8

CAS — 671-16-9 (procarbazine); 366-70-1 (procarbazine hydrochloride).

ATC — L01XB01.

ATC Vet — QL01XB01.

UNII — XH0NPH5ZX8.

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

USP 36: (Procarbazine Hydrochloride). Store in airtight containers. Protect from light.

Uses and Administration

Procarbazine hydrochloride is a methylhydrazine derivative whose antineoplastic effect, although not fully understood, may resemble that of the alkylating agents; it appears to inhibit protein and nucleic acid synthesis and suppress mitosis. It does not show cross-resistance with other cytotoxic drugs.

Its main use is the treatment of Hodgkin's disease (p. 696.1) when it is usually given with other drugs. Procarbazine has also been used in the treatment of non-Hodgkin's lymphomas (p. 696.3) and refractory solid tumours.

Doses of procarbazine hydrochloride are calculated in terms of procarbazine; procarbazine hydrochloride 116 mg is equivalent to about 100 mg of procarbazine. Procarbazine is given orally. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* In combination regimens such as MOPP (with chlormethine, vincristine, and prednisone), procarbazine hydrochloride is given in doses equivalent to procarbazine 100 mg/m² daily for 10 to 14 days of each 4- to 6-week cycle. If used as a single agent, a dose equivalent to 50 mg of procarbazine daily, increased by 50 mg daily to 250 to 300 mg daily in divided doses has been suggested in the UK, while in the USA the recommended regimen is 2 to 4 mg/kg daily for the first week, subsequently increased to 4 to 6 mg/kg daily, doses being given to the nearest 50 mg. These doses are continued until maximum response is achieved or leucopenia, thrombocytopenia, or other signs of toxicity occur. Maintenance doses are usually 50 to 150 mg daily in the UK, given until a total dose of at least 6 g has been reached; in the USA maintenance doses of 1 to 2 mg/kg daily are given. Procarbazine treatment should be withheld if toxicity occurs, and restarted upon recovery. For doses in children, see below.

Administration in children. Procarbazine hydrochloride is used in children mainly for Hodgkin's disease when it is usually given with other drugs. It has also been used for other advanced lymphomas or solid tumours. In combination regimens such as MOPP (with chlormethine, vincristine, and prednisone), procarbazine hydrochloride is given to children in equivalent doses to adults, see above. If used as a single agent, an initial oral dose equivalent to procarbazine 50 mg/m² daily for the first week is suggested in the USA (UK licensed product information suggests a dose of 50 mg), increased to 100 mg/m² thereafter until maximum response or toxicity occurs. US licensed product information suggests the dose may be reduced to 50 mg/m² for maintenance when maximum response has been obtained. Procarbazine treatment should be withheld if toxicity occurs, and restarted upon recovery.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects associated with procarbazine are gastrointestinal disturbances such as anorexia, nausea and vomiting (although patients may soon become tolerant), and bone-marrow depression. Leucopenia and thrombocytopenia may be delayed with a nadir at about 4 weeks after a dose, and recovery usually within 6 weeks. Anaemia, haemolysis, and bleeding tendencies have been reported.

Neurotoxicity is also common, with central effects such as somnolence, depression, nervousness or confusion, headache, hallucinations, and dizziness, and peripheral neuropathies including paraesthesias and decreased reflexes. Lethargy, ataxia, and sleep disorders have also occurred, and tremors, convulsions, and coma have been reported.

Other adverse effects reported include fever and myalgia, pulmonary fibrosis or pneumonitis, haematuria, urinary frequency, skin reactions including dermatitis, pruritus, and hyperpigmentation, tachycardia, orthostatic hypotension, ocular defects, infertility, and hepatic impairment.

Procarbazine is a carcinogen, mutagen, and teratogen.

Procarbazine should be used with caution in patients with hepatic or renal impairment, and is contra-indicated if impairment is severe. The haematological status of the patient should be determined at least every 3 or 4 days and hepatic and renal function determined weekly. Care is also advisable in patients with phaeochromocytoma, epilepsy, or cardiovascular or cerebrovascular disease. Treatment should be interrupted if allergic skin reactions occur.

Handling and disposal. *Urine* produced for up to 48 hours after a dose of procarbazine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Procarbazine is a weak MAOI and the possibility of reactions with other drugs and food, although very rare, must be borne in mind—for details of MAOI reactions see p. 444.3 and p. 445.1. Procarbazine may enhance the sedative effects of other CNS depressants. A disulfiram-like reaction has been reported with alcohol and the effects of antihypertensive agents may be enhanced.

Antiepileptics. Use with enzyme-inducing antiepileptics is associated with an increased risk of hypersensitivity reactions to procarbazine, possibly through a reactive intermediate generated by induction of the cytochrome P450 isoenzyme CYP3A subfamily.[1] Non-enzyme-inducing antiepileptics might be more appropriate in patients with brain tumours in whom procarbazine therapy is anticipated.

1. Lehmann DF, *et al.* Anticonvulsant usage is associated with an increased risk of procarbazine hypersensitivity reactions in patients with brain tumors. *Clin Pharmacol Ther* 1997; 62: 225–9.

Pharmacokinetics

Procarbazine is readily absorbed from the gastrointestinal tract. It crosses the blood-brain barrier and diffuses into the CSF. A plasma half-life of about 10 minutes has been reported. Procarbazine is rapidly metabolised (mainly in liver and kidneys) and only about 5% is excreted unchanged in the urine. The remainder is oxidised to *N*-isopropylterephthalamic acid and excreted in the urine, up to about 70% of a dose being excreted in 24 hours. Some of the drug is excreted as carbon dioxide and methane via the lungs. During oxidative breakdown in the body hydrogen peroxide is formed which may account for some of the drug's actions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Natulan†; *Canad.* Matulane; *Fr.*: Natulan; *Ger.*: Natulan; *Gr.*: Natulan; *Ital.* Natulan; *Neth.*: Natulan; *Rus.*: Natulan (Натулан); *S.Afr.* Natulan; *Singapore*: Natulan; *Spain*: Natulan†; *Switz.*: Natulan *USA*: Matulane.

Pharmacopoeial Preparations

USP 36: Procarbazine Hydrochloride Capsules.

Raltitrexed *(BAN, USAN, rINN)*

D-1694; ICI-D1694; Raltitreksed; Raltitreksedi; Raltitrexedum; ZD-1694; Ралтитрексед.

N-{5-[3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl(methyl)amino]-2-thenoyl}-L-glutamic acid.

$C_{21}H_{22}N_4O_6S$=458.5

CAS — 112887-68-0.

ATC — L01BA03.

ATC Vet — QL01BA03.

UNII — FCB9EGG971.

Uses and Administration

Raltitrexed is a folate analogue that is a potent and specific inhibitor of the enzyme thymidylate synthase, which is involved in the synthesis of DNA. It has been used in the treatment of advanced colorectal cancer (p. 706.3) and has also been tried in breast cancer (p. 702.1) and other solid neoplasms.

The recommended initial dose of raltitrexed in patients with normal renal function is 3 mg/m² given by intravenous infusion over 15 minutes. Subsequent doses, which should be reduced by up to 50% depending on the severity of initial toxicity, may be given at intervals of 3 weeks provided toxicity has resolved.

A full blood count should be performed before each dose and treatment withheld if the white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p. 730.3). Hepatic and renal function should also be tested. It is essential that doses be adjusted in renal impairment (see below).

References.

1. Gunasekara NS, Faulds D. Raltitrexed: a review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer. *Drugs* 1998; 55: 423–35.
2. Cunningham D, *et al.* Efficacy, tolerability and management of raltitrexed (Tomudex) monotherapy in patients with advanced colorectal cancer: a review of phase II/III trials. *Eur J Cancer* 2002; 38: 478–86.
3. Scheithauer W, *et al.* Randomized multicenter phase II trial of oxaliplatin plus irinotecan versus raltitrexed as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2002; 20: 165–72.
4. Feliu J, *et al.* Raltitrexed in the treatment of elderly patients with advanced colorectal cancer: an active and low toxicity regimen. *Eur J Cancer* 2002; 38: 1204–11.
5. Comella P, *et al.* Oxaliplatin plus raltitrexed and leucovorin-modulated 5-fluorouracil i.v. bolus: a salvage regimen for colorectal cancer patients. *Br J Cancer* 2002; 86: 1871–5.
6. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; 359: 1555–63.
7. van Meerbeeck JP, *et al.* Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; 23: 6881–9.
8. Ducreux M, *et al.* FFCD 9601 Collaborative Group. Randomised trial comparing three different schedules of infusional 5FU and raltitrexed alone as first-line therapy in metastatic colorectal cancer. Final results of the Fédération Francophone de Cancérologie Digestive (FFCD) 9601 trial. *Oncology* 2006; 70: 222–30.
9. Wilson KS, *et al.* Adjuvant therapy with raltitrexed in patients with colorectal cancer intolerant of 5-fluorouracil: British Columbia Cancer Agency experience. *Cancer Invest* 2007; 25: 711–14.
10. Hind D, *et al.* The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2008; 12: 1–182.
11. Popov I, *et al.* Raltitrexed (Tomudex) versus standard leucovorin-modulated bolus 5-fluorouracil: results from the randomised phase III Pan-European Trial in Adjuvant Colon Cancer 01 (PETACC-1). *Eur J Cancer* 2008; 44: 2204–11.
12. Wilson KS, Malfair Taylor SC. Raltitrexed: optimism and reality. *Expert Opin Drug Metab Toxicol* 2009; 5: 1447–54.

Administration in renal impairment. It is essential that doses of raltitrexed be adjusted in renal impairment (creatinine clearance less than 65 mL/minute) as fatalities have been associated with the failure to make such adjustments (see Toxicity, under Adverse Effects, p. 851.1). The dosage

interval should be increased from 3 to 4 weeks and the dose adjusted on the basis of creatinine clearance (CC) as follows:

- CC of 55 to 65 mL/minute, 2.25 mg/m²
- CC of 25 to 54 mL/minute, 1.5 mg/m²(in some countries, adjustment of the dose to a percentage of the full dose equivalent to the value of the CC in mL/minute is suggested in this group, e.g. reduction to 30% in those with a CC of 30 mL/minute, or 40% if CC is 40 mL/minute)
- CC less than 25 mL/minute, treatment contra-indicated

Adverse Effects, Treatment, and Precautions

Raltitrexed produces bone marrow depression, usually mild to moderate, with leucopenia, anaemia, and, less frequently, thrombocytopenia. The nadir of the white cell count usually occurs 7 to 14 days after a dose, with recovery by the third week. Full blood counts should be monitored before each dose, and treatment may be withheld and restarted at reduced doses if needed (see Uses and Administration, p. 850.3). Gastrointestinal toxicity is also common, with nausea and vomiting, diarrhoea, and anorexia; mucositis may occur. Gastrointestinal bleeding has been reported rarely. Reversible increases in liver enzyme values have occurred. Other adverse effects include weakness and malaise, fever, pain, headache, rashes, desquamation, arthralgia, muscle cramps, weight loss, dehydration, peripheral oedema, alopecia, increased sweating, taste disturbance, and conjunctivitis. Cellulitis and sepsis have been reported. The use of folinic acid 25 mg/m² every 6 hours intravenously has been suggested in licensed product information for patients who develop very severe toxicity.

Raltitrexed should be given with care to patients with hepatic impairment and should be avoided if impairment is severe. It should also be avoided in severe renal impairment and be given in reduced doses in moderate impairment, based on creatinine clearance (see Administration in Renal Impairment, p. 850.3). Care is also advisable in debilitated or elderly patients or in patients who have had radiotherapy.

Raltitrexed is teratogenic; pregnancy should be avoided while either partner is receiving the drug and for at least 6 months after treatment. It may impair male fertility.

Toxicity. A large multicentre study comparing raltitrexed with fluorouracil plus folinic acid was suspended in 1999 due to an excess of deaths in the raltitrexed arm.[1] This decision has led to some controversy,[1-3] as in 11 of the 17 deaths in patients taking raltitrexed there was evidence that the dose had not been correctly adjusted to take account of renal function. In addition, and further confusing the issue, the incidence of reported serious adverse effects was lower in raltitrexed-treated patients than in controls. A further study[4] reported an increased rate of raltitrexed-related deaths compared with fluorouracil-based regimens. Almost all of the 18 deaths were caused by gastrointestinal and haematological toxicity, and in 3 of these the dose of raltitrexed had not been adjusted for toxicity.

1. Anonymous. Drug-company decision to end cancer trial. *Lancet* 1999; **354:** 1045.
2. Ford HER, Cunningham D. Safety of raltitrexed. *Lancet* 1999; **354:** 1824–5.
3. Kerr D. Safety of raltitrexed. *Lancet* 1999; **354:** 1825.
4. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.

Interactions

Raltitrexed should not be given with folic or folinic acid, which may impair its cytotoxic action. (For the deliberate use of folinic acid to counteract the effects of raltitrexed in patients with severe toxicity, see above.)

Pharmacokinetics

After intravenous doses raltitrexed has triphasic pharmacokinetics, with an initial rapid decline from peak plasma concentrations followed by a slow terminal elimination phase. Raltitrexed is actively transported into cells and metabolised to active polyglutamate forms. The remainder of a dose is excreted unchanged, about 50% of a dose appearing in the urine, and about 15% in the faeces. The terminal elimination half-life is about 8 days. Clearance is markedly reduced in renal impairment.

References.

1. Clarke SJ, *et al.* Clinical and preclinical pharmacokinetics of raltitrexed. *Clin Pharmacokinet* 2000; **39:** 429–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tomudex; *Austral.*: Tomudex; *Austria*: Tomudex; *Belg.*: Tomudex; *Braz.*: Tomudex; *Canad.*: Tomudex; *Cz.*: Tomudex; *Fr.*: Tomudex; *Hung.*: Tomudex; *Irl.*: Tomudex; *Ital.*: Tomudex; *Mex.*: Tomudex; *Norw.*: Tomudex; *Philipp.*: Tomudex†; *Port.*: Tomudex; *Rus.*: Tomudex (Томудекс); *Singapore*: Tomudex; *Spain*: Tomudex; *Switz.*: Tomudex; *Turk.*: Tomudex; *UK*: Tomudex.

Ramucirumab *(USAN, rINN)*

IMC-1121B; Ramucirumabum; Рамуцирумаб.
CAS — 947687-13-0.
UNII — D99YVK4L0X.

Profile

Ramucirumab is a human monoclonal antibody that targets the vascular endothelial growth factor receptor-2 (VEGFR-2). It is under investigation for the treatment of various solid tumours, including those of the breast, gastrointestinal tract, and lung.

References.

1. Krupitskaya Y, Wakelee HA. Ramucirumab, a fully human mAb to the transmembrane signaling tyrosine kinase VEGFR-2 for the potential treatment of cancer. *Curr Opin Investig Drugs* 2009; **10:** 597–605.
2. Spratlin JL, *et al.* Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G_1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol* 2010; **28:** 780–7.
3. Spratlin J. Ramucirumab (IMC-1121B): monoclonal antibody inhibition of vascular endothelial growth factor receptor-2. *Curr Oncol Rep* 2011; **13:** 97–102.

Ranimustine *(rINN)*

MCNU; NSC-0270516; Ranimustina; Ranimustinum; Ranomustine; Ранимустин.
Methyl 6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-α-D-glucopyranoside.
$C_{10}H_{18}ClN_3O_7$=327.7
CAS — 58994-96-0.
ATC — L01AD07.
ATC Vet — QL01AD07.
UNII — RYH2T97J77.

Profile

Ranimustine is a nitrosourea derivative with general properties similar to those of carmustine (p. 761.2). It is used intravenously in the treatment of malignant neoplasms in usual doses of 50 to 90 mg/m² every 6 to 8 weeks according to haematological response.

References.

1. Wada M, *et al.* Induction therapy consisting of alternating cycles of ranimustine, vincristine, melphalan, dexamethasone and interferon alpha (ROAD-IN) and a randomized comparison of interferon alpha maintenance in multiple myeloma: a co-operative study in Japan. *Br J Haematol* 2000; **109:** 805–14.
2. Hatano N, *et al.* Efficacy of post operative adjuvant therapy with human interferon beta, MCNU and radiation (IMR) for malignant glioma: comparison among three protocols. *Acta Neurochir (Wien)* 2000; **142:** 633–8.
3. Wakabayashi T, *et al.* Initial and maintenance combination treatment with interferon-beta, MCNU (ranimustine), and radiotherapy for patients with previously untreated malignant glioma. *J Neurooncol* 2000; **49:** 57–62.
4. Mizuno H, *et al.* Superior efficacy of MMCP regimen compared with VMCP and MMPP regimens in the treatment of multiple myeloma. *Intern Med* 2002; **41:** 290–4.
5. Takenaka T, *et al.* Phase III study of ranimustine, cyclophosphamide, vincristine, melphalan, and prednisolone (MCNU-COP/MP) versus modified COP/MP in multiple myeloma: a Japan clinical oncology group study, JCOG 9301. *Int J Hematol* 2004; **79:** 165–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Cymerin.

Ranpirnase *(USAN, rINN)*

P-30 Protein; Ranpirnasa; Ranpirnasum; Раппирназа.
CAS — 196488-72-9.

NOTE. Ranpirnase has been incorrectly stated to contain ergotamine. The name Onconase has been used as a trade mark for ranpirnase.

Profile

Ranpirnase is a ribonuclease reported to have antineoplastic properties. It is under investigation in the treatment of malignant mesothelioma. Ranpirnase has also been investigated in the management of solid tumours. It is also reported to have activity *in vitro* against HIV.

Regorafenib *(USAN, rINN)*

Bay-73-4506; Regorafenib; Regorafenibum; Регорафениб.
4-[4-[[[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide.
$C_{21}H_{15}ClF_4N_4O_3$=482.8
CAS — 755037-03-7 (anhydrous regorafenib); 1019206-88-2 (regorafenib hydrate).
ATC — L01XE21.
ATC Vet — QL01XE21.
UNII — 24T2A1DOYB.

Profile

Regorafenib is an oral inhibitor of several receptor tyrosine kinases. It is used for the treatment of patients with metastatic colorectal cancer (p. 706.3) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, a vascular endothelial growth factor inhibitor, and an epidermal growth factor receptor inhibitor (if *KRAS* wild-type). Regorafenib is also used in those with locally-advanced unresectable or metastatic gastrointestinal stromal tumours (see Soft Tissue Sarcoma, p. 718.2) that have been previously treated with imatinib and sunitinib. The recommended dose is 160 mg orally once daily for the first 21 days of each 28-day cycle. Treatment is continued until patients no longer benefit, or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Regorafenib should be taken at the same time each day with a low-fat meal. If a daily dose is missed, the next day's dose should not be doubled. Doses may need to be adjusted or treatment withheld or permanently stopped for severe toxicity.

It is also under investigation for the treatment of various other malignant neoplasms.

Hepatotoxicity has occurred and may be severe; deaths have been reported. Liver function should be monitored before, and every 2 weeks during the first 2 months of treatment; thereafter, monitoring should be monthly. Regorafenib is metabolised by the cytochrome P450 isoenzyme CYP3A4 and by the uridine diphosphate glucuronosyltransferase enzyme UGT1A9 and concomitant use of strong CYP3A4 inhibitors and inducers should be avoided.

References.

1. Wilhelm SM, *et al.* Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011; **129:** 245–55.
2. Grothey A. Regorafenib in metastatic colorectal cancer. *Clin Adv Hematol Oncol* 2012; **10:** 324–5.
3. Grothey A, *et al.* CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381:** 303–12.
4. Demetri GD, *et al.* GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381:** 295–302.
5. Festino L, *et al.* Critical appraisal of the use of regorafenib in the management of colorectal cancer. *Cancer Manag Res* 2013; **5:** 49–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Stivarga; *Switz.*: Stivarga; *UK*: Stivarga; *USA*: Stivarga.

Ridaforolimus *(USAN, rINN)*

AP-23573; Deforolimus; MK-8669; Ridaforolimusum; Ридафоролимус.
(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*)-12-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-[(Dimethylphosphinoyl)oxy]-3-methoxycyclohexyl]-1-methylethyl}-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone.
$C_{53}H_{84}NO_{14}P$=990.2
CAS — 572924-54-0.
ATC — L01XE19.
ATC Vet — QL01XE19.
UNII — 48Z35KB15K.

NOTE. The name Jenzyl has been used as a trade mark for ridaforolimus.

Profile

Ridaforolimus is an analogue of sirolimus (p. 1970.2). It inhibits the 'mammalian target of rapamycin' (mTOR), interfering with the cell cycle, and is under investigation for the treatment of malignancies such as breast, endometrial, prostate, and lung cancer.

References.

1. Mita MM, *et al.* Phase I trial of the novel mammalian target of rapamycin inhibitor deforolimus (AP23573; MK-8669) administered intravenously daily for 5 days every 2 weeks to patients with advanced malignancies. *J Clin Oncol* 2008; **26:** 361–7.
2. Rizzieri DA, *et al.* A phase 2 clinical trial of deforolimus (AP23573, MK-8669), a novel mammalian target of rapamycin inhibitor, in patients with relapsed or refractory hematologic malignancies. *Clin Cancer Res* 2008; **14:** 2756–62.

3. Hartford CM, *et al.* A phase I trial to determine the safety, tolerability, and maximum tolerated dose of deforolimus in patients with advanced malignancies. *Clin Cancer Res* 2009; **15**: 1428–34.
4. Mahalingam D, *et al.* Targeting the mTOR pathway using deforolimus in cancer therapy. *Future Oncol* 2009; **5**: 291–303.

Rituximab *(BAN, USAN, rINN)*

IDEC-102; IDEC-C2B8; R-105; Rituksimab; Rituksimabi; Rituximabum; Ритуксимаб.

Immunoglobulin G1 (human-mouse monoclonal IDEC-C2B8 γ1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer.

CAS — 174722-31-7.
ATC — L01XC02.
ATC Vet — QL01XC02.
UNII — 4F4X42SYQ6.

Uses and Administration

Rituximab is a chimeric monoclonal antibody that binds specifically to the CD20 antigen. Rituximab is used in the treatment of non-Hodgkin's lymphomas (p. 696.3), as monotherapy in relapsed or refractory low-grade or follicular lymphoma, or in first-line regimens for follicular lymphoma with combination chemotherapy, such as CVP (cyclophosphamide, vincristine, and prednisolone). Rituximab monotherapy may also be used in patients with low-grade stable disease after first-line treatment with CVP chemotherapy. It is also indicated for maintenance therapy in patients with follicular lymphoma who respond to induction chemotherapy that may or may not have contained rituximab. Rituximab is also used with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) or other anthracycline-based regimens for CD20-positive diffuse large B-cell non-Hodgkin's lymphoma. Rituximab also forms part of the combination regimen employing ibritumomab tiuxetan (p. 804.3). Rituximab is also used with combination chemotherapy for chronic lymphocytic leukaemia (p. 693.3). Rituximab with methotrexate is used in adults with severe active rheumatoid arthritis (p. 853.3) who have had an inadequate response to, or are intolerant of, other disease-modifying antirheumatic drugs (DMARDs), including at least one TNF inhibitor; in the USA, it may also be used in moderate disease. Rituximab plus corticosteroids is used in adults with Wegener's granulomatosis (p. 1615.2) and microscopic polyangiitis (p. 1610.2).

Rituximab is licensed for use by intravenous infusion over several hours, diluted in sodium chloride 0.9% or glucose 5% to a final concentration of between 1 and 4 mg/mL. The first infusion is normally begun at a rate of 50 mg/hour; this may be increased in increments of 50 mg/hour every 30 minutes to a maximum of 400 mg/hour, if well tolerated. Subsequent doses may be begun at a rate of 100 mg/hour, and increased in increments of 100 mg/hour every 30 minutes to a maximum of 400 mg/hour.

In the UK for the *treatment* of refractory or relapsed follicular **lymphoma**, rituximab is given as a single agent in a usual dose of 375 mg/m² once weekly for 4 doses; in the USA 4 or 8 doses may be given. Patients in either country may be re-treated after relapse for a further 4 doses. When given with combination chemotherapy for previously untreated follicular lymphoma, or for diffuse large B-cell lymphoma (with CHOP), rituximab 375 mg/m² is given on day 1 of the chemotherapy cycle, after the corticosteroid component of the regimen, for up to a total of 8 cycles. In patients previously treated with 6 to 8 cycles of CVP chemotherapy for low-grade lymphoma and who have not progressed, rituximab 375 mg/m² may be given once weekly for 4 doses, repeated every 6 months, for up to 16 doses.

In the regimen with ibritumomab tiuxetan, rituximab is usually given at a dose of 250 mg/m², within 4 hours before the ibritumomab infusions.

For *maintenance* treatment in those with follicular lymphoma who have responded to induction chemotherapy, rituximab is given as monotherapy. In previously untreated patients rituximab 375 mg/m² is started 2 months after the last dose of induction chemotherapy and given once every 2 months. In the UK this is continued until disease progression or for a maximum of 2 years, whereas in the USA, 12 doses of rituximab are given for maintenance. In the UK rituximab maintenance is also used in those with refractory or relapsed disease that responds to subsequent induction treatment with a combination regimen; 375 mg/m² is started 3 months after the last dose of induction chemotherapy and given once every 3 months. Maintenance treatment is continued until disease progression or for a maximum of 2 years.

In the treatment of **chronic lymphocytic leukaemia**, the recommended dose of rituximab is 375 mg/m², given on the day before chemotherapy in cycle 1, followed by 500 mg/m² given on day 1 of each subsequent cycle, for up to 6 cycles in total; chemotherapy is given after the rituximab infusion. Prophylactic hydration and allopurinol or rasburicase is recommended, starting 48 hours before rituximab, to reduce the risk of tumour lysis syndrome; in the UK, those with high lymphocyte counts are given intravenous corticosteroids before rituximab to reduce the incidence and severity of infusion reactions.

In the treatment of **rheumatoid arthritis**, rituximab is given in a dose of 1 g, for 2 doses; the infusions are separated by 2 weeks. It is given with methotrexate, and intravenous corticosteroids are recommended before each infusion to reduce the incidence and severity of infusion reactions. Licensed product information states that subsequent courses should be given every 24 weeks or based on clinical evaluation, but no sooner than every 16 weeks; however, guidance issued by NICE in the UK recommends that rituximab should be given no more often than every 6 months.

For the treatment of **Wegener's granulomatosis** and **microscopic polyangiitis**, rituximab is given in a dose of 375 mg/m² once weekly for 4 doses; corticosteroids are also given to treat severe vasculitic symptoms, preferably beginning within 14 days before rituximab is started, and continuing during and after rituximab therapy.

General reviews.

1. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141**: 149–69.
2. McDonald V, Leandro M. Rituximab in non-haematological disorders of adults and its mode of action. *Br J Haematol* 2009; **146**: 233–46.

Administration. *RATE.* Licensed product information states that rituximab infusions should be given at a specific rate (see Uses and Administration, above). In an effort to reduce infusion times, faster rates have been investigated. One study gave the first infusion of rituximab in cycle 1 as in the licensed product information, but subsequent infusions were given over 90 minutes, with 20% of the dose given in the first 30 minutes, and the remaining 80% over 60 minutes; the total dose was delivered in 250 mL. Rapid infusion was well tolerated with no serious infusion reactions; 10 out of 150 patients who had an adverse reaction with the first cycle (given at the standard licensed rate) tolerated subsequent rapid infusion without event, and 8 patients were not premedicated with corticosteroids.[1] Another study also reported that rituximab infusions given over 90 minutes, with or without corticosteroids, were well tolerated and safe.[2] In another study, 40 patients were given rituximab; the first infusion was given as licensed and averaged 5 hours. All subsequent infusions were given over 1 hour. It was reported that even those patients who had shown some hypersensitivity during the first infusion were able to tolerate the rapid infusion without problems.[3] A survey found that the majority of chemotherapy units in the UK were infusing second and subsequent rituximab infusions over 90 minutes if patients had no significant reactions to the initial rituximab infusion. In this study 54 patients were given an initial infusion over 90 minutes and, if no serious reactions were noted, were given subsequent infusions over 60 minutes; the 1-hour infusion was well tolerated in all patients.[4]

1. Sehn LH, *et al.* Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood* 2007; **109**: 4171–3.
2. Salar A, *et al.* Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. *Eur J Haematol* 2006; **77**: 338–40.
3. Provencio M, *et al.* Rapid-infusion rituximab in lymphoma treatment. *Ann Oncol* 2006; **17**: 1027–8.
4. Tuthill M, *et al.* Rapid infusion of rituximab over 60 min. *Eur J Haematol* 2009; **82**: 322–5.

ROUTE. Rituximab has been used *intralesionally* in the treatment of cutaneous B-cell lymphoma. There are reports of benefit, with long-term remission in some patients,[1] but rapid recurrence in others.[2] In a study of 8 patients, intralesional rituximab was given to 6 patients, in doses of 10 to 30 mg per lesion, 3 times weekly; if clinical remission was incomplete, another cycle of 3 injections was given 1 month later. Two patients were treated intravenously with weekly infusions for 4 weeks. Complete remission was seen in all 8 patients. No relapse was seen in those given intravenous therapy, but recurrences were seen in 4 of the 6 patients treated intralesionally. Moderate pain was reported during intralesional injection.[3]

Rituximab has also been used *intrapleurally* for the treatment of malignant pleural effusions in a patient with non-Hodgkin's lymphoma, in whom effusions continued to increase despite systemic chemotherapy and chest drainage. An initial test dose of rituximab 50 mg in 50 mL of sterile saline was given as a bolus into the right pleural cavity on day 1. This was followed by 200 mg in 100 mL on day 2 into the left cavity, and 400 mg in 100 mL on day 3 into the right cavity; both doses were given over 5 minutes. The therapy was well tolerated, and the effusions resolved within 2 weeks. The patient received 4 courses of intravenous rituximab consolidation therapy during a follow-up of 6 months; the effusions did not recur.[4]

Massive ascites developed in a patient with stage IV mantle cell lymphoma that was refractory to conventional chemotherapy (including intravenous rituximab added to the CHOP regimen). A palliative experimental treatment with *intraperitoneal* rituximab was given in a dose of 600 mg in 500 mL of sodium chloride 0.9%, and instilled over 4 hours. This was applied weekly for 11 courses, each time after drainage of ascites. No systemic adverse effects were noted, and the general status of the patient improved significantly; ascites resolved completely and partial remission of intra-abdominal lymph nodes and splenomegaly was noted. The patient remained asymptomatic for more than 6 months.[5]

Patients with CNS lymphoma have been treated with *intraventricular* or *intrathecal* doses of rituximab. Dose ranged from 10 to 40 mg in volumes of 1 to 4 mL, and an equivalent volume of CSF was removed before intraventricular use. Rituximab therapy was reported to be effective in those with leptomeningeal involvement, but solid parenchymal tumours progressed or showed only minor response.[6] A further study of intrathecal rituximab in patients with acute lymphoblastic leukaemia and CNS disease reported complete remission in 5 patients, with no clinical evidence of neurotoxicity after 2 years of follow-up. Rituximab 10 mg was diluted in 6 mL of saline and given intrathecally every week for 4 consecutive weeks.[7]

1. Paul T, *et al.* Intralesional rituximab for cutaneous B-cell lymphoma. *Br J Dermatol* 2001; **144**: 1239–43.
2. Roguedas AM, *et al.* Intralesional therapy with anti-CD20 monoclonal antibody rituximab: local and systemic efficacy in primary cutaneous B-cell lymphoma. *Br J Dermatol* 2005; **152**: 541–4.
3. Kerl K, *et al.* Intralesional and intravenous treatment of cutaneous B-cell lymphomas with the monoclonal anti-CD20 antibody rituximab: report and follow-up of eight cases. *Br J Dermatol* 2006; **155**: 1197–1200.
4. Schmidt MH, *et al.* Intrapleural instillation of rituximab for the treatment of malignant pleural effusions in NHL. *Haematologica* 2004; **89**: e133–e134.
5. Crysandt M, *et al.* Intraperitoneal application of rituximab in refractory mantle cell lymphoma with massive ascites resulting in local and systemic response. *Eur J Haematol* 2007; **79**: 546–9.
6. Schulz H, *et al.* Intraventricular treatment of relapsed central nervous system lymphoma with the anti-CD20 antibody rituximab. *Haematologica* 2004; **89**: 753–4.
7. Jaime-Pérez JC, *et al.* Effectiveness of intrathecal rituximab in patients with acute lymphoblastic leukaemia relapsed to the CNS and resistant to conventional therapy. *Br J Haematol* 2009; **144**: 794–5.

Administration in children. Although not licensed in the UK or the USA for use in children, there are reports of benefit in children with various diseases, such as autoimmune haemolytic anaemia, immune thrombocytopenia (see also below and p. 853.1, respectively), and post-transplantation lymphoproliferative disease,[1] as well as rheumatoid arthritis, and SLE.[2] Standard doses of 375 mg/m² weekly have usually been given, in most cases for a median course of 4 doses.

1. Giulino LB, *et al.* Treatment with rituximab in benign and malignant hematologic disorders in children. *J Pediatr* 2007; **150**: 338–44.
2. El-Hallak M, *et al.* Clinical effects and safety of rituximab for treatment of refractory pediatric autoimmune diseases. *J Pediatr* 2007; **150**: 376–82.

Blood disorders, non-malignant. *HAEMOLYTIC ANAEMIA.* Rituximab has been used in the treatment of both adult and children with severe refractory auto-immune haemolytic anaemia (p. 1122.2) of various causes,[1] including warm,[2-4] cold,[5-7] and mixed[8,9] disease.

1. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141**: 149–69.
2. Quartier P, *et al.* Treatment of childhood autoimmune haemolytic anaemia with rituximab. *Lancet* 2001; **358**: 1511–13.
3. Gottardo NG, *et al.* Successful induction and maintenance of long-term remission in a child with chronic relapsing autoimmune hemolytic anemia using rituximab. *Pediatr Hematol Oncol* 2003; **20**: 557–61.
4. Svahn J, *et al.* Rituximab-based immunosuppression for autoimmune haemolytic anaemia in infants. *Br J Haematol* 2009; **145**: 96–100.
5. Sparling TG, *et al.* Remission of cold hemagglutinin disease induced by rituximab therapy. *Can Med Assoc J* 2001; **164**: 1405.
6. Engelhardt M, *et al.* Severe cold hemagglutinin disease (CHD) successfully treated with rituximab. *Blood* 2002; **100**: 1922–3.
7. Berentsen S, *et al.* Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. *Blood* 2004; **103**: 2925–8.
8. Morselli M, *et al.* Mixed warm and cold autoimmune hemolytic anemia: complete recovery after 2 courses of rituximab treatment. *Blood* 2002; **99**: 3478–9.
9. Webster D, *et al.* Prompt response to rituximab of severe hemolytic anemia with both cold and warm autoantibodies. *Am J Hematol* 2004; **75**: 258–9.

HAEMORRHAGIC DISORDERS. Although data are limited, reports suggest that rituximab may be an effective alternative for the treatment of acquired haemophilia (p. 1126.3) after established therapies have failed.[1,2] Durable responses have been reported after rituximab was used first-line or as salvage therapy;[3] the usual intravenous dose used was 375 mg/m² once weekly for 4 weeks. Patients with high autoantibody titres may only achieve a partial response, or be slow to respond, but increasing the number of doses of rituximab or using it with cyclophosphamide and/or corticosteroids may improve response. Rituximab may be an effective alternative for those patients unable to have cytotoxic therapy.

An analysis[4] of the use of rituximab in 49 patients with congenital haemophilia (haemophilia A or B) concluded

that about half of haemophiliacs with inhibitors resistant to previous immune tolerance regimens could be durably rescued with rituximab, and that the highest responses were seen in adult haemophiliacs with mild or moderate disease who were given rituximab as part of a protocol that included factor VIII concentrates or other immunosuppressive drugs.

1. Maillard H, *et al.* Rituximab in postpartum-related acquired hemophilia. *Am J Med* 2006; **119:** 86–8.
2. Stachnik JM. Rituximab in the treatment of acquired hemophilia. *Ann Pharmacother* 2006; **40:** 1151–7.
3. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141:** 149–69.
4. Franchini M, *et al.* Immune tolerance with rituximab in congenital haemophilia with inhibitors: a systematic literature review based on individual patients' analysis. *Haemophilia* 2008; **14:** 903–12.

IMMUNE THROMBOCYTOPENIA. Rituximab has been reported[1-3] to be effective in patients, including children and infants, with immune thrombocytopenia (p. 1606.1) refractory to standard treatments. Some consider it to be a possible alternative treatment, with good response rates and durable responses obtained in both adults and children.[4] Two patterns of response have been seen: within 4 weeks, or until several weeks or even months after the start of rituximab, suggesting additional mechanisms of action besides depletion of autoantibodies. While most studies used rituximab in a usual intravenous dose of 375 mg/m^2 once weekly for 4 weeks, lower doses (including a single dose regimen for children) have been used. Re-treatment of patients who relapse after an initial response to rituximab is also an option, and rituximab has been used alone or with other drugs.[4] However, a review[5] cautioned against the indiscriminate use of rituximab in this patient population, given the lack of controlled data.

1. Zaja F, *et al.* The B-cell compartment as the selective target for the treatment of immune thrombocytopenias. *Haematologica* 2003; **88:** 538–46.
2. Bengtson KL, *et al.* Successful use of anti-CD20 (rituximab) in severe, life-threatening childhood immune thrombocytopenic purpura. *J Pediatr* 2003; **143:** 670–3.
3. Wang J, *et al.* Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. *J Pediatr* 2005; **146:** 217–21.
4. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141:** 149–69.
5. Arnold DM, *et al.* Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med* 2007; **146:** 25–33.

THROMBOTIC MICROANGIOPATHIES. Rituximab has been reported[1-3] to be of benefit in relapsed or refractory thrombotic thrombocytopenic purpura (see under Plasma, p. 1159.1). Time to response has ranged from less than 1 week to about 13 weeks;[4] durable remissions have been reported.[5] Most patients are reported to have received the standard intravenous dose of rituximab 375 mg/m^2 once weekly for 4 weeks; however, some patients required prolonged therapy, whereas others responded with only 1 or 2 doses.[4]

1. Zheng X, *et al.* Remission of chronic thrombotic thrombocytopenic purpura after treatment with cyclophosphamide and rituximab. *Ann Intern Med* 2003; **138:** 105–8.
2. Reddy PS, *et al.* Rituximab in the treatment of relapsed thrombotic thrombocytopenic purpura. *Ann Hematol* 2005; **84:** 232–5.
3. Kosugi S, *et al.* Rituximab provided long-term remission in a patient with refractory relapsing thrombotic thrombocytopenic purpura. *Int J Hematol* 2005; **81:** 433–6.
4. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. *Br J Haematol* 2008; **141:** 149–69.
5. Ling HT, *et al.* Sustained response with rituximab in patients with thrombotic thrombocytopenic purpura: a report of 13 cases and review of the literature. *Am J Hematol* 2009; **84:** 418–21.

Castleman's disease. Castleman's disease is a rare lymphoproliferative disorder, often associated with HIV infection (p. 957.2) and thought to be caused by the same virus (human herpesvirus 8) as Kaposi's sarcoma. No standard treatment has been established. Responses to rituximab therapy have been reported in two small open-label studies in patients with HIV-associated Castleman's disease;[1,2] rituximab 375 mg/m^2 was given intravenously once weekly for 4 weeks. However, exacerbation of Kaposi's sarcoma lesions may be a problem.

1. Gérard L, *et al.* Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus-associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. *J Clin Oncol* 2007; **25:** 3350–6.
2. Bower M, *et al.* Brief communication: rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med* 2007; **147:** 836–9.

Eye disorders. Orbital pseudolymphomas are uncommon benign tumours which usually affect the lachrymal gland, orbital soft tissue, or extra-ocular muscles. Clinical presentation includes painless onset of ptosis, proptosis, diplopia, or eyelid swelling. There are reports of durable response to rituximab.[1]

1. Witzig TE, *et al.* Treatment of benign orbital pseudolymphomas with the monoclonal anti-CD20 antibody rituximab. *Mayo Clin Proc* 2007; **82:** 692–9.

Glomerular kidney disease. In a report of 5 patients with corticosteroid-resistant nephrotic syndrome, 4 patients had a complete remission and 1 patient had a partial remission after treatment with rituximab in standard doses for 4 weeks. Complete remission was maintained in 3 patients, despite tapering of corticosteroids and calcineurin inhibitors.[1] The limited evidence for such use has subsequently been reviewed.[2]

1. Bagga A, *et al.* Rituximab in patients with the steroid-resistant nephrotic syndrome. *N Engl J Med* 2007; **356:** 2751–2.
2. Haffner D, Fischer DC. Nephrotic syndrome and rituximab: facts and perspectives. *Pediatr Nephrol* 2009; **24:** 1433–8.

Malignant neoplasms. Reviews.

1. NICE. Rituximab for aggressive non-Hodgkin's lymphoma (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/65_rituximab_nonhodgkins_fullguidance.pdf (accessed 07/09/09)
2. Avivi I, *et al.* Clinical use of rituximab in haematological malignancies. *Br J Cancer* 2003; **89:** 1389–94.
3. Held G, *et al.* Rituximab for the treatment of diffuse large B-cell lymphomas. *Expert Rev Anticancer Ther* 2006; **6:** 1175–86.
4. van Oers MH. Rituximab maintenance in indolent lymphoma: indications and controversies. *Curr Oncol Rep* 2007; **9:** 378–83.
5. Schulz H, *et al.* Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 24/07/08).
6. Molina A. A decade of rituximab: improving survival outcomes in non-Hodgkin's lymphoma. *Annu Rev Med* 2008; **59:** 237–50.
7. NICE. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkins lymphoma: review of technology appraisal guidance 37 (issued February 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA137guidance.pdf (accessed 07/09/09)
8. Kapoor P, *et al.* Anti-CD20 monoclonal antibody therapy in multiple myeloma. *Br J Haematol* 2008; **141:** 135–48.
9. Gisselbrecht C. Use of rituximab in diffuse large B-cell lymphoma in the salvage setting. *Br J Haematol* 2008; **143:** 607–21.
10. Vidal L, *et al.* Rituximab as maintenance therapy for patients with follicular lymphoma. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2009 (accessed 07/09/09).
11. NICE. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (issued July 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/TA174FullGuidance.pdf (accessed 07/09/09)
12. Hagemeister F. Rituximab for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 2010; **70:** 261–72.
13. Gao G, *et al.* A systematic review and meta-analysis of immunochemotherapy with rituximab for B-cell non-Hodgkin's lymphoma. *Acta Oncol* 2010; **49:** 3–12.
14. Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma. *Drugs* 2010; **70:** 1445–76.

Multiple sclerosis. A single course of rituximab has been reported to reduce inflammatory brain lesions and clinical relapses in relapsing-remitting multiple sclerosis (p. 996.3);[1] the small study was not designed to assess long-term safety or uncommon adverse effects.

1. Hauser SL, *et al.* HERMES Trial Group. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008; **358:** 676–88.

Myasthenia gravis. Rituximab has been tried[1] in a few patients with myasthenia gravis (p. 684.1).

1. Nelson RP, *et al.* Rituximab for the treatment of thymoma-associated and de novo myasthenia gravis: 3 cases and review. *J Clin Neuromusc Dis* 2009; **10:** 170–7.

Organ and tissue transplantation. Rituximab is a treatment option for patients with chronic graft-versus-host disease (GVHD; see Haematopoietic Stem Cell Transplantation, p. 1937.1). Available data suggest that rituximab may be particularly effective for patients with extensive corticosteroid-refractory chronic GVHD manifesting as thrombocytopenia, or for those with sclerodermatous, cutaneous, or rheumatological involvement.[1] Post-transplant lymphoproliferative disorder (PTLD) after solid organ transplantation (see p. 1936.2 *et seq*) is rare but life-threatening; many cases, especially more aggressive lymphomas, do not respond to the usual first-line therapy of reduction in immunosuppression. Rituximab and/or chemotherapy have been used for PTLD. Some recommend that patients with Epstein-Barr virus (EBV) positive and early-onset PTLD be given rituximab monotherapy if reduction in immunosuppression fails; treatment with chemotherapy is reserved for those who fail to respond to rituximab. More aggressive treatment, including the use of rituximab with combination chemotherapy (given sequentially or concurrently), should be considered initially, along with reduction of immunosuppressive treatment, in those patients with CD20-positive or high-grade PTLDs. The use of granulocyte colony-stimulating factors and antibacterials as prophylaxis against infectious complications should be considered in this high-risk population.[2] Rituximab has been investigated as induction therapy for patients undergoing renal transplantation, but a small study reported an excess risk of acute cellular rejection in those given rituximab.[3]

1. Bates JS, *et al.* Clinical utility of rituximab in chronic graft-versus-host disease. *Ann Pharmacother* 2009; **43:** 316–21.
2. Lee J-J, *et al.* Role of chemotherapy and rituximab for treatment of posttransplant lymphoproliferative disorder in solid organ transplantation. *Ann Pharmacother* 2007; **41:** 1648–59.
3. Clatworthy MR, *et al.* B-cell-depleting induction therapy and acute cellular rejection. *N Engl J Med* 2009; **360:** 2683–5.

Pemphigus. Rituximab has been reported to be of benefit in pemphigus vulgaris (p. 1687.1) and its use has been reviewed.[1,2] In a review of 17 cases, it was used in patients with severe and widespread disease that had not responded to usual therapy with corticosteroids and immunosuppressants. A dose of 375 mg/m^2 once weekly was used and most patients were given a course of 4 doses. Most patients showed some improvement from rituximab, including 9 who were free of clinical disease for more than 6 months and 5 who had a partial response. However, although concomitant therapy could be reduced in 8 patients, only 2 were able to stop systemic corticosteroids and immunosuppressants; in 6 cases this information was not reported. Rituximab might therefore be useful for remission induction when corticosteroids have not been effective, but long-term follow-up is needed. Rituximab with normal immunoglobulins has also been reported to be effective in patients with refractory pemphigus vulgaris.[3]

Rituximab has also been reported to be of benefit in pemphigus foliaceus,[4-6] a less common variant of pemphigus. A single cycle of 4 weekly infusions of rituximab was reported to achieve complete remission in 12 of 14 patients with pemphigus vulgaris and 6 of 7 patients with pemphigus foliaceus; 2 patients in the former group achieved delayed complete remission. Of these 20 patients, 6 with pemphigus vulgaris and 3 with pemphigus foliaceus had a relapse; 2 of these 9 patients were given a second course of rituximab and again achieved complete remission. After 34 months of follow-up, 18 patients were free of disease, and 8 of these were not receiving any systemic therapy.[7]

1. El Tal AK, *et al.* Rituximab: a monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 2006; **55:** 449–59.
2. Schmidt E, *et al.* Rituximab in severe pemphigus. *Ann N Y Acad Sci* 2009; **1173:** 683–91.
3. Ahmed AR, *et al.* Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; **355:** 1772–9.
4. Goebeler M, *et al.* Rapid response of treatment-resistant pemphigus foliaceus to the anti-CD20 antibody rituximab. *Br J Dermatol* 2003; **149:** 899–901.
5. Arin MJ, *et al.* Anti-CD20 monoclonal antibody (rituximab) in the treatment of pemphigus. *Br J Dermatol* 2005; **153:** 620–5.
6. Fernando SL, O'Connor KS. Treatment of severe pemphigus foliaceus with rituximab. *Med J Aust* 2008; **189:** 289–90.
7. Joly P, *et al.* A single cycle of rituximab for the treatment of severe pemphigus. *N Engl J Med* 2007; **357:** 545–52.

Rheumatoid arthritis. Rituximab is of benefit in patients with rheumatoid arthritis (p. 13.2) refractory to standard therapy.[1-4] The ability of rituximab to prevent articular damage, its efficacy for extra-articular manifestations, the efficacy and safety of repeated courses, and long-term effects on the immune system remain to be determined.[5] Radiographic data from a placebo-controlled study showed a trend towards less progression of structural joint damage with a course of rituximab (2 doses); assessment was made at 24 weeks.[6] In a consensus statement, European and Canadian rheumatologists stated that re-treatment with rituximab may be considered after week 24 in those who respond to initial therapy.[7]

1. Edwards JCW, *et al.* Efficacy of B-cell—targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; **350:** 2572–81.
2. Summers KM, Kockler DR. Rituximab treatment of refractory rheumatoid arthritis. *Ann Pharmacother* 2005; **39:** 2091–5.
3. Higashida J, *et al.* Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-α treatment. *J Rheumatol* 2005; **32:** 2109–15.
4. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
5. Looney RJ. B cell-targeted therapy for rheumatoid arthritis: an update on the evidence. *Drugs* 2006; **66:** 625–39.
6. Cohen SB, *et al.* Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006; **54:** 2793–2806.
7. Smolen JS, *et al.* Working Group on the Rituximab Consensus Statement. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007; **66:** 143–50.

Scleroderma. Rituximab is under investigation for the management of scleroderma (p. 1942.3).

Skin disorders. In addition to reports of efficacy in pemphigus (see above), rituximab has been reported to be of benefit in refractory cases of pemphigoid[1] and epidermolysis bullosa acquisita.[2,3]

1. Schmidt E, *et al.* Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol* 2007; **156:** 352–6.
2. Crichlow SM, *et al.* A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol* 2007; **156:** 194–6.
3. Sadler E, *et al.* Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol* 2007; **157:** 417–19.

Systemic lupus erythematosus. Rituximab has been investigated for the treatment of SLE (p. 1613.3),[1-3] but results of controlled studies have been disappointing.

1. Sfikakis PP, *et al.* Rituximab anti-B-cell therapy in systemic lupus erythematosus: pointing to the future. *Curr Opin Rheumatol* 2005; **17:** 550–7.
2. García-Carrasco M, *et al.* Use of rituximab in patients with systemic lupus erythematosus: an update. *Autoimmun Rev* 2009; **8:** 343–8.
3. Hughes G. Rituximab in lupus and beyond: the state of the art. *Lupus* 2009; **18:** 639–44.

Thyroid disorders. Rituximab has been investigated in the management of Graves' disease (see Hyperthyroidism, p. 2332.2), including Graves' ophthalmopathy.[1,2]

1. Nielsen CH, *et al.* B-cell depletion with rituximab in the treatment of autoimmune diseases: Graves' ophthalmopathy the latest addition to an expanding family. *Expert Opin Biol Ther* 2007; 7: 1061–78.
2. Heemstra KA, *et al.* Rituximab in relapsing Graves' disease, a phase II study. *Eur J Endocrinol* 2008; 159: 609–15.

Vasculitic syndromes. Rituximab has been reported to be of benefit in treating vasculitic syndromes (p. 1615.2), including those associated with antineutrophil cytoplasmic antibodies (ANCA-associated vasculitis).[1-4] Similar efficacy to cyclophosphamide has been reported,[3,4] with some suggestion that rituximab may be more effective in relapsing disease.[4] Successful treatment of scleritis associated with Wegener's granulomatosis has also been described.[5] Safety and efficacy have also been reported[6] with the use of rituximab in patients with refractory Henoch-Schönlein purpura (see Hypersensitivity Vasculitis, p. 1606.1).

1. Keogh KA, *et al.* Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; 52: 262–8.
2. Ferraro AJ, *et al.* Effective therapeutic use of rituximab in refractory Wegener's granulomatosis. *Nephrol Dial Transplant* 2005; 20: 622–5.
3. Jones RB, *et al.* European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211–20.
4. Stone JH, *et al.* RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221–32.
5. Cheung CMG, *et al.* Successful treatment of Wegener's granulomatosis associated scleritis with rituximab. *Br J Ophthalmol* 2005; 89: 1542.
6. Donnithorne KJ, *et al.* Rituximab therapy for severe refractory chronic Henoch-Schönlein purpura. *J Pediatr* 2009; 155: 136–9.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Infusion of rituximab has been associated with a cytokine release syndrome of fever, chills, and rigors, usually within 2 hours of beginning therapy (see also Infusion-related Reactions, below). Other reported symptoms include pruritus, urticaria, rashes, dyspnoea, bronchospasm, angioedema, transient hypotension, and flushing; myocardial infarction, ventricular fibrillation, and cardiogenic shock can occur. Asthenia, headache, rhinitis, and hypertension may also be associated with infusion reactions. Severe cases may be associated with tumour lysis syndrome (and its associated electrolyte abnormalities such as hyperuricaemia, hyperkalaemia, hypocalcaemia, and hyperphosphataemia), acute renal failure, acute respiratory failure, and death. Hypersensitivity reactions manifest similarly to the cytokine release syndrome, but usually occur within minutes of starting infusion. Mucocutaneous reactions, some fatal, and including Stevens-Johnson syndrome or toxic epidermal necrolysis have also occurred. A reaction resembling serum sickness has been reported.

Patients with an extensive tumour burden, pulmonary tumour infiltration or pulmonary insufficiency may be at increased risk of severe infusion reactions and should be treated with caution and possibly a decreased initial infusion rate. Therapy should be interrupted in patients who develop severe symptoms and only resumed, at up to half the previous rate, once all signs and symptoms have resolved. Premedication with analgesics, antihistamines, and possibly corticosteroids is recommended in all patients before receiving rituximab.

Use of rituximab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML), and fatalities have been reported. In most cases, patients had multiple risk factors, including long-term treatment with combination chemotherapy or immunosuppression, or were undergoing haematopoietic stem cell transplantation. Patients should be monitored regularly for new or worsening neurological clinical manifestations suggestive of PML; rituximab should be permanently stopped if PML develops.

Reactivation of hepatitis B virus (HBV) has occurred in some patients; fulminant hepatitis, hepatic failure, and fatalities have been reported. Patients at high risk of HBV infection should be screened before starting rituximab therapy and carriers should be monitored for signs of active infection or hepatitis during and for several months after therapy. Rituximab should be stopped if viral hepatitis develops. Other serious infections, which may be fatal, can occur with rituximab.

Haematological adverse effects including lymphopenia, leucopenia, neutropenia, thrombocytopenia, and anaemia have occurred in some patients; effects are usually considered mild and reversible. Complete blood and platelet counts should be monitored regularly. Exacerbation of heart failure and angina pectoris has also been reported, and other cardiac events include arrhythmias and tachycardia. Gastrointestinal disturbances may also occur. Abdominal pain, bowel obstruction, and perforation, in some cases fatal, have been reported with rituximab, usually with combination chemotherapy.

References.
1. Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. *Arthritis Res Ther* 2005; 7 (suppl 3): S19–S25.
2. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005; 31: 456–73.
3. Ram R, *et al.* The late adverse events of rituximab therapy—rare but there! *Leuk Lymphoma* 2009; 50: 1083–95.

Effects on the blood. Late-onset neutropenia (defined as neutropenia occurring 30 days after the last dose) has been reported in patients receiving rituximab.[1] Acute and potentially severe thrombocytopenia associated with rituximab therapy has also been reported occasionally.[2,3] Haemolytic anaemia occurred in a patient given 4 doses of rituximab, plus corticosteroid therapy, for refractory pemphigus vulgaris.[4] Although there was a drop in haemoglobin after the first and second doses of rituximab, concentrations then stabilised; the reticulocyte count remained high throughout treatment.

1. Rios-Fernández R, *et al.* Late-onset neutropenia following rituximab treatment in patients with autoimmune diseases. *Br J Dermatol* 2007; 157: 1271–3.
2. Dhand S, Bahrain H. Rituximab-induced severe acute thrombocytopenia: a case report and review of literature. *Cancer Invest* 2008; 26: 913–15.
3. Ram R, *et al.* Rituximab-associated acute thrombocytopenia: an underdiagnosed phenomenon. *Am J Hematol* 2009; 84: 247–50.
4. Li WW, *et al.* Haemolytic anaemia following rituximab treatment in a patient with pemphigus vulgaris. *Br J Dermatol* 2009; 161: 205–6.

Effects on the eyes. About 20 minutes after the start of a rituximab infusion, a patient developed bilateral conjunctivitis without pain, lachrymation, or discharge. No other clinical manifestations of a hypersensitivity reaction were apparent, and the conjunctivitis resolved spontaneously, about 30 minutes after the end of the infusion. No recurrence was evident with subsequent rituximab therapy.[1]

1. Marinella MA. Bilateral conjunctivitis due to rituximab. *Ann Pharmacother* 2007; 41: 1318.

Effects on the gastrointestinal tract. In November 2006 the manufacturer noted that 47 cases of bowel obstruction (9 fatal) and 37 cases of gastrointestinal perforation (4 fatal) had been reported in patients given rituximab.[1] Interpretation of data was difficult due to confounding factors; however, a contributory role of rituximab could not be excluded. The mean time to onset of symptoms was 6 days (range 1 to 77 days) for documented perforation. Complaints of abdominal pain, especially early in a course of rituximab treatment, should prompt thorough diagnostic evaluation and treatment.

There have been reports of ulcerative colitis when rituximab was used to deplete B-lymphocytes in Graves' disease[2] and nephrotic syndrome.[3] A severe exacerbation of pre-existing ulcerative colitis occurred in a patient with refractory disease given rituximab as salvage therapy.[4]

1. Roche, Canada. Reports of bowel obstruction and gastrointestinal perforation with RITUXAN (rituximab) (issued 10th November 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/rituxan_3_hpc-cps-eng.php (accessed 30/07/08)
2. El Fassi D, *et al.* Ulcerative colitis following B lymphocyte depletion with rituximab in a patient with Graves' disease. *Gut* 2008; 57: 714–15.
3. Ardelean DS, *et al.* Severe ulcerative colitis after rituximab therapy. *Pediatrics* 2010; 126: e243–e246.
4. Goetz M, *et al.* Exacerbation of ulcerative colitis after rituximab salvage therapy. *Inflamm Bowel Dis* 2007; 13: 1365–8.

Effects on the lungs. Pulmonary reactions have been reported with rituximab use,[1] including reversible interstitial pneumonia[2-4] and interstitial fibrosis.[5] A fatal intra-alveolar haemorrhage in 1 patient was attributed to a hypersensitivity reaction to rituximab;[6] a further case of alveolar haemorrhage associated with interstitial lung disease has been reported.[7]

1. Wagner SA, *et al.* Rituximab-induced interstitial lung disease. *Am J Hematol* 2007; 82: 916–19.
2. Burton C, *et al.* Interstitial pneumonitis related to rituximab therapy. *N Engl J Med* 2003; 348: 2690–1.
3. Jullien V, *et al.* Une pneumopathie alvéolo-interstitielle hypoxémiante associée à la prise de rituximab. *Rev Mal Respir* 2004; 21: 407–10.
4. Swords R, *et al.* Interstitial pneumonitis following rituximab therapy for immune thrombocytopenic purpura (ITP). *Am J Hematol* 2004; 77: 103–4.
5. Leon RJ, *et al.* Rituximab-induced acute pulmonary fibrosis. *Mayo Clin Proc* 2004; 79: 949, 953.
6. Alexandrescu DT, *et al.* Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma. *Leuk Lymphoma* 2004; 45: 2321–5.
7. Heresi GA, *et al.* Interstitial pneumonitis and alveolar hemorrhage complicating use of rituximab: case report and review of the literature. *Respiration* 2008; 76: 449–53.

Effects on the nervous system. As of December 2006, the FDA had received a total of 24 reports of progressive multifocal leukoencephalopathy (PML) in patients given rituximab.[1] PML is a fatal demyelinating disease that follows reactivation of latent JC or PK polyomavirus (also known as papovavirus) in the CNS; the virus is present in about 80% of adults. In the first 12 cases reported to the FDA, 10 patients tested positive for the JC virus and 1 had confirmed BK virus. PML presents with rapidly progressive focal neurological deficits including hemiparesis, paraesthesias, visual-field deficits, ataxia, and behavioural and cognitive changes.[2] In a report of 57 cases,[3] 52 patients had haematological malignancies and 5 had auto-immune disorders; all patients had received previous immunosuppressive therapies, including alkylating agents, purine analogues, corticosteroids, or drugs to prevent allogeneic stem cell or solid organ rejection. The case-fatality rate was 90%.

There have also been reports[4,5] of *reversible* posterior leukoencephalopathy syndrome with rituximab. Symptoms have varied between patients, with drowsiness, confusion, hallucinations, nausea, and vomiting occurring in one,[4] and hypertension, headache, blurred vision, and seizures in another.[5]

1. FDA. Rituximab (marketed as Rituxan): progressive multifocal leukoencephalopathy (PML). *FDA Drug Safety Newsletter* 2007; 1: 3–5. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109158.pdf (accessed 21/07/10)
2. MHRA/CHM. Rituximab and efalizumab: progressive multifocal leukoencephalopathy. *Drug Safety Update* 2008; 2 (5): 3–4. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON033504&RevisionSelectionMethod=LatestReleased (accessed 07/09/09)
3. Carson KR, *et al.* Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* 2009; 113: 4834–40.
4. Sánchez-Carteyron A, *et al.* Posterior reversible encephalopathy syndrome after rituximab infusion in neuromyelitis optica. *Neurology* 2010; 74: 1471–3.
5. Mavragani CP, *et al.* A case of reversible posterior leucoencephalopathy syndrome after rituximab infusion. *Rheumatology (Oxford)* 2004; 43: 1450–1.

Infection. In addition to progressive multifocal leukoencephalopathy associated with JC or BK virus reactivation (see Effects on the Nervous System, above), rituximab therapy for lymphomas is associated with an increased risk of viral infection or reactivation, notably from hepatitis B and CMV;[1,2] there is less evidence of any increased risk of serious infection in patients treated with rituximab for rheumatoid arthritis.[3]

Hepatitis C reactivation has also been reported in a patient after rituximab was added to the chemotherapy regimen.[4] In another patient, chronic hepatitis was caused by a persistent hepatitis E infection with active viral replication, in a patient receiving maintenance therapy for lymphoma with rituximab.[5]

1. Aksoy S, *et al.* Rituximab-related viral infections in lymphoma patients. *Leuk Lymphoma* 2007; 48: 1307–12.
2. Aksoy S, *et al.* Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. *Leuk Lymphoma* 2009; 50: 357–65.
3. Salliot C, *et al.* Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis* 2009; 68: 25–32.
4. Hsieh C-Y, *et al.* Rituximab-induced hepatitis C virus reactivation after spontaneous remission in diffuse large B-cell lymphoma. *J Clin Oncol* 2008; 26: 2584–6.
5. Ollier L, *et al.* Chronic hepatitis after hepatitis E virus infection in a patient with non-Hodgkin lymphoma taking rituximab. *Ann Intern Med* 2009; 150: 430–1.

Infusion-related reactions. By November 1998 there had been 74 cases of serious infusion-related reactions to rituximab reported worldwide, with 8 fatal cases.[1] An estimated 12 000 to 14 000 patients had been treated.

The reaction usually occurs within the first 2 hours of infusion and the underlying mechanism is believed to be a severe cytokine release syndrome, with some elements of tumour lysis syndrome.[1-3] In one series of cases tumour necrosis factor-α and interleukin-6 levels were found to peak 90 minutes after the onset of the infusion, and these elevated cytokine levels coincided with infusion-related symptoms.[2] The reaction is usually most marked after the first infusion and subsequent infusions are usually tolerated, emphasising that this is not a true hypersensitivity reaction.[4]

Patients with a high tumour burden (lesions over 10 cm in diameter or more than 500 000 circulating malignant cells/mm^3), a history of pulmonary infiltration or insufficiency, or underlying cardiac disease are believed to be at greater risk of severe reactions.[1,2,4] The UK CSM recommends that premedication with an analgesic and an antihistamine should always be given before rituximab, and corticosteroids should be considered.[1] However, serious or fatal reactions have occurred despite such premedication.[3,4] Alternative infusion schedules and/or combination therapy with chemotherapeutic drugs may be required to decrease the tumour burden before rituximab therapy.[2,4]

1. CSM/MCA. Rituximab (MabThera): serious infusion-related adverse reactions. *Current Problems* 1999; 25: 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 26/04/06)
2. Winkler U, *et al.* Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukaemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999; 94: 2217–24.
3. Lim L-C, *et al.* Fatal cytokine release syndrome with chimeric anti-CD20 monoclonal antibody rituximab in a 71-year-old patient with chronic lymphocytic leukaemia. *J Clin Oncol* 1999; 17: 1962–3.
4. Byrd JC, *et al.* Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-

related side effects and rapid blood tumor clearance. *J Clin Oncol* 1999; 17: 791–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rituximab 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 29/09/11)

Pregnancy. Giving 4 cycles of rituximab (with doxorubicin, vincristine, and prednisolone) to a pregnant woman with lymphoma, from 21 weeks of gestation until delivery at 35 weeks, resulted in no adverse effects to either the mother or the infant.[1] In another report, a 31-year-old woman was diagnosed with non-Hodgkin's lymphoma during pregnancy. She received 6 cycles of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Two months after treatment, she spontaneously delivered a premature but healthy infant. Patient and child were clinically assessed every 3 months; the infant's B cells were severely diminished at birth but recovered over 6 to 12 weeks. Rituximab concentrations in both mother and child also decreased as expected. No adverse effects were seen during 16 months of follow-up.[2] In 2 case reports of rituximab use during the first trimester of pregnancy, no significant adverse effects on the neonates were seen; transient granulocytopenia and lymphopenia were reported.[3,4] A 35-year-old woman diagnosed with Burkitt's lymphoma in week 15 of pregnancy received 4 weekly infusions of rituximab starting in week 16, followed by four courses of rituximab with CHOP, and then 2 courses of CHOP alone. In week 41, a healthy infant was delivered by caesarean section. Both the mother and child had very high serum concentrations of rituximab at birth with a complete absence of B cells; rituximab levels in the cord blood serum were three times that in the mother's serum. However, B-cell recovery was reported to be rapid, and no overt infectious complications were seen in the child up to the age of 26 months; growth and developmental status were also normal.[5] Nonetheless, licensed product information advises against rituximab use during pregnancy, given the potential for B-cell depletion in the fetus; women of child-bearing potential should use effective contraceptive methods during treatment and for up to 12 months after therapy.

1. Herold M, *et al.* Efficacy and safety of a combined rituximab chemotherapy during pregnancy. *J Clin Oncol* 2001; 19: 3439.
2. Decker M, *et al.* Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. *Lancet Oncol* 2006; 7: 693–4. Correction. *ibid.*: 706.
3. Kimby E, *et al.* Safety of rituximab therapy during the first trimester of pregnancy: a case history. *Eur J Haematol* 2004; 72: 292–5.
4. Ojeda-Uribe M, *et al.* Administration of rituximab during the first trimester of pregnancy without consequences for the newborn. *J Perinatol* 2006; 26: 252–5.
5. Friedrichs B, *et al.* The effects of rituximab treatment during pregnancy on a neonate. *Haematologica* 2006; 91: 1426–7.

Interactions

Statins. It has been reported that, in a laboratory study, statins significantly decreased rituximab cytotoxicity, suggesting that statins may induce conformational changes in CD20 through cholesterol depletion, resulting in impaired binding of rituximab. While noting that there are no clinical data to support withholding statins during rituximab therapy, the authors advised that it might be prudent to consider doing so.[1] However, a subsequent prospective study[2] found no evidence that concomitant statin therapy in patients with diffuse large B-cell lymphoma or follicular lymphoma had any adverse effect on response to rituximab-based therapy; event-free survival was actually improved in patients with follicular lymphoma who took statins, regardless of other therapy.

1. Rabinowitz I. Interaction between statins and rituximab in non-Hodgkin's lymphoma. *J Clin Oncol* 2008; 26: 5486.
2. Nowakowski GS, *et al.* Statin use and prognosis in patients with diffuse large B-cell lymphoma and follicular lymphoma in the rituximab era. *J Clin Oncol* 2010; 28: 412–17.

Pharmacokinetics

The mean peak plasma concentration of rituximab has been reported to increase with successive infusions; however, considerable interindividual variation is seen. Serum concentrations are negatively correlated with tumour burden and the number of circulating B-cells. The mean terminal half-life is about 20 days. Rituximab is bound to B lymphocytes, and is detectable in the body for 3 to 6 months after treatment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: MabThera; *Austral.*: MabThera; *Austria*: MabThera; *Belg.*: MabThera; *Braz.*: MabThera; *Canad.*: Rituxan; *Chile*: MabThera; *Cz.*: MabThera; *Denm.*: MabThera; *Fin.*: MabThera; *Fr.*: MabThera; *Ger.*: MabThera; *Gr.*: MabThera; *Hong Kong*: MabThera; *Hung.*: MabThera; *India*: MabThera; *Indon.*: MabThera; *Irl.*: MabThera; *Israel*: MabThera; *Ital.*: MabThera; *Jpn*: Rituxan; *Malaysia*: MabThera; *Mex.*: MabThera; *Neth.*: MabThera; *Norw.*: MabThera; *NZ*: MabThera; *Philipp.*: MabThera; *Pol.*: MabThera; *Port.*: MabThera; *Rus.*: MabThera (МабТера); *S.Afr.*: MabThera; *Singapore*: MabThera; *Spain*: MabThera; *Swed.*: MabThera; *Switz.*: MabThera; *Thai.*: MabThera; *Turk.*: MabThera; *UK*: MabThera; *Ukr.*: MabThera (МаБтера); *USA*: Rituxan; *Venez.*: MabThera.

Romidepsin *(USAN, rINN)*

Depsipeptide; FK-228; FR-901228; NSC-630176; Romidepsina; Romidepsine; Romidepsinum; Ромидепсин.

(1*S*,4*S*,10*S*,16*E*,21*R*)-7-[(2*Z*)Ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone.

$C_{24}H_{36}N_4O_6S_2$=540.7

CAS — 128517-07-7.

ATC — L01XX39.

ATC Vet — QL01XX39.

UNII — CX3T89XQBK.

NOTE. The name Chromadax has been used as a trade mark for romidepsin.

Uses and Administration

Romidepsin is a histone deacetylase inhibitor used for the treatment of cutaneous T-cell lymphoma (see Mycosis Fungoides, p. 698.3) and peripheral T-cell lymphoma. It is given intravenously; the reconstituted solution is diluted in 500 mL of sodium chloride 0.9% and infused over 4 hours. The initial dose is romidepsin 14 mg/m² on days 1, 8, and 15 of a 28-day cycle. Treatment should be withheld for severe haematological toxicity or for moderate or severe non-haematological toxicity, except alopecia, see below. Romidepsin may be continued for as long as there is benefit from treatment and toxicity allows.

Romidepsin is under investigation in the treatment of solid tumours.

References.

1. Piekarz RL, *et al.* Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2009; 27: 5410–17.
2. Whittaker SJ, *et al.* Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol* 2010; 28: 4485–91.
3. Piekarz RL, *et al.* Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood* 2011; 117: 5827–34.
4. Yang LPH. Romidepsin: in the treatment of T-cell lymphoma. *Drugs* 2011; 71: 1469–80.
5. Coiffier B, *et al.* Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol* 2012; 30: 631–6.

Administration in subsequent cycles. Romidepsin treatment should be withheld for severe haematological toxicity or for moderate or severe non-haematological toxicity, except alopecia.

- For grade 3 or 4 neutropenia or thrombocytopenia, romidepsin may be restarted at 14 mg/m² when the cytopenia returns to an absolute neutrophil count of 1500 cells/mm³ and/or a platelet count of 75 000 cells/mm³
- For grade 4 febrile neutropenia or thrombocytopenia that requires a platelet transfusion, treatment should be delayed until the cytopenia has returned to baseline measurements or grade 1 or less, and the romidepsin dose permanently reduced to 10 mg/m²
- For grade 2 or 3 non-haematological toxicity, romidepsin may be restarted at 14 mg/m² when toxicity has returned to baseline measurements or grade 1 or less
- For grade 4 non-haematological toxicity, or if grade 3 toxicity recurs, treatment should be delayed until toxicity has returned to baseline measurements or grade 1 or less, and the romidepsin dose permanently reduced to 10 mg/m²

Romidepsin treatment should be stopped if grade 3 or 4 non-haematological toxicities recur after dose reduction.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Romidepsin can cause haematological adverse effects such as thrombocytopenia, leucopenia, and anaemia; blood counts should be monitored during treatment and the dose adjusted if necessary, see above. Arrhythmias, QT prolongation, and other ECG changes have also been noted during romidepsin treatment. Potassium and magnesium concentrations should be within the normal range before starting treatment, and ECG and electrolyte monitoring should be considered at baseline and periodically during treatment in patients with congenital long QT syndrome, a history of cardiovascular disease, or those taking antiarrhythmics or medicines that prolong the QT interval. Electrolyte disturbances such as hypokalaemia and hypophosphataemia have also been reported during treatment. Hyperuricaemia can occur, and patients with advanced-stage disease or high tumour burden should be monitored for the development of tumour lysis syndrome.

Gastrointestinal disturbances, fatigue, fever, and infections are common adverse effects of romidepsin. Other reported effects include oedema, dyspnoea, taste disturbances, hypotension, dermatitis, pruritus, increases in liver enzyme concentrations, hypoalbuminaemia, and hyperglycaemia. There have been isolated cases of cardiopulmonary adverse events and acute renal failure, including fatalities.

Due to a lack of data romidepsin should be used with caution in patients with end-stage renal disease or with moderate or severe hepatic impairment.

Interactions

Romidepsin is metabolised by the cytochrome P450 isoenzyme CYP3A4 and its concentration may be affected by CYP3A4 inhibitors or inducers given at the same time. Strong CYP3A4 inhibitors and inducers should be avoided during romidepsin treatment, and caution is advised if moderate CYP3A4 inhibitors are given. Romidepsin is also a substrate of P-glycoprotein, and caution is advised if it is given with P-glycoprotein inhibitors as increased concentrations of romidepsin are likely.

A prolonged prothrombin time (PT) and an elevated international normalised ratio (INR) has been reported in a patient given romidepsin while taking warfarin; monitoring of these parameters is advised if romidepsin is to be given with a coumarin anticoagulant.

Pharmacokinetics

Romidepsin is highly bound to plasma proteins (about 93%). It is mainly metabolised by the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP3A5, CYP1A1, CYP2B6, and CYP2C19 play a minor role. During usual intravenous dosing, the terminal half-life is about 3 hours.

References.

1. Klimek VM, *et al.* Tolerability, pharmacodynamics, and pharmacokinetics studies of depsipeptide (romidepsin) in patients with acute myelogenous leukemia or advanced myelodysplastic syndromes. *Clin Cancer Res* 2008; 14: 826–32.
2. Woo S, *et al.* Population pharmacokinetics of romidepsin in patients with cutaneous T-cell lymphoma and relapsed peripheral T-cell lymphoma. *Clin Cancer Res* 2009; 15: 1496–1503.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Istodax.

Rostaporfin *(USAN, rINN)*

Rostaporfina; Rostaporfine; Rostaporfinum; SnET2; Tin Ethyl Etiopurpurin; Tin etiopurpurin dichloride; Ростапорфин.

(*OC*-6-13)-Dichloro[ethyl (18*R*,19*R*)-3,4,20,21-tetradehydro-4,9,14,19-tetraethyl-18,19-dihydro-3,8,13,18-tetramethyl-20-phorbinecarboxylato (2-)-N^{23},N^{24},N^{25},N^{26}]tin.

$C_{37}H_{42}Cl_2N_4O_2Sn$=764.4

CAS — 284041-10-7; 114494-17-6.

UNII — 466G63QE7G.

NOTE. The names Photrex and Purlytin have been used as trade marks for rostaporfin.

Profile

Rostaporfin is a photosensitiser that is under investigation in the photodynamic therapy of neovascular (wet) age-related macular degeneration (p. 880.2). It has also been investigated for photodynamic therapy of malignant neoplasms.

Ruxolitinib Phosphate *(USAN, rINNM)*

Fosfato de ruxolitinib; INC-424 (ruxolitinib); INCB-018424 salt; Ruxolitinib Phosphate de; Ruxolitinibi Phosphas; Руксолитиниба Фосфат.

(3*R*)-3-Cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile phosphate (1:1).

$C_{17}H_{18}N_6.H_3O_4P$=404.4

CAS — 941678-49-5 (ruxolitinib); 1092939-17-7 (ruxolitinib phosphate).

UNII — 436LRU32HS.

Uses and Administration

Ruxolitinib is an inhibitor of the Janus-associated tyrosine kinases JAK1 and JAK2, and is used in the treatment of intermediate- or high-risk myelofibrosis (p. 856.1). It is

given orally as the phosphate, but doses are expressed in terms of the base; 13.2 mg of ruxolitinib phosphate is equivalent to about 10 mg of ruxolitinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

The recommended starting dose for myelofibrosis is based on platelet count:

- > 200 000 cells/mm³: 20 mg orally twice daily
- 100 000 to 200 000 cells/mm³: 15 mg orally twice daily

The dose is adjusted according to efficacy and tolerability. If efficacy is insufficient, and providing platelet and neutrophil counts are adequate, the daily dose may be increased in 10-mg increments to a maximum of 25 mg twice daily. Doses should not be increased in the first 4 weeks of treatment and, after that, not more often than every 2 weeks. Treatment should be stopped after 6 months if there has been no reduction in spleen size or improvement in symptoms.

Doses should be reduced if platelet counts fall, to avoid thrombocytopenia (see Administration in Toxicity, below). If ruxolitinib is stopped for reasons other than thrombocytopenia, the dose may be reduced gradually; a reduction of 10 mg each week has been suggested. Doses should also be reduced in patients with hepatic or renal impairment (see below).

If a potent cytochrome P450 isoenzyme inhibitor must also be used, ruxolitinib should be started at a dose of 10 mg twice daily in patients with a platelet count of ≥ 100 000 cells/mm³; those with a count below this should avoid ruxolitinib altogether.

Ruxolitinib is under investigation in the treatment of polycythaemia vera.

Administration in hepatic impairment. A starting dose of ruxolitinib 10 mg orally twice daily is suggested for patients with hepatic impairment and a platelet count of 100 000 to 150 000 cells/mm³. Ruxolitinib should be avoided in patients with hepatic impairment and lower platelet counts.

Administration in renal impairment. The dose of ruxolitinib should be reduced in patients with renal impairment. Starting doses (given below) have been recommended based on platelet count and renal function. Further dose adjustment should be made according to response.

Patients with renal impairment that is moderate (creatinine clearance 30 to 59 mL/min) or severe (15 to 29 mL/min):

- platelet count 100 000 to 150 000 cells/mm³: 10 mg orally twice daily
- platelet count < 100 000 cells/mm³: avoid ruxolitinib

Ruxolitinib should not be given to patients with end-stage renal disease not requiring dialysis (creatinine clearance < 15 mL/min).

Patients with end-stage renal disease on dialysis:

- platelet count > 200 000 cells/mm³: 20 mg orally
- platelet count 100 000 to 200 000 cells/mm³: 15 mg orally
- subsequent doses should be given on dialysis days, after the dialysis session

Administration in toxicity. The dose of ruxolitinib may need to be reduced to avoid thrombocytopenia during therapy. Adjustments are made in relation to the platelet count and the dose of ruxolitinib at the time of platelet decline.

- platelets 100 000 to < 125 000 cells/mm³: the dose should be no more than 15 mg orally twice daily (or 20 mg twice daily if the dose at the time of platelet decline was 25 mg twice daily)
- platelets 75 000 to < 100 000 cells/mm³: the dose should be no more than 10 mg orally twice daily
- platelets 50 000 to < 75 000 cells/mm³: the dose should be no more than 5 mg orally twice daily
- platelets < 50 000 cells/mm³: withhold ruxolitinib

If ruxolitinib treatment has been interrupted because of thrombocytopenia, it may be restarted after the platelet count rises to an acceptable level above 50 000 cells/mm³. The dose used should be at least 5 mg twice daily below the dose at interruption, and no more than the following maximum recommended doses:

- platelets ≥ 125 000 cells/mm³: maximum 20 mg orally twice daily
- platelets 100 000 to < 125 000 cells/mm³: maximum 15 mg orally twice daily
- platelets 75 000 to < 100 000 cells/mm³: maximum 10 mg orally twice daily for at least 2 weeks, which may be increased to 15 mg twice daily if stable
- platelets 50 000 to < 75 000 cells/mm³: 5 mg orally twice daily for at least 2 weeks, which may be increased to 10 mg twice daily if stable
- platelets < 50 000 cells/mm³: continue to withhold ruxolitinib

Myelofibrosis. An early phase study of ruxolitinib in 153 patients reported improvements in signs and symptoms of advanced myelofibrosis[1] (p. 695.1). However, follow-up over 3 years in 51 of these patients found that treatment had been stopped in 40% because of disease progression or loss or lack of response, and in 34% because of toxicity with or without disease progression or lack of response.[2]

1. Verstovsek S, *et al.* Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med* 2010; 363: 1117–27.
2. Tefferi A, *et al.* Long-term outcome of treatment with ruxolitinib in myelofibrosis. *N Engl J Med* 2011; 365: 1455–7.

Adverse Effects, Treatment, and Precautions

The most common adverse effect of ruxolitinib phosphate is myelosuppression, which is manifest as thrombocytopenia and anaemia to some degree in most patients while neutropenia occurs less frequently. These effects are dose-related and generally managed by dose reduction or withholding treatment. Complete blood counts and platelet counts should be measured before starting ruxolitinib, every 2 to 4 weeks until doses are stabilised, then as clinically indicated.

Bruising is common in patients given ruxolitinib; petechiae, ecchymosis, contusion, haematoma, and injection-site haematoma have all been reported. Other adverse effects include dizziness, headache, weight gain, and flatulence. Low-grade elevations of alanine and aspartate transaminases and cholesterol have also been reported. Patients given ruxolitinib are at risk of developing serious infection, and any active infection should be treated before starting ruxolitinib.

Dose reductions are recommended in patients with hepatic or renal impairment.

Withdrawal. Withdrawal effects after stopping ruxolitinib have been described in 5 patients being treated for myelofibrosis.[1] Acute relapse of symptoms and splenomegaly were accompanied by other signs and symptoms that included worsening of cytopenias, respiratory distress, pleural and pericardial effusion, and syndromes similar to septic shock and disseminated intravascular coagulation. The effects generally started within days after ruxolitinib was stopped because of loss of treatment benefit or adverse effects, even after the dose had been tapered in some cases.

1. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. *Mayo Clin Proc* 2011; 86: 1188–91.

Interactions

Ruxolitinib phosphate is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4 can increase the concentrations and prolong the half-life of ruxolitinib. The dose of ruxolitinib should be adjusted when it is used with potent inhibitors such as ketoconazole (see Uses and Administration, p. 855.3). No dose adjustment is considered necessary in general when ruxolitinib is given with mild or moderate inhibitors such as erythromycin.

Inducers of CYP3A4 such as rifampicin can reduce concentrations of ruxolitinib but with an associated increase in exposure to its active metabolites. Patients should be closely monitored and the dose of ruxolitinib adjusted as necessary.

Pharmacokinetics

Ruxolitinib phosphate is well absorbed from the gastrointestinal tract, with a peak plasma concentration occurring 1 to 2 hours after an oral dose. It is about 97% bound to plasma proteins, mainly albumin. Ruxolitinib is eliminated by metabolism, mainly through the cytochrome P450 isoenzyme CYP3A4. There are several active metabolites that together contribute 18% of the overall pharmacodynamics of ruxolitinib. About 74% of a dose is excreted in the urine and about 22% via the faeces. The mean elimination half-life of ruxolitinib is about 3 hours, but that of ruxolitinib plus its metabolites is about 5.8 hours.

References.

1. Shilling AD, *et al.* Metabolism, excretion, and pharmacokinetics of [^{14}C] INCB018424, a selective Janus tyrosine kinase 1/2 inhibitor, in humans. *Drug Metab Dispos* 2010; 38: 2023–31.
2. Shi JG, *et al.* The pharmacokinetics, pharmacodynamics, and safety of orally dosed INCB018424 phosphate in healthy volunteers. *J Clin Pharmacol* 2011; 51: 1644–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Jakavi; *Norw.*: Jakavi; *Switz.*: Jakavi; *UK*: Jakavi; *USA*: Jakafi.

Sabarubicin *(rINN)*

MEN-10755; Sabarubicina; Sabarubicine; Sabarubicinum; Сабарубицин.

(7*S*,9*S*)-7-[[4-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl]oxy]-6,9,11-trihydroxy-9-(hydroxyacetyl)-7,8,9,10-tetrahydrotetracene-5,12-dione.

$C_{32}H_{37}NO_{13}$=643.6

CAS — 211100-13-9.

UNII — XS499WOZ93.

Profile

Sabarubicin, an anthracycline, is an analogue of doxorubicin (p. 782.3). It acts as a potent topoisomerase II inhibitor and is under investigation for the treatment of various solid tumours, such as cancers of the lung, ovary, breast, and prostate. Myelosuppression is the main adverse effect.

References.

1. Jones K. MEN-10755. Menarini. *Curr Opin Investig Drugs* 2003; 4: 1473–8.
2. Caponigro F, *et al.* A phase II study of sabarubicin (MEN-10755) as second line therapy in patients with locally advanced or metastatic platinum/taxane resistant ovarian cancer. *Invest New Drugs* 2005; 23: 85–9.
3. Fiedler W, *et al.* A study from the EORTC new drug development group: open label phase II study of sabarubicin (MEN-10755) in patients with progressive hormone refractory prostate cancer. *Eur J Cancer* 2006; 42: 200–204.

Sapacitabine *(USAN, rINN)*

CS-682; CYC-682; Sapacitabina; Sapacitabinum Сапацитабин.

N-[1-(2-Cyano-2-deoxy-β-D-arabinofuranosyl)-2-oxo-1,2-dihydropyrimidin-4-yl]hexadecanamide.

$C_{26}H_{42}N_4O_5$=490.6

CAS — 151823-14-2.

UNII — W335P73C3L.

Profile

Sapacitabine is an oral nucleoside analogue that is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndromes, cutaneous T-cell lymphoma, and lung cancer.

References.

1. Delaunoit T, *et al.* A phase I clinical and pharmacokinetic study of CS-682 administered orally in advanced malignant solid tumors. *Invest New Drugs* 2006; 24: 327–33.
2. Kantarjian H, *et al.* Phase I clinical and pharmacokinetic study of oral sapacitabine in patients with acute leukemia and myelodysplastic syndrome. *J Clin Oncol* 2010; 28: 285–91.

Satraplatin *(USAN, rINN)*

BMS-182751; BMY-45594; JM-216; Satraplatine; Satraplatino; Satraplatinum; Сатраплатин.

(*OC*-6-43)-Bis(acetato)amminedichloro(cyclohexylamine)platinum.

$C_{10}H_{22}Cl_2N_2O_4Pt$=500.3

CAS — 129580-63-8.

ATC — L01XA04.

ATC Vet — QL01XA04.

UNII — 8D7B37T28G.

NOTE. The name Orplatna has been used as a trade mark for satraplatin.

Profile

Satraplatin is an analogue of cisplatin (p. 766.1) with generally similar properties, but which is well absorbed after oral dosage. It has been investigated for its antineoplastic properties in the treatment of prostate cancer and other solid tumours. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

References.

1. Kelland LR. An update on satraplatin: the first orally available platinum anticancer drug. *Expert Opin Invest Drugs* 2000; 9: 1373–82.
2. Vouillamoz-Lorenz S, *et al.* Pharmacokinetics of satraplatin (JM216), an oral platinum (IV) complex under daily oral administration for 5 or 14 days. *Anticancer Res* 2003; 23: 2757–65.
3. Sternberg CN, *et al.* Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone-refractory prostate cancer. *Oncology* 2005; 68: 2–9.
4. Sternberg CN. Satraplatin in the treatment of hormone-refractory prostate cancer. *BJU Int* 2005; 96: 990–4.
5. McKeage MJ. Satraplatin in hormone-refractory prostate cancer and other tumour types: pharmacological properties and clinical evaluation. *Drugs* 2007; 67: 859–69.
6. Ricart AD, *et al.* Satraplatin, an oral platinum, administered on a five-day every-five-week schedule: a pharmacokinetic and food effect study. *Clin Cancer Res* 2009; 15: 3866–71.
7. Sternberg CN, *et al.* Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol* 2009; 27: 5431–8.
8. Bhargava A, Vaishampayan UN. Satraplatin: leading the new generation of oral platinum agents. *Expert Opin Invest Drugs* 2009; 18: 1787–97.

Seocalcitol (BAN, rINN)

CB-1089; EB-1089; Séocalcitol; Seocalcitolum; Сеокальцитол.
(5*Z*,7*E*,22*E*,24*E*)-24a,26a,27a-Trihomo-9,10-secocholesta-5,7,10(19),22,24-pentaene-1α,3β,25-triol.
$C_{30}H_{46}O_3$=454.7
CAS — 134404-52-7.
UNII — Q0OZ0D9223.

Profile

Seocalcitol is a vitamin D analogue that has been investigated for the treatment of hepatocellular carcinoma and prostate cancer.

Siplizumab (USAN, rINN)

Medi-507; Siplizumabum; Сиплизумаб.
CAS — 288392-69-8.

Profile

Siplizumab is a humanised anti-CD2 monoclonal antibody under investigation for the treatment of non-Hodgkin's lymphoma and psoriasis, as well as for its immunomodulatory effects after transplantation.

References.

1. Pruett TL, *et al.* Safety profile, pharmacokinetics, and pharmacodynamics of siplizumab, a humanized anti-CD2 monoclonal antibody, in renal allograft recipients. *Transplant Proc* 2009; **41**: 3655–61.
2. Adkins D, *et al.* Safety profile and clinical outcomes in a phase I, placebo-controlled study of siplizumab in acute graft-versus-host disease. *Transplantation* 2009; **88**: 198–202.
3. O'Mahony D, *et al.* EBV-related lymphoproliferative disease complicating therapy with the anti-CD2 monoclonal antibody, siplizumab, in patients with T-cell malignancies. *Clin Cancer Res* 2009; **15**: 2514–22.
4. Langley RG, *et al.* Safety profile of intravenous and subcutaneous siplizumab, an anti-CD2 monoclonal antibody, for the treatment of plaque psoriasis: results of two randomized, double-blind, placebo-controlled studies. *Int J Dermatol* 2010; **49**: 818–28.
5. Brochstein JA, *et al.* Phase-1 study of siplizumab in the treatment of pediatric patients with at least grade II newly diagnosed acute graft-versus-host disease. *Pediatr Transplant* 2010; **14**: 233–41.

Sipuleucel-T (USAN)

APC-8015.
CAS — 917381-47-6.
UNII — 8Q622VDR18.

Pharmacopoeias. In *US*.

USP 36: (Sipuleucel-T). The active components of sipuleucel-T are autologous antigen presenting cells (APCs) and a recombinant protein, PAP-GM-CSF that consists of human prostatic acid phosphatase (PAP) fused through the *C*-terminus to the *N*-terminus of human granulocyte-macrophage colony-stimulating factor (GM-CSF) by a Gly-Ser linker. It is prepared using a patient's own peripheral blood mononuclear cells. Store at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Sipuleucel-T is a personalised cancer vaccine (p. 757.3) prepared by combining a recombinant human fusion protein with antigen-presenting cells isolated from the patient's blood. It is used in the treatment of metastatic, hormone-refractory prostate cancer (p. 712.3). The patient's peripheral blood cells are sampled by leucapheresis about 3 days before the scheduled dose and sent for combination with the protein. The resulting suspension is given as 3 infusions, at intervals of about 2 weeks. Doses are given intravenously over 60 minutes; an in-line filter should not be used. Premedication is recommended (see below), and the infusion rate may be decreased or the infusion stopped if an infusion reaction occurs.

References.

1. Patel PH, Kockler DR. Sipuleucel-T: a vaccine for metastatic, asymptomatic, androgen-independent prostate cancer. *Ann Pharmacother* 2008; **42**: 91–8.
2. Higano CS, *et al.* Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer* 2009; **115**: 3670–9.

Adverse Effects, Treatment, and Precautions

Acute infusion reactions have occurred frequently with sipuleucel-T, including fever, chills, dyspnoea, bronchospasm, nausea, vomiting, fatigue, asthenia, dizziness, headache, muscle ache, hypertension, and tachycardia. Patients with cardiac or pulmonary conditions should be closely monitored. Oral premedication with paracetamol and an antihistamine is recommended, about 30 minutes before infusion. If an infusion reaction occurs, the infusion rate may be decreased, or the infusion stopped depending on the severity of the reaction. Supportive care should also be given.

Cerebrovascular adverse effects have also been reported, such as haemorrhagic and ischaemic strokes. There have been isolated cases of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumour flare. Other possible adverse effects (some of which may be associated with the accompanying leucapheresis procedure) include pain, haematuria, anaemia, muscle spasms, rash, tremor, paraesthesia, citrate toxicity, gastrointestinal disturbances, peripheral oedema, cough, and respiratory-tract and urinary-tract infections. Some patients who required a central venous catheter for treatment with sipuleucel-T developed infections, including sepsis.

Sipuleucel-T is a personalised treatment, and is only suitable for autologous use. It is not routinely tested for transmissible infectious diseases, and healthcare workers should observe handling precautions. Use with immunosuppressants or chemotherapy has not been studied, and caution is advised, as sipuleucel-T is designed to stimulate the immune system. Consideration should be given to stopping or reducing immunosuppressant therapy, if appropriate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Provenge.

Sizofiran (rINN)

Schizophyllan; Sizofirán; Sizofiranum; Сизофиран.
Poly[3→1-(*O*-β-D-glucopyranosyl-(1→3)-*O*-[β-D-glucopyranosyl-(1→6)]-*O*-β-D-glucopyranosyl-(1→3)-*O*-β-D-glucopyranosyl)→1].
$(C_{24}H_{40}O_{20})_n$
CAS — 9050-67-3.

Profile

Sizofiran is a polysaccharide obtained from cultures of the basidiomycete fungus *Schizophyllum commune*. It is reported to have antineoplastic and immunomodulating activity and is given with radiotherapy in malignant neoplasms of the cervix (p. 704.2). It is given by intramuscular injection in usual doses of 40 mg weekly. It has also been tried with chemotherapy or radiotherapy in other malignant neoplasms. Hypersensitivity reactions, including anaphylactoid shock, may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Sonifilan.

Sobuzoxane (rINN)

MST-16; Sobuzoxano; Sobuzoxanum; Собузоксан.
4,4'-Ethylenebis[1-(hydroxymethyl)-2,6-piperazinedione] bis(isobutyl carbonate).
$C_{22}H_{34}N_4O_{10}$=514.5
CAS — 98631-95-9.
UNII — R1308VH37P.

Profile

Sobuzoxane is an orally active inhibitor of topoisomerase II that is used for its antineoplastic properties in the treatment of non-Hodgkin's lymphomas and adult T-cell leukaemia/lymphoma. Adverse effects include myelosuppression, bleeding tendency, renal and hepatic dysfunction, gastrointestinal disturbances, alopecia, headache, and fever.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Okamoto T, *et al.* Long-term administration of oral low-dose topoisomerase II inhibitors, MST-16 and VP-16, for refractory or relapsed non-Hodgkin's lymphoma. *Acta Haematol (Basel)* 2000; **104**: 128–30.
2. Inoue Y, *et al.* Durable remission by sobuzoxane in an HIV-seronegative patient with human herpesvirus 8-negative primary effusion lymphoma. *Int J Hematol* 2004; **79**: 271–5.
3. Swift LP, *et al.* The cardio-protecting agent and topoisomerase II catalytic inhibitor sobuzoxane enhances doxorubicin-DNA adduct mediated cytotoxicity. *Cancer Chemother Pharmacol* 2008; **61**: 739–49.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Perazolin.

Sorafenib (BAN, USAN, rINN)

BAY-43-9006; Sorafénib; Sorafenibum; Сорафений6.
4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*²-methylpyridine-2-carboxamide.
$C_{21}H_{16}ClF_3N_4O_3$=464.8
CAS — 284461-73-0.
ATC — L01XE05.
ATC Vet — QL01XE05.
UNII — 9ZOQ3TZI87.

Sorafenib Tosilate (BANM, rINNM)

BAY-54-9085; Sorafénib, Tosilate de; Sorafenib, tosilato de; Sorafenib Tosylate (USAN); Sorafenibi Tosilas; Сорафениба Тозилат.
4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*²-methylpyridine-2-carboxamide 4-methylbenzenesulfonate.
$C_{21}H_{16}ClF_3N_4O_3$, $C_7H_8O_3S$=637.0
CAS — 475207-59-1.
ATC — L01XE05.
ATC Vet — QL01XE05.
UNII — 5T62Q3B36J.

Uses and Administration

Sorafenib is an inhibitor of multiple intracellular and cell surface kinases thought to be involved in angiogenesis. It is given orally as the tosilate but doses are expressed in terms of the base; sorafenib tosilate 274 mg is equivalent to about 200 mg of sorafenib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Sorafenib is used in the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. The recommended oral dose is 400 mg twice daily, given at least 1 hour before or 2 hours after food. Treatment is continued until no clinical benefit is seen or until unacceptable toxicity occurs. Doses are reduced to 400 mg once daily if toxicity occurs; further reduction to a single dose of 400 mg every other day may be necessary.

Sorafenib is under investigation for the treatment of locally unresectable and metastatic melanoma.

References.

1. Rini BI. Sorafenib. *Expert Opin Pharmacother* 2006; **7**: 453–61.
2. Escudier B, *et al.* TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; **356**: 125–34. Correction. *ibid.*; **357**: 203.
3. McKeage K, Wagstaff AJ. Sorafenib: in advanced renal cancer. *Drugs* 2007; **67**: 475–83.
4. Grandinetti CA, Goldspiel BR. Sorafenib and sunitinib: novel targeted therapies for renal cell cancer. *Pharmacotherapy* 2007; **27**: 1125–44.
5. Takimoto CH, Awada A. Safety and anti-tumor activity of sorafenib (Nexavar) in combination with other anti-cancer agents: a review of clinical trials. *Cancer Chemother Pharmacol* 2008; **61**: 535–48.
6. Hiles JJ, Kolesar JM. Role of sunitinib and sorafenib in the treatment of metastatic renal cell carcinoma. *Am J Health-Syst Pharm* 2008; **65**: 123–31.
7. Keating GM, Santoro A. Sorafenib: a review of its use in advanced hepatocellular carcinoma. *Drugs* 2009; **69**: 223–40.
8. Escudier B, *et al.* TARGET Study Group. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009; **27**: 3312–18.
9. Merseburger AS, *et al.* Sorafenib reveals efficacy in sequential treatment of metastatic renal cell cancer. *Expert Rev Anticancer Ther* 2009; **9**: 1429–34.
10. Hasskarl J. Sorafenib. *Recent Results Cancer Res* 2010; **184**: 61–70.

Administration in hepatic or renal impairment. Sorafenib is mainly metabolised in the liver. Hepatic impairment might reduce exposure to sorafenib. However, exposure is comparable in patients with mild or moderate (Child-Pugh A and B) impairment to that in patients with normal hepatic function. Licensed product information therefore states that no dose adjustment is needed in patients with mild to moderate impairment. No data are available on patients with severe (Child-Pugh C) hepatic impairment.

Licensed product information states that no dose adjustment is needed in patients with mild, moderate, or severe renal impairment, but that no data are available for patients on dialysis.

A study[1] involving patients with varying degrees of hepatic or renal impairment recommended the following empirical starting doses of oral sorafenib, based on tolerability and the development of dose-limiting toxicity in patient cohorts with hepatic impairment:

- mild hepatic dysfunction (bilirubin between upper limit of normal (ULN) and 1.5 X ULN and/or AST > ULN): a standard dose of 400 mg twice daily
- moderate hepatic dysfunction (bilirubin between 1.5 and 3 X ULN, any value of AST): 200 mg twice daily
- severe dysfunction (bilirubin over 3 X ULN, any value of AST): patients were unable to tolerate even 200 mg every third day; however, a separate cohort defined as having very severe dysfunction (albumin less than 25 micro-

grams/mL and any values of bilirubin and AST) were able to tolerate 200 mg daily

Based on the patient cohorts with renal impairment, the following empirical recommendations for initial dose were made:

- mild renal impairment (creatinine clearance (CC) between 59 and 40 mL/minute): the standard dose of 400 mg twice daily
- moderate renal impairment (CC between 39 and 20 mL/minute): 200 mg twice daily
- severe renal impairment (CC less than 20 mL/minute): a dose could not be defined due to low patient numbers enrolled in this cohort
- patients on haemodialysis: 200 mg daily

1. Miller AA, *et al.* Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. *J Clin Oncol* 2009; 27: 1800–5.

Age-related macular degeneration. Two patients with recurrent exudative age-related macular degeneration (AMD; p. 880.2) elected to have oral sorafenib added to their treatment in an attempt to decrease the number of intra-ocular injections; they were treated with 200 mg three times weekly. Vision stabilised or improved in both patients, and neither patient developed serious adverse effects. Although oral sorafenib is not licensed for AMD, the authors suggested that further study of this regimen for refractory or recurrent exudative AMD was warranted.[1]

1. Diago T, *et al.* Ranibizumab combined with low-dose sorafenib for exudative age-related macular degeneration. *Mayo Clin Proc* 2008; 83: 231–4.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. Diarrhoea and dermatological toxicities such as palmar-plantar syndrome and rash are the most common adverse effects with sorafenib. Treatment may include topical therapies, or dose adjustment, or temporary interruption of sorafenib. Congestive heart failure, cardiac ischaemia, and myocardial infarction have been reported with sorafenib, and treatment should be interrupted or stopped in patients who develop ischaemia and/or infarction. Mild to moderate hypertension can occur, which may be manageable with antihypertensive therapy, but severe or persistent hypertension or hypertensive crisis despite treatment, may force sorafenib to be stopped. Blood pressure should be regularly monitored. There is an increased risk of bleeding with sorafenib and fatalities have been reported; if severe enough to need intervention, the drug should be permanently stopped. Leucopenia, lymphopenia, anaemia, neutropenia, and thrombocytopenia are common. Hypophosphataemia and transient disturbances in liver function tests can occur. Elevations in lipase and amylase concentrations are very common. Fatal hepatitis has been reported. Pancreatitis can occur. Renal failure is common. Other adverse effects include alopecia, pruritus, dry skin, erythema, acne, flushing, exfoliative dermatitis, hoarseness, gastrointestinal disturbances, arthralgia, myalgia, asthenia, pain, and peripheral neuropathy. Tinnitus, depression, and erectile dysfunction are often reported, as are pyrexia, flu-like illness, and weight decrease. Gastrointestinal perforation has been reported rarely; therapy should be stopped if it occurs. Reversible posterior leukoencephalopathy has also occurred rarely, as have symptoms suggestive of interstitial lung disease, including pneumonitis and acute respiratory distress syndrome. Other uncommon adverse events include hypersensitivity reactions, changes in thyroid function, hyponatraemia, gynaecomastia, rhinorrhoea, Stevens-Johnson syndrome, and squamous cell carcinoma of the skin. Angioedema and radiation-recall dermatitis can also occur.

References.

1. Robert C, *et al.* Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005; 6: 491–500.
2. Strumberg D, *et al.* Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: is rash associated with treatment outcome? *Eur J Cancer* 2006; 42: 548–56.
3. Veronese ML, *et al.* Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol* 2006; 24: 1363–9.
4. Yang C-H, *et al.* Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol* 2008; 158: 592–6.
5. Lipworth AD, *et al.* Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology* 2009; 77: 257–71.
6. Lee WJ, *et al.* Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Br J Dermatol* 2009; 161: 1045–51.

Effects on the blood. Reversible erythrocytosis occurred in 5 patients treated with sorafenib or sunitinib; onset was relatively rapid over 1 to 2 weeks, reaching a peak at 4 to 9 weeks after the start of tyrosine kinase inhibitor treatment.[1]

1. Alexandrescu DT, *et al.* Secondary erythrocytosis produced by the tyrosine kinase inhibitors sunitinib and sorafenib. *J Clin Oncol* 2008; 26: 4047–8.

Effects on the cardiovascular system. A meta-analysis[1] of data involving 4599 patients indicated that 23.4% of those given *sorafenib* developed hypertension; about 5% of sorafenib-treated patients developed severe (grade 3 or 4) hypertension. This represented a relative risk of developing high blood pressure 6.1 times that of patients not given sorafenib. Hypertension may also develop with other angiogenesis inhibitors; relative risk has been shown to be similar with high-dose *bevacizumab*, and there is evidence of a slightly smaller risk (incidence of hypertension 22.5%, relative risk 3.89) with *sunitinib*.

An observational study[2] in patients taking either sorafenib or sunitinib found that about a third of patients had a cardiovascular event; median duration of tyrosine kinase inhibitor therapy at event occurrence was 8 weeks. Some patients were asymptomatic, with biochemical signs and ECG changes only, whereas others had mild to life-threatening clinical symptoms. All symptomatic and some asymptomatic patients received cardiovascular treatment, recovered, and were considered eligible to resume treatment with the tyrosine kinase inhibitor. The authors considered cardiovascular monitoring as well as prophylactic treatment to be essential; this might allow for continued treatment of the underlying cancer. It was also noted that cardiotoxicity might mimic disease progression.

For reference to the incidence of cardiotoxicity with *lapatinib* see Effects on the Heart, p. 815.3.

1. Wu S, *et al.* Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. *Lancet Oncol* 2008; 9: 117–23.
2. Schmidinger M, *et al.* Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2008; 26: 5204–12.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sorafenib 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 27/09/11)

Interactions

For a general discussion of antineoplastic drug interactions, see p. 733.3. Sorafenib is metabolised by the cytochrome P450 isoenzyme CYP3A4. Rifampicin can reduce exposure to sorafenib. Other inducers of this enzyme (such as carbamazepine, dexamethasone, St John's wort, phenobarbital, and phenytoin) may also reduce blood concentrations of sorafenib. However, ketoconazole did not alter exposure to sorafenib and other drugs that inhibit CYP3A4 are considered unlikely to alter the metabolism of sorafenib.

In vitro studies have indicated that sorafenib itself inhibits the cytochrome P450 isoenzymes CYP3A4, CYP2C19, and CYP2D6, but use of sorafenib with midazolam, or omeprazole, or dextromethorphan did not alter the exposure to any of these drugs; interactions with drugs that are substrates of these enzymes are considered unlikely.

Sorafenib inhibits the cytochrome P450 isoenzyme CYP2C9 *in vitro*, and may increase concentrations of its substrates. Use with warfarin may affect the INR, see Antineoplastics, under Warfarin, p. 1532.2.

Sorafenib also inhibits the isoenzymes CYP2B6 and CYP2C8 *in vitro*, and drug interactions with substrates of these may occur.

Sorafenib may increase exposure to docetaxel, doxorubicin, and irinotecan; variable effects on fluorouracil have been reported. Variable effects have also been seen with paclitaxel; use of continuous sorafenib with paclitaxel and carboplatin caused an increase in sorafenib exposure, an increase in paclitaxel exposure, and an increase in the exposure to 6α-hydroxypaclitaxel, while carboplatin pharmacokinetics were unaffected. Licensed product information states that the clinical significance of these increases is unknown. However, when sorafenib was given 2 days before, and then on the same day as carboplatin plus paclitaxel, it had no significant effect on the pharmacokinetics of paclitaxel; licensed product information advocates no dose adjustments when these 3 drugs are given in this way. Higher mortality was seen in a subset of patients with squamous cell lung carcinoma treated with sorafenib, carboplatin, and paclitaxel compared with those treated with carboplatin plus paclitaxel alone; no definitive cause was identified.

Neomycin interferes with enterohepatic recycling of sorafenib, resulting in decreased exposure to sorafenib.

Pharmacokinetics

Peak plasma concentrations of sorafenib occur about 3 hours after an oral dose. Absorption is reduced by about 30% after a high-fat meal. Plasma protein binding is about 99.5%. Sorafenib is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP3A4. It also undergoes glucuronidation. The elimination half-life of sorafenib is about 25 to 48 hours. About 96% of a dose is excreted within 14 days, with 77%, mostly as unchanged drug, recovered in the faeces, and 19% in the urine as glucuronidated metabolites.

References.

1. Clark JW, *et al.* Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. *Clin Cancer Res* 2005; 11: 5472–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nexavar; *Austral.*: Nexavar; *Austria*: Nexavar; *Belg.*: Nexavar; *Braz.*: Nexavar; *Canad.*: Nexavar; *Chile*: Nexavar; *China*: Nexavar (多吉美); *Cz.*: Nexavar; *Denm.*: Nexavar; *Fr.*: Nexavar; *Ger.*: Nexavar; *Gr.*: Nexavar; *Hong Kong*: Nexavar; *Hung.*: Nexavar; *Indon.*: Nexavar; *Irl.*: Nexavar; *Israel*: Nexavar; *Ital.*: Nexavar; *Malaysia*: Nexavar; *Mex.*: Nexavar; *Neth.*: Nexavar; *Norw.*: Nexavar; *NZ*: Nexavar; *Philipp.*: Nexavar; *Pol.*: Nexavar; *Port.*: Nexavar; *Rus.*: Nexavar (Нексавар); *S.Afr.*: Nexavar; *Singapore*: Nexavar; *Spain*: Nexavar; *Swed.*: Nexavar; *Switz.*: Nexavar; *Thai.*: Nexavar; *Turk.*: Nexavar; *UK*: Nexavar; *USA*: Nexavar.

Streptozocin *(USAN, rINN)*

Estreptozocina; NSC-85998; Streptotsosiini; Streptozocine; Streptozocinum; Streptozosin; Streptozotocin; U-9889; Стрептозоцин.

2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose.

$C_8H_{15}N_3O_7$=265.2

CAS — 18883-66-4.

ATC — L01AD04.

ATC Vet — QL01AD04.

UNII — 5W494URQ81.

Storage. Licensed product information recommends that the freeze-dried streptozocin preparation be stored at 2 degrees to 8 degrees and protected from light.

Uses and Administration

Streptozocin is an antibiotic antineoplastic belonging to the nitrosoureas (see Carmustine, p. 761.2) and is used, alone or with other antineoplastics, mainly in the treatment of pancreatic endocrine (islet-cell) tumours (p. 716.3). It is given by intravenous injection or infusion in doses of 1 g/m² weekly, increased if necessary after 2 weeks to up to 1.5 g/m². Alternatively doses of 500 mg/m² may be given daily for 5 days and repeated every 6 weeks.

It has also been tried in other tumours including exocrine pancreatic cancer and prostate cancer.

Streptozocin has also been given by intra-arterial infusion (but see Adverse Effects below).

Full blood counts, and renal and hepatic function tests should be performed routinely during treatment; doses should be reduced or treatment withdrawn if renal toxicity occurs.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Cumulative nephrotoxicity is common with streptozocin and may be severe and irreversible. Mild proteinuria may be the first sign of toxicity. Intra-arterial use may be associated with more rapid development of nephrotoxicity.

Other adverse effects include severe nausea and vomiting and alterations in liver function or occasionally severe hepatotoxicity. Myelosuppression may occur but is rarely severe. Confusion, lethargy, and depression have been reported in some patients given streptozocin by 5-day continuous infusion. Streptozocin may affect glucose metabolism. A diabetogenic effect has been reported; hypoglycaemia attributed to the release of insulin from damaged cells has also occurred.

Streptozocin is irritant to tissues and extravasation may lead to local ulceration and necrosis.

Streptozocin should be used with extreme care in patients with pre-existing renal impairment.

Handling and disposal. Methods for the destruction of streptozocin *waste* by reaction with hydrobromic acid in glacial acetic acid or by oxidation with a solution of pota-

sium permanganate in sulfuric acid.[1] Residues produced by either method were free of mutagenic activity.

1. Castegnaro M. *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications* 73. Lyon: WHO/International Agency for Research on Cancer, 1985.

Interactions

Streptozocin should not be given with other potentially nephrotoxic drugs. For increased doxorubicin toxicity when given with streptozocin see p. 785.2.

Phenytoin. It has been suggested that because phenytoin appeared to protect the beta cells of the pancreas from the cytotoxic effects of streptozocin, its use with streptozocin should be avoided in patients being treated for pancreatic tumours.[1]

1. Koranyi L, Gero L. Influence of diphenylhydantoin on the effect of streptozotocin. *BMJ* 1979; **1**: 127.

Pharmacokinetics

After intravenous doses streptozocin is rapidly cleared from the blood and distributed to body tissues, particularly the liver, kidneys, intestines, and pancreas. It is extensively metabolised, mainly in the liver and perhaps the kidney, and excreted principally in the urine as metabolites and a small amount of unchanged drug. About 60 to 70% of an intravenous dose is excreted in urine within 24 hours. Some is also excreted via the lungs. Streptozocin itself does not cross the blood-brain barrier but its metabolites are found in the CSF.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Zanosar; *Fr.*: Zanosar; *Gr.*: Zanosar; *Israel*: Zanosar†; *Switz.*: Zanosar†; *USA*: Zanosar.

Sunitinib Malate *(BANM, USAN, rINNM)*

Malato de sunitinib; PHA-290940AD; SU-010398; SU-011248 (sunitinib); Sunitinib, Malate de; Sunitinibi Malas; Сунитиниба малат.

N-[2-(Diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide hydrogen (2*S*)-2-hydroxybutanedioate.

$C_{22}H_{27}FN_4O_2.C_4H_6O_5$=532.6

CAS — 557795-19-4 (sunitinib); 341031-54-7 (sunitinib malate).

ATC — L01XE04.

ATC Vet — QL01XE04.

UNII — LVX8N1UT73.

Uses and Administration

Sunitinib malate is an inhibitor of several receptor tyrosine kinases. It is used for the treatment of gastrointestinal stromal tumours (GIST; see Soft-tissue Sarcoma, p. 718.2) after disease progression during imatinib treatment, or in patients intolerant to imatinib. It is also used for the treatment of advanced and/or metastatic renal cell carcinoma (RCC; p. 708.3). It is also licensed in some countries for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET; p. 716.3).

Sunitinib is given orally as the malate, but doses are expressed in terms of the base; sunitinib malate 66.8 mg is equal to about 50 mg of sunitinib. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

For the treatment of GISTs or RCC, the recommended dose is 50 mg once daily, for 4 weeks of a 6-week treatment cycle. Doses may be increased or decreased in steps of 12.5 mg, based on individual tolerability. UK licensed product information recommends that the daily dose should not normally exceed 75 mg nor be decreased below 25 mg.

For the treatment of pNETs, the recommended dose of sunitinib is 37.5 mg once daily; doses are given continuously. Dose modification is made in steps of 12.5 mg, based on individual tolerability; doses above 50 mg daily in pNETs have not been evaluated.

Use of inhibitors or inducers of CYP3A4 may increase or decrease sunitinib plasma concentrations. If no alternative is available, a dose reduction of sunitinib to a minimum of 37.5 mg daily for GIST or RCC, or 25 mg daily for pNET, should be considered if it is given with a strong CYP3A4 inhibitor. Doses can be increased to a maximum of 87.5 mg daily for GIST or RCC, or 62.5 mg daily for pNET, if sunitinib is given with a CYP3A4 inducer; the patient should be closely monitored for toxicity.

References.

1. Motzer RJ, *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24**: 16–24.
2. Faivre S, *et al.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2006; **24**: 25–35.
3. Motzer RJ, *et al.* Sunitinib malate for the treatment of solid tumours: a review of current clinical data. *Expert Opin Invest Drugs* 2006; **15**: 553–61.
4. Motzer RJ, *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; **295**: 2516–24.
5. Deeks ED, Keating GM. Sunitinib. *Drugs* 2006; **66**: 2255–66.
6. Demetri GD, *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368**: 1329–38.
7. Motzer RJ, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356**: 115–24.
8. Goodman VL, *et al.* Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res* 2007; **13**: 1367–73.
9. O'Brien MF, *et al.* Sunitinib therapy in renal cell carcinoma. *BJU Int* 2008; **101**: 1339–42.
10. Socinski MA. The current status and evolving role of sunitinib in non-small cell lung cancer. *J Thorac Oncol* 2008; **3** (suppl 2): S119–S123.
11. Kulke MH, *et al.* Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol* 2008; **26**: 3403–10.

Adverse Effects, Treatment, and Precautions

Common adverse effects of sunitinib include gastrointestinal disturbances, anorexia, headache, fatigue, fever, hypertension, hypothyroidism, mouth pain or irritation, dry mouth, mucosal inflammation, oedema, taste disturbances, arthralgia, and myalgia. Myelosuppression is common, and complete blood counts should be performed at the beginning of each treatment cycle. Other effects include dizziness, paraesthesia, dyspnoea, alopecia, Yellow skin discoloration and chromaturia can occur. Other dermatological effects include depigmentation of the hair or skin, dryness, rash, exfoliative dermatitis, or palmar-planter syndrome. Gastrointestinal perforation has been reported rarely; fatalities have been reported in patients with intra-abdominal malignancies.

Decreases in left ventricular ejection fraction (LVEF) have occurred with sunitinib; baseline and periodic evaluations of LVEF should be taken. Patients should be monitored for signs of congestive cardiac failure and therapy interrupted or stopped if they occur. Dose reductions may be necessary in patients who show no signs of heart failure but who show decreases in LVEF. Sunitinib may prolong the QT interval and should be used with caution in patients with a history of this, who are taking antiarrhythmics, or who have pre-existing cardiac disease, bradycardia, or electrolyte disturbances.

There is an increased risk of bleeding at all sites; epistaxis is the most common treatment-related bleeding event but fatal pulmonary haemorrhage has occurred in patients with lung cancer. Pulmonary embolism or venous thromboembolic events may occur. Patients under stresses such as surgery, trauma, or severe infection should be monitored for adrenal insufficiency. Increases in serum amylase and lipase concentrations have been seen and there are rare reports of pancreatitis and hepatic failure. There are also rare reports of seizures and reversible posterior leukoencephalopathy syndrome.

Effects on the blood. For a report of reversible erythrocytosis in patients given sunitinib or sorafenib, see Effects on the Blood, under Sorafenib, p. 858.1.

Effects on the cardiovascular system. A retrospective review in 75 patients given repeating cycles of sunitinib in phase I/II studies of its efficacy for gastrointestinal stromal tumours found that cardiovascular events occurred in 8, of whom 6 developed congestive heart failure.[1] Of 36 patients given the subsequently approved dose, 10 had reductions in left ventricular ejection fraction of at least 10%. Hypertension developed in 35 of the 75 patients, and it was suggested that left ventricular dysfunction might be due to a combination of hypertension and a direct toxic effect on heart muscle.

For the relative risk of developing hypertension with sunitinib, and results of a study analysing cardiotoxicity of sunitinib and sorafenib, see under Sorafenib, p. 858.2.

1. Chu TF, *et al.* Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007; **370**: 2011–19.

Effects on the kidneys. For a report of haemolytic-uraemic syndrome after the use of bevacizumab and sunitinib, see Effects on the Kidneys, under Bevacizumab, p. 748.2.

Effects on the musculoskeletal system. As of 31st January 2010, the German manufacturer (*Pfizer*) reported 27 cases of osteonecrosis of the jaw (similar to that seen with the bisphosphonates, see under Bisphosphonates, p. 1176.3) related to sunitinib therapy.[1] There are other reports in cancer patients treated with sunitinib,[2-6] the majority of whom had also received treatment with intravenous bisphosphonates.However, in one case,[4] the patient had never received bisphosphonates, but had previously had dental extraction.

There have been similar reports of bisphosphonate-related osteonecrosis of the jaw in patients given bevacizumab (see under Bevacizumab, p. 748.2) and it has been postulated that the strong anti-angiogenic action of these drugs contributed to oral mucosal breakdown and the subsequent development of osteonecrosis of the jaw.[3] Caution is advised when sunitinib and bisphosphonates are used together or sequentially,[1] and dental care precautions similar to those in patients prescribed bisphosphonates (see under Bisphosphonates, p. 1175.2) are recommended.

1. Kalanovic D, Fricker R. Pfizer, Germany. Mögliches Risiko für das Auftreten einer Kiefernekrose bei mit Sunitinib (Sutent) behandelten Krebspatienten bei gleichzeitiger oder vorheriger Anwendung von Bisphosphonaten (issued 30/11/2010). Available at: http://www.bfarm.de/SharedDocs/1_Downloads/DE/Pharmakovigilanz/rote-HandBriefe/2010/sunitinib.pdf?__blob=publicationFile (accessed 17/12/10)
2. Brunello A, *et al.* Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma. *Bone* 2009; **44**: 173–5.
3. Ayllon J, *et al.* Osteonecrosis of the jaw under bisphosphonate and antiangiogenic therapies: cumulative toxicity profile? *Ann Oncol* 2009; **20**: 600–1.
4. Koch FP, *et al.* Osteonecrosis of the jaw related to sunitinib. *Oral Maxillofac Surg* 2011; **15**: 63–6.
5. Bozas G, *et al.* Osteonecrosis of the jaw after a single bisphosphonate infusion in a patient with metastatic renal cancer treated with sunitinib. *Onkologie* 2010; **33**: 321–3.
6. Hoefert S, Eufinger H. Sunitinib may raise the risk of bisphosphonate-related osteonecrosis of the jaw: presentation of three cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **110**: 463–9.

Effects on the nervous system. Coma has been reported with sunitinib; therapy was immediately stopped and the patient regained consciousness within 24 hours.[1]

1. Arnaud L, *et al.* Transient sunitinib-induced coma in a patient with fibromyxoid sarcoma. *J Clin Oncol* 2008; **26**: 1569–71.

Effects on the skin. Palmar-plantar syndrome is a well-recognised adverse effect of several tyrosine kinase inhibitors, including sunitinib.[1] A patient developed palmar-plantar syndrome and rashes resembling seborrhoeic dermatitis while taking sunitinib. Therapy was stopped and the rash was treated with a topical corticosteroid; blisters on the palms and soles resolved with desquamation.[2] In another report,[3] 5 out of 40 patients treated with sunitinib developed erythema and desquamation in the scrotal and inguinal areas; these effects decreased or disappeared after the drug was stopped, and reappeared upon restarting sunitinib. Histological analysis of 3 specimens mimicked the pathological features of psoriasis. Pyoderma gangrenosum has also been reported.[4]

1. Lipworth AD, *et al.* Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology* 2009; **77**: 257–71.
2. Tsai K-Y, *et al.* Hand-foot syndrome and seborrheic dermatitis-like rash induced by sunitinib in a patient with advanced renal cell carcinoma. *J Clin Oncol* 2006; **24**: 5786–8.
3. Billemont B, *et al.* Scrotal cutaneous side effects of sunitinib. *N Engl J Med* 2008; **359**: 975–6.
4. ten Prcyhaus K, *et al.* Pyoderma gangrenosum: another cutaneous side-effect of sunitinib? *Br J Dermatol* 2008; **159**: 242–3.

Effects on thyroid function. Hypothyroidism is common after sunitinib therapy. A cohort study found that 36% of patients developed hypothyroidism after an average of 50 weeks of therapy. The incidence of hypothyroidism increased with the duration of therapy, and the effect was not transient; patients needed replacement therapy with levothyroxine. Mild thyrotoxicosis may precede the onset of hypothyroidism. Although the mechanism is not clear, the drug may cause destructive thyroiditis. Patients should be screened for hypothyroidism and serum concentrations of thyroid-stimulating hormone (TSH) measured at suggested intervals of 2 to 3 months.[1]

1. Desai J, *et al.* Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med* 2006; **145**: 660–4.

Mucositis. Sunitinib has been reported to cause stomatitis, characterised by bullous and erosive lesions with widespread lichenoid and necrotising areas.[1]

1. Mignogna MD, *et al.* Sunitinib adverse event: oral bullous and lichenoid mucositis. *Ann Pharmacother* 2009; **43**: 546–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sunitinib 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 27/09/11)

Tumour lysis syndrome. Tumour lysis syndrome has been reported after treatment with sunitinib; electrolytes and renal function should be closely monitored.[1,2]

1. Nicholaou T, *et al.* Tumour lysis syndrome in a patient with renal-cell carcinoma treated with sunitinib malate. *Lancet* 2007; **369**: 1923–4.
2. Saylor PJ, Reid TR. Tumor lysis syndrome after treatment of a gastrointestinal stromal tumor with the oral tyrosine kinase inhibitor sunitinib. *J Clin Oncol* 2007; **25**: 3544–6.

Interactions

Sunitinib is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4 to produce an active metabolite, which is further metabolised by CYP3A4. Ketoconazole increased exposure to sunitinib, and use with other potent inhibitors of CYP3A4 (such as other azole antifungals, macrolide antibacterials, HIV-protease inhibitors, or grapefruit juice) may also increase sunitinib concentrations. Conversely, use with rifampicin decreased exposure to sunitinib, and inducers of CYP3A4 (such as dexamethasone, phenytoin, carbamazepine, phenobarbital, or St John's wort) may decrease plasma sunitinib concentrations. If the use of alternative drugs is not feasible, dose adjustments of sunitinib may be necessary (see Uses and Administration, p. 859.1).

Antineoplastics. The US manufacturer of *bevacizumab* has recommended that it should not be used with sunitinib after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1]

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm126434.pdf (accessed 21/07/10)

Pharmacokinetics

Peak plasma concentrations occur 6 to 12 hours after an oral dose of sunitinib. Bioavailability is unaffected by food. Sunitinib is metabolised mainly via the cytochrome P450 isoenzyme CYP3A4 to its primary active metabolite, which itself is then further metabolised via CYP3A4. Plasma protein binding of sunitinib and its metabolite is about 95% and 90%, respectively; plasma elimination half-lives are 40 to 60 hours, and 80 to 110 hours, respectively. Sunitinib is excreted mainly in faeces; about 16% is found in urine, as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sutent; ***Austral.***: Sutent; ***Austria***: Sutent; ***Belg.***: Sutent; ***Braz.***: Sutent; ***Canad.***: Sutent; ***Chile***: Sutent; ***China***: Sutent (索坦); ***Cz.***: Sutent; ***Denm.***: Sutent; ***Fr.***: Sutent; ***Ger.***: Sutent; ***Gr.***: Sutent; ***Hong Kong***: Sutent; ***Hung.***: Sutent; ***Irl.***: Sutent; ***Israel***: Sutent; ***Ital.***: Sutent; ***Jpn***: Sutent; ***Malaysia***: Sutent; ***Mex.***: Sutent; ***Neth.***: Sutent; ***Norw.***: Sutent; ***NZ***: Sutent; ***Philipp.***: Sutent; ***Pol.***: Sutent; ***Port.***: Sutent; ***Rus.***: Sutent (Сутент); ***S.Afr.***: Sutent; ***Singapore***: Sutent; ***Spain***: Sutent; ***Swed.***: Sutent; ***Switz.***: Sutent; ***Thai.***: Sutent; ***Turk.***: Sutent; ***UK***: Sutent; ***Ukr.***: Sutent (Сутент); ***USA***: Sutent.

Talactoferrin Alfa *(USAN, rINN)*

LF-00; rhLF; Talactoferrin; Talactoferrina alfa; Talactoferrine Alfa; Talactoferrinum Alfa; Талактоферрин Альфа.

Lactoferrin (recombinant human LF00).

CAS — 308240-58-6.

UNII — 7A055A9QRR.

Profile

Talactoferrin alfa is a recombinant form of human lactoferrin (p. 2539.3) that acts on the immune system as a dendritic cell recruiter and activator. An oral formulation is under investigation for the treatment of malignancies such as non-small cell lung cancer and renal cell carcinoma. It is also being investigated as an oral treatment for sepsis, and topically as a wound healing agent for diabetic foot ulcers.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.

1. Hayes TG, *et al.* Phase I trial of oral talactoferrin alfa in refractory solid tumors. *Invest New Drugs* 2006; 24: 233–40.
2. Lyons TE, *et al.* Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. *Am J Surg* 2007; 193: 49–54.
3. Jonasch E, *et al.* Phase 2 trial of talactoferrin in previously treated patients with metastatic renal cell carcinoma. *Cancer* 2008; 113: 72–7.
4. Hayes TG, *et al.* Phase IB trial of oral talactoferrin in the treatment of patients with metastatic solid tumors. *Invest New Drugs* 2010; 28: 156–62.

Talaporfin Sodium *(USAN, rINNM)*

LS-11; ME-2906; Monoaspartyl Chlorin e6 (talaporfin); Mono-L-aspartyl chlorin (talaporfin); Natrii Talaporfinum; NPe-6 (talaporfin); Talaporfina sódica; Talaporfine Sodique; Taporfin Sodium; Натрий Талапорфин.

Tetrasodium *N*-[[(7*S*,8*S*)-3-carboxy-7-(2-carboxyethyl)-13-ethenyl-18-ethyl-7,8-dihydro-2,8,12,17-tetramethyl-21*H*,23*H*-porphin-5-yl]acetyl]-L-aspartate.

$C_{38}H_{41}N_5Na_4O_9$=803.7

CAS — 110230-98-3 (talaporfin); 220201-34-3 (talaporfin sodium).

UNII — L63605PZ70.

NOTE. The names Aptocine and Laserphyrin have been used as trade marks for talaporfin sodium.

Profile

Talaporfin sodium is a photosensitiser that is used for the photodynamic therapy (see under Porfimer Sodium, p. 849.1) of lung cancer. It is also under investigation for the treatment of other tumours, such as hepatocellular carcinoma and metastatic colorectal cancer.

References.

1. Wang S, *et al.* Talaporfin sodium. *Expert Opin Pharmacother* 2010; 11: 133–40.

Tamibarotene *(rINN)*

AM-80; NSC-608000; Tamibarotène; Tamibaroteno; Tamibarotenum; Тамибаротен.

N-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)terephthalamic acid.

$C_{22}H_{25}NO_3$=351.4

CAS — 94497-51-5.

UNII — 08V52GZ3H9.

Profile

Tamibarotene is a synthetic retinoid that is given orally for the treatment of relapsed or refractory acute promyelocytic leukaemia. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Malignant neoplasms. Tamibarotene has been used to induce remission in patients with acute promyelocytic leukaemia (see Acute Myeloid Leukaemias, p. 693.1) who relapsed after successful remission induction with tretinoin.[1,2] Twenty-four patients received tamibarotene at a daily oral dose of 6 mg/m^2; 14 patients obtained complete remission after a median of 41 days.[1] Reported adverse effects include hypercholesterolaemia, hypertriglyceridaemia,[1,3] cheilitis, xerosis, gastrointestinal disturbances, bone pain, headache, dermatitis, liver damage, and leucocytosis; in one case, retinoic acid syndrome occurred.[1]

1. Tobita T, *et al.* Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. *Blood* 1997; 90: 967–73.
2. Shinjo K, *et al.* Good prognosis of patients with acute promyelocytic leukemia who achieved second complete remission (CR) with a new retinoid, Am80, after relapse from CR induced by all-trans-retinoic acid. *Int J Hematol* 2000; 72: 470–3.
3. Takeuchi M, *et al.* Relapsed acute promyelocytic leukemia previously treated with all-trans retinoic acid: clinical experience with a new synthetic retinoid, Am-80. *Leuk Lymphoma* 1998; 31: 441–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Amnolake.

Tamoxifen Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de tamoxifeno; ICI-46474; Tamoksifeenisitraatti; Tamoksifen Sitrat; Tamoksifeno citratas; Tamoxifen citrát; Tamoxifencitrat; Tamoxifén-citrát; Tamoxifène, citrate de; Tamoxifeni Citras; Tamoxifeno, citrato de; Тамоксифена Цитрат.

(*Z*)-2-[4-(1,2-Diphenylbut-1-enyl)phenoxy]ethyldimethylamine citrate.

$C_{26}H_{29}NO.C_6H_8O_7$=563.6

CAS — 10540-29-1 (tamoxifen); 54965-24-1 (tamoxifen citrate).

ATC — L02BA01.

ATC Vet — QL02BA01.

UNII — 7FRV7310N6.

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

Ph. Eur. 8: (Tamoxifen Citrate). A white or almost white, polymorphic, crystalline powder. Slightly soluble in water and in acetone; soluble in methyl alcohol.

USP 36: (Tamoxifen Citrate). A white, fine, crystalline powder. Very slightly soluble in water, in alcohol, in acetone, and in chloroform; soluble in methyl alcohol. Protect from light.

Uses and Administration

Tamoxifen is an oestrogen antagonist with actions similar to those of clomifene citrate (see p. 2259.1). It may also inhibit the production or release of cellular growth factors and induce apoptosis. It is used in the adjuvant endocrine therapy of node-positive breast cancer, in the treatment of metastatic disease, and for prophylaxis in women a increased risk including those with ductal carcinoma in situ It has been tried in some other malignancies including tumours of the ovary and in malignant melanoma Tamoxifen is also used to stimulate ovulation in women with anovulatory infertility. See also the cross-references below.

Tamoxifen is given orally as the citrate but doses are calculated in terms of the base; tamoxifen citrate 15.2 mg is equivalent to about 10 mg of tamoxifen. In the treatment of **breast cancer**, usual doses are tamoxifen 20 mg daily, in 2 divided doses or as a single daily dose. Doses of up to 40 mg daily may be given but no additional benefit has been found. Adjuvant therapy is normally continued for up to 5 years, although the optimum duration is still uncertain (p. 702.1). To reduce breast cancer incidence in women at high risk of the disease, the licensed dose of tamoxifen is 20 mg daily for 5 years.

In the treatment of anovulatory **infertility** the usual dose is tamoxifen 20 mg daily on days 2 to 5 of the menstrual cycle, increased if necessary in subsequent cycles up to 80 mg daily. In women with irregular menstruation the initial course may be begun on any day, and a second course begun at a higher dose after 45 days if there has been no response. If the patient responds with menstruation, subsequent courses may begin on day 2 of the cycle.

A topical formulation of 4-hydroxytamoxifen, a metabolite of tamoxifen, is under investigation for the treatment of cyclic mastalgia.

An oral formulation of the tamoxifen metabolite, endoxifen, is under investigation, see Metabolism, p. 864.1.

Reviews.

1. Kramer R, Brown P. Should tamoxifen be used in breast cancer prevention? *Drug Safety* 2004; 27: 979–89.
2. Singh Ranger G. Current concepts in the endocrine therapy of breast cancer: tamoxifen and aromatase inhibitors. *J Clin Pharm Ther* 2005; 30: 313–17.
3. Morales L, *et al.* Choosing between an aromatase inhibitor and tamoxifen in the adjuvant setting. *Curr Opin Oncol* 2005; 17: 559–65.
4. Poole R, Paridaens R. The use of third-generation aromatase inhibitors and tamoxifen in the adjuvant treatment of postmenopausal patients with hormone-dependent breast cancer: evidence based review. *Curr Opin Oncol* 2007; 19: 564–72.
5. Munshi A, Singh P. Tamoxifen in breast cancer: not so easy to write off. *Breast* 2008; 17: 121–4.
6. Beguerie JR, *et al.* Tamoxifen vs. non-tamoxifen treatment for advanced melanoma: a meta-analysis. *Int J Dermatol* 2010; 49: 1194–1202.

Breast disorders, non-malignant. *GYNAECOMASTIA.* Tamoxifen, usually in doses of 10 mg twice daily, has been reported to be effective[1-7] in reducing pain, swelling, and breast size in men or pubertal boys with gynaecomastia (p. 2264.3). Tamoxifen has been recommended as a drug of choice in patients requiring drug therapy, given for 3 months to see if a response occurs.[7] It has also been reported to be effective for the prevention and treatment of gynaecomastia and breast pain caused by the nonsteroidal anti-androgen bicalutamide,[8-11] which is used in the treatment of prostate cancer (see Gynaecomastia under Adverse Effects and Precautions of Flutamide, p. 799.1). A randomised study[12] in patients with prostate cancer treated with bicalutamide found that a daily schedule of tamoxifen was more effective than a weekly schedule in preventing gynaecomastia. In addition, switching to a weekly schedule after a daily schedule was followed by a dramatic increase in the development of gynaecomastia and mastalgia; this became apparent after 6 months of treatment, probably as a result of the study design, in which 2 months of daily treatment was given before switching to the weekly schedule, causing a loading effect.

1. Jefferys DB. Painful gynaecomastia treated with tamoxifen. *BMJ* 1979; 1: 1119–20.
2. Hooper PD. Puberty gynaecomastia. *J R Coll Gen Pract* 1985; 35: 142.
3. McDermott MT, *et al.* Tamoxifen therapy for painful idiopathic gynecomastia. *South Med J* 1990; 83: 1283–5.
4. Ting AC, *et al.* Comparison of tamoxifen with danazol in the management of idiopathic gynecomastia. *Am Surg* 2000; 66: 38–40.
5. Lawrence SE, *et al.* Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. *J Pediatr* 2004; 145: 71–6.
6. Hanavadi S, *et al.* The role of tamoxifen in the management of gynaecomastia. *Breast* 2006; 15: 276–80.
7. Braunstein GD. Gynecomastia. *N Engl J Med* 2007; 357: 1229–37.
8. Saltzstein D, *et al.* Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. *Prostate Cancer Prostatic Dis* 2005; 8: 75–83.
9. Perdonà S, *et al.* Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. *Lancet Oncol* 2005; 6: 295–300.
10. Di Lorenzo G, *et al.* Gynecomastia and breast pain induced by adjuvant therapy with bicalutamide after radical prostatectomy in patients with prostate cancer: the role of tamoxifen and radiotherapy. *J Urol (Baltimore)* 2005; 174: 2197–2203.
11. Fradet Y, *et al.* Tamoxifen as prophylaxis for prevention of gynaecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. *Eur Urol* 2007; 52: 106–14.
12. Bedognetti D, *et al.* An open, randomised, multicentre, phase 3 trial comparing the efficacy of two tamoxifen schedules in preventing gynaecomastia induced by bicalutamide monotherapy in prostate cancer patients. *Eur Urol* 2010; 57: 238–45.

MASTALGIA. Tamoxifen 20 mg daily has been shown to be effective in patients with both cyclic and non-cyclic mastalgia,[1] and improvement has also been reported at a lower dose of 10 mg daily.[2] However, there is concern about the use of tamoxifen in otherwise healthy premenopausal women,[3-5] particularly since many patients relapse on withdrawal,[2] and it has been recommended[6,7] that tamoxifen be reserved for patients who fail to respond to other drugs (see p. 2265.1).

A topical formulation of 4-hydroxytamoxifen, a metabolite of tamoxifen, is under investigation in the treatment of cyclic mastalgia.

1. Fentiman IS, *et al.* Double-blind controlled trial of tamoxifen therapy for mastalgia. *Lancet* 1986; i: 287–8.
2. Fentiman IS, *et al.* Studies of tamoxifen in women with mastalgia. *Br J Clin Pract* 1989; 43 (suppl 68): 34–6.
3. Anonymous. Tamoxifen for benign breast disease. *Lancet* 1986; i: 305.
4. Smallwood JA, Taylor I. Tamoxifen for mastalgia. *Lancet* 1986; i: 680–1.
5. Fentiman IS, *et al.* Tamoxifen for mastalgia. *Lancet* 1986; i: 681.
6. Gateley CA, Mansel RE. Management of the painful and nodular breast. *Br Med Bull* 1991; 47: 284–94.
7. Anonymous. Cyclical breast pain: what works and what doesn't. *Drug Ther Bull* 1992; 30: 1–3.

Cardiovascular disorders. Tamoxifen has been reported to have a generally favourable effect on lipid profiles (see Effects on Blood Lipids, under Adverse Effects, p. 862.1) suggesting it may have cardiovascular benefits.[1] A cohort study of adjuvant tamoxifen found that the drug reduced the incidence of myocardial infarction,[2] and a randomised study of the same therapy also showed a trend towards a decrease in mortality from coronary heart disease.[3] However, in a much larger breast cancer prevention study, tamoxifen did not reduce the risk of, and mortality from, ischaemic heart disease, neither of which differed between placebo and tamoxifen recipients.[4,5] This lack of difference was independent of pre-existing cardiovascular disease.[5] A review[6] noted that while the available data suggested an overall benefit, most of them came from studies in women at low absolute risk of myocardial infarction; studies in men at high absolute risk would be needed to determine whether tamoxifen and related drugs were suitable as cardioprotectants.

1. Pritchard KI, Abramson BL. Cardiovascular health and aromatase inhibitors. *Drugs* 2006; 66: 1727–40.
2. McDonald CC, *et al.* Scottish Cancer Trials Breast Group. Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomised trial. *BMJ* 1995; 311: 977–80.
3. Costantino JP, *et al.* Coronary heart disease mortality and adjuvant tamoxifen therapy. *J Natl Cancer Inst* 1997; 89: 776–82.
4. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; 90: 1371–88.
5. Reis SE, *et al.* Cardiovascular effects of tamoxifen in women with and without heart disease: breast cancer prevention trial. *J Natl Cancer Inst* 2001; 93: 16–21.
6. Grainger DJ, Schofield PM. Tamoxifen for the prevention of myocardial infarction in humans: preclinical and early clinical evidence. *Circulation* 2005; 112: 3018–24.

Disorders related to the menstrual cycle. Apart from cyclic mastalgia (see above) tamoxifen has been used in cases in which disorders were linked to the hormonal changes of the menstrual cycle, including menorrhagia due to myometrial hypertrophy,[1] an auto-immune dermatitis due to post-ovulatory rises in serum progesterone[2,3] (see Effects on the Skin under Progesterone, p. 2301.3), and premenstrual migraine.[4] However, tamoxifen was thought to be a cause of recurrent migraines in another patient, because of its action at oestrogen receptors.[5] Tamoxifen has also been tried in primary dysmenorrhoea.[6]

1. Fraser IS. Menorrhagia due to myometrial hypertrophy: treatment with tamoxifen. *Obstet Gynecol* 1987; 70: 505–6.
2. Wojnarowska F, *et al.* Progesterone-induced erythema multiforme. *J R Soc Med* 1985; 78: 407–8.
3. Stephens CJM, *et al.* Autoimmune progesterone dermatitis responding to tamoxifen. *Br J Dermatol* 1989; 121: 135–7.
4. O'Dea JPK, Davis EH. Tamoxifen in the treatment of menstrual migraine. *Neurology* 1990; 40: 1470–1.
5. Mathew P, Fung F. Recapitulation of menstrual migraine with tamoxifen. *Lancet* 1999; 353: 467–8.
6. Pierzyński P, *et al.* Effect of short-term, low-dose treatment with tamoxifen in patients with primary dysmenorrhea. *Gynecol Endocrinol* 2006; 22: 698–703.

Infertility. Tamoxifen is reported to be as effective as clomifene in the treatment of anovulatory infertility (p. 2253.1) in women,[1-3] and may be useful in women in whom abnormal cervical mucus acts as a barrier to spermatozoa.[4] In infertile men, however, results are reportedly contradictory, with some studies reporting increase in sperm density and improved pregnancy rates while others failed to find any effect.[5] The addition of testosterone may improve outcomes, however, and a later study of men with idiopathic oligozoospermia reported that tamoxifen with testosterone improved sperm variables and pregnancy rates compared with a placebo group (there was no comparison with tamoxifen alone).[6]

1. Messinis IE, Nillius SJ. Comparison between tamoxifen and clomiphene for induction of ovulation. *Acta Obstet Gynecol Scand* 1982; 61: 377–9.
2. Boostanfar R, *et al.* A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. *Fertil Steril* 2001; 75: 1024–6.
3. Steiner AZ, *et al.* Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. *Hum Reprod* 2005; 20: 1511–15.
4. Annapurna V, *et al.* Effect of two anti-estrogens, clomiphene citrate and tamoxifen, on cervical mucus and sperm-cervical mucus interaction. *Int J Fertil* 1997; 42: 215–18.
5. Howards SS. Treatment of male infertility. *N Engl J Med* 1995; 332–17.
6. Adamopoulos DA, *et al.* Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. *Fertil Steril* 2003; 80: 914–20.

Malignant neoplasms. For reference to the use of tamoxifen in malignant neoplasms of breast, ovary, and in cutaneous melanoma, see p. 702.1, p. 711.2, and p. 714.3. The most common use of tamoxifen is for the endocrine therapy of oestrogen-receptor positive early or advanced breast cancer, where there seems to be a clear benefit. How long such therapy should be continued remains uncertain although continuing therapy beyond 5 years may not increase the overall benefit. However, extending therapy by following 5 years of tamoxifen therapy with several years of an aromatase inhibitor such as letrozole (see, p. 817.2) does seem to provide additional benefit.

Extension of tamoxifen use to the attempted prophylaxis of breast cancer has proved controversial (see p. 703.2). Nonetheless, evidence that tamoxifen can reduce short-term incidence of breast cancer in some women at increased risk has been seen, and tamoxifen has been approved for such use in the USA.

Osteoporosis. Tamoxifen has been reported to have favourable effects on bone mass,[1-3] and current use has been associated with a substantial reduction in osteoporotic fractures.[4] However, any general role in the prevention of osteoporosis (p. 1168.1) seems unlikely given concerns about the carcinogenicity of tamoxifen. The effects are reported to be comparable in magnitude to those of calcium supplementation, and less than those of oestrogens (see also p. 2246.1) or bisphosphonates. It has been suggested that such an effect on bone would provide an additional benefit in women receiving tamoxifen for the prophylaxis of breast cancer,[5] although others dispute the benefits.[6]

1. Love RR, *et al.* Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992; 326: 852–6.
2. Love RR, *et al.* Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Arch Intern Med* 1994; 154: 2585–8.
3. Grey AB, *et al.* The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. *Am J Med* 1995; 99: 636–41.
4. Cooke AL, *et al.* Tamoxifen use and osteoporotic fracture risk: a population-based analysis. *J Clin Oncol* 2008; 26: 5227–32.
5. Powles TJ. The case for clinical trials of tamoxifen for prevention of breast cancer. *Lancet* 1992; 340: 1145–7.
6. Fugh-Berman A, Epstein S. Tamoxifen: disease prevention or disease substitution? *Lancet* 1992; 340: 1143–5.

Precocious puberty. Tamoxifen has been reported to be beneficial in the treatment of precocious puberty (p. 2254.1).

Retroperitoneal fibrosis. Tamoxifen may be a viable therapeutic option in the treatment of adults with retroperitoneal fibrosis (p. 1612.1).[1-3] Tamoxifen was successful in treating a prepubertal child with disease that was unresponsive to high-dose corticosteroids.[4]

1. Moroni G, *et al.* Long-term outcome of idiopathic retroperitoneal fibrosis treated with surgical and/or medical approaches. *Nephrol Dial Transplant* 2006; 21: 2485–90.
2. van Bommel EFH, *et al.* Brief communication: tamoxifen therapy for nonmalignant retroperitoneal fibrosis. *Ann Intern Med* 2006; 144: 101–6.
3. Costanzi S, *et al.* A paraneoplastic retroperitoneal fibrosis resistant to corticosteroids treated with tamoxifen. *Clin Nephrol* 2008; 70: 172–5.
4. Dedeoglu F, *et al.* Successful treatment of retroperitoneal fibrosis with tamoxifen in a child. *J Rheumatol* 2001; 28: 1693–5.

Adverse Effects

The most frequent adverse effects of tamoxifen are hot flushes. Other adverse effects include fluid retention, nausea, gastrointestinal intolerance, vaginal bleeding or discharge, pruritus vulvae, rashes, dry skin, and alopecia. There have also been reports of dizziness, headache, depression, confusion, fatigue, and muscle cramps. There may be an increased tendency to thromboembolism, and pulmonary embolism has occurred. Tumour pain and flare may be a sign of response, but hypercalcaemia, sometimes severe, has developed in patients with bony metastases. Transient thrombocytopenia and leucopenia have been reported. Blurred vision and loss of visual acuity, corneal opacities, retinopathies, and cataracts have occurred rarely. Tamoxifen has been associated with increased liver enzymes, and rarely with cholestasis and hepatitis. Hypertriglyceridaemia has occurred. Uterine fibroids and endometrial changes including hyperplasia and polyps may occur, and an increased incidence of endometrial carcinoma, and rarely uterine sarcoma, has been reported. Suppression of menstruation may occur in premenopausal women and cystic ovarian swellings have occasionally occurred. Very rare cases of interstitial pneumonitis have been reported.

Carcinogenicity. Tamoxifen has a stimulant effect on the endometrium (probably by acting as a partial oestrogen agonist) and its use has been associated with the development of endometrial polyps[1,2] and endometriosis,[3] and an increased risk of endometrial cancer.[4-6] The risk, which increases with duration of therapy, is generally agreed to be modest, and the clinical benefit in women with breast cancer outweighs any increased risk of endometrial neoplasm.[7-10] Women taking tamoxifen to prevent breast cancer have been estimated to have a 2.53-fold greater risk of developing endometrial carcinoma than untreated women.[11] The risk may increase with more prolonged use and a case-control study has reported that long-term (over 2 years) users may have a worse prognosis if endometrial cancer develops, due to less favourable history and stage.[12] Another case-control study showed that the relative risk of endometrial cancer increased with duration of tamoxifen treatment, up to at least 10 years. Risk was not associated with the daily dose of tamoxifen, and was comparable in pre- and postmenopausal women.[13]

It has been recommended that women with breast cancer taking tamoxifen should have annual gynaecological examinations, and any unusual symptoms, including abnormal bleeding or spotting should be investigated promptly.[14] Women taking tamoxifen for prophylaxis of breast cancer should be monitored carefully for endometrial hyperplasia. If atypical hyperplasia develops, tamoxifen should be stopped while the condition is treated and a hysterectomy should be considered before tamoxifen is restarted.[14] However, up to 39% of postmenopausal women taking tamoxifen show endometrial changes and as these seldom progress to cancer, the value of routine endometrial biopsies has been questioned.[8,9,14,15] Transvaginal ultrasonography has been used as a noninvasive method of endometrial screening, but has a high rate of false-positive results.[16] It has been suggested that colour doppler ultrasonography, which distinguishes vascularised lesions such as polyps and carcinomas from avascular atrophic lesions, may be a useful alternative.[17] There is some evidence that a levonorgestrel-releasing intra-uterine device can protect against benign endometrial polyps induced by tamoxifen.[18]

Although rare, there is an increase in the risk of uterine sarcoma in women receiving tamoxifen. Between 1978, when tamoxifen was first marketed in the USA, and April 2001, the FDA was aware of 43 cases in women who had been receiving tamoxifen; there had also been reports in 116 women in other countries.[19] Although less than the expected rate in this population, this was considered to be due to underreporting. An evaluation of data from 39 451 breast cancer patients initially treated with tamoxifen found that the overall risk of uterine corpus cancer was more than doubled with the use of tamoxifen; the risk of rare but aggressive forms of uterine tumours, notably malignant mixed mullerian tumours, was increased more than fourfold.[20]

Tamoxifen has been shown to form DNA adducts in *rat* livers, and there has been speculation that it may cause liver cancer in humans. However, there is considerable interspecies variation in the metabolism of tamoxifen and several large-scale clinical studies did not find an increase in liver carcinogenicity in humans.[10] No substantial increase in liver or colorectal cancer has been seen in tamoxifen-treated patients,[21] and there is little evidence of any increased risk for oesophageal cancer.[21,22] Stomach cancer was the most frequently seen secondary cancer in a Japanese cohort study,[21] and a Swedish cohort study concluded that women with breast cancer were at increased risk of gastric adenocarcinoma, and that tamoxifen therapy might play a role.[22] Results from a case-control study in the UK suggested that tamoxifen treatment did not increase the risk of ovarian cancer (although non-hormonal chemotherapy might).[23]

Although in treated women with breast cancer adjuvant tamoxifen reduces the risk of developing a second primary malignancy in the contralateral breast, a case-control study has suggested that 5 or more years of tamoxifen treatment increases the risk, should such a malignancy develop, that it will be oestrogen-receptor negative, and hence harder to treat.[24]

1. Corley D, *et al.* Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy. *Obstet Gynecol* 1992; 79: 111–16.
2. Buijs C, *et al.* Tamoxifen and uterine abnormalities. *J Clin Oncol* 2004; 22: 2505–7.
3. Cano A, *et al.* Tamoxifen and the uterus and endometrium. *Lancet* 1989; i: 376.
4. Fornander T, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989; i: 117–20.
5. Gusberg SB. Tamoxifen for breast cancer: associated endometrial cancer. *Cancer* 1990; 65: 1463–4.
6. van Leeuwen FE, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994; 343: 448–52.
7. Baum M, *et al.* Endometrial cancer during tamoxifen treatment. *Lancet* 1994; 343: 1291.
8. Bissett D, *et al.* Gynaecological monitoring during tamoxifen therapy. *Lancet* 1994; 344: 1244.
9. Neven P, Vergote I. Should tamoxifen users be screened for endometrial lesions? *Lancet* 1998; 351: 155–7.

10. Stearns V, Gelmann EP. Does tamoxifen cause cancer in humans? *J Clin Oncol* 1998; 16: 779–92.
11. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; 90: 1371–88.
12. Bergman L, *et al.* Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. *Lancet* 2000; 356: 881–7.
13. Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. *J Natl Cancer Inst* 2005; 97: 375–84.
14. American College of Obstetrics and Gynaecologists. ACOG Committee Opinion: tamoxifen and endometrial cancer. *Int J Gynaecol Obstet* 1996; 53: 197–9.
15. Barakat RR, *et al.* Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. *J Clin Oncol* 2000; 18: 3459–63.
16. Gerber B, *et al.* Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol* 2000; 18: 3464–70.
17. Aleem FA, Predanic M. Endometrial changes in patients on tamoxifen. *Lancet* 1995; 346: 1292–3.
18. Chin J, *et al.* Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2009 (accessed 20/04/10).
19. Wysowski DK, *et al.* Uterine sarcoma associated with tamoxifen use. *N Engl J Med* 2002; 346: 1832–3.
20. Curtis RE, *et al.* Risk of malignant mixed mullerian tumors after tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004; 96: 70–4.
21. Matsuyama Y, *et al.* Second cancers after adjuvant tamoxifen therapy for breast cancer in Japan. *Ann Oncol* 2000; 11: 1537–43.
22. Chandanos E, *et al.* Tamoxifen exposure and risk of oesophageal and gastric adenocarcinoma: a population-based cohort study of breast cancer patients in Sweden. *Br J Cancer* 2006; 95: 118–22.
23. Swerdlow AJ, Jones ME. Ovarian cancer risk in premenopausal and perimenopausal women treated with Tamoxifen: a case-control study. *Br J Cancer* 2007; 96: 850–5.
24. Li CI, *et al.* Adjuvant hormonal therapy for breast cancer and risk of hormone receptor-specific subtypes of contralateral breast cancer. *Cancer Res* 2009; 69: 6865–70.

Effects on the blood. Pancytopenia developed shortly after beginning tamoxifen therapy in an elderly woman, and persisted for some years;[1] the patient eventually developed very severe leucopenia and died of infection. Thrombocytopenia has also been reported.[2]

1. Miké V, *et al.* Fatal neutropenia associated with long-term tamoxifen therapy. *Lancet* 1994; 344: 541–2.
2. Nastroğlu N, *et al.* Tamoxifen induced-thrombocytopenia: it does occur. *Med Oncol* 2007; 24: 453–4.

Effects on blood lipids. Tamoxifen has been reported to have a generally favourable effect on serum lipid profiles.[1] Patients with breast cancer and subsequent chemotherapy-induced ovarian failure developed marked increases in total cholesterol and low-density lipoprotein levels: adjuvant tamoxifen was found to decrease these serum lipid concentrations to below baseline concentrations. No significant changes in high-density lipoprotein or serum triglyceride concentrations were seen.[2] However, some cases of increased serum triglycerides, mainly in women with pre-existing hypertriglyceridaemia, have been reported.[3-5] Pancreatitis has also resulted.[5] It has been suggested that tamoxifen should be used with caution in patients with hypertriglyceridaemia.[3,4]

1. Love RR, *et al.* Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Ann Intern Med* 1991; 115: 860–4.
2. Vehmanen L, *et al.* Tamoxifen treatment reverses the adverse effects of chemotherapy-induced ovarian failure on serum lipids. *Br J Cancer* 2004; 91: 476–81.
3. Kanel KT, *et al.* Delayed severe hypertriglyceridaemia from tamoxifen. *N Engl J Med* 1997; 337: 281.
4. Colls BM, George PM. Severe hypertriglyceridaemia and hypercholesterolaemia associated with tamoxifen use. *Clin Oncol* 1998; 10: 270–1.
5. Sakhri J, *et al.* Severe acute pancreatitis due to tamoxifen-induced hypertriglyceridemia with positive rechallenge. *JOP* 2010; 11: 382–4.

Effects on bones and joints. Arthralgia has been reported as an adverse effect of generic tamoxifen therapy; however, a crossover study[1] involving 121 postmenopausal women who developed new onset arthralgia during tamoxifen treatment for breast cancer found that arthralgia resolved in 114 when generic tamoxifen was swapped for another brand (*Nolvadex; AstraZeneca, UK*). Arthralgia recurred when the patients resumed taking a generic. It was suggested that possibly the generic tablets included an excipient responsible for symptoms, or Nolvadex contained an excipient with a protective effect.

1. Blencowe NS, *et al.* The use of Nolvadex in the treatment of generic Tamoxifen-associated small joint arthralgia. *Breast* 2010; 19: 243–5.

Effects on the cardiovascular system. *ISCHAEMIC HEART DISEASE.* For discussion of whether the effects of tamoxifen on lipid profiles can alter the incidence of ischaemic heart disease, see Cardiovascular Disorders under Uses and Administration, p. 861.1.

STROKE. An excess risk of stroke was seen in tamoxifen compared with placebo recipients (5 cases versus 1) in a study of adjuvant tamoxifen.[1] A statistically non-significant increase in stroke was also seen in a study on the use of tamoxifen for breast cancer prevention (0.5 excess cases per 1000 women per year).[2] A meta-analysis[3] of 9 studies for prevention or treatment of breast cancer, involved data from 39 601 women, of whom 19 954 received tamoxifen. It concluded that use of tamoxifen increased the risk of ischaemic stroke by 82%, and the risk of any stroke by 29%; however, the absolute increase in risk was small.

In contrast, a case-control study of 11 045 women with breast cancer, found that tamoxifen use was not associated with an increased risk of first stroke.[4]

A time-dependent effect of adjuvant tamoxifen has been seen, with significantly increased morbidity and mortality from cerebrovascular disease, including stroke, during the active treatment period; risk was significantly decreased after treatment was stopped.[5]

1. Dignam JJ, Fisher B. Occurrence of stroke with tamoxifen in NSABP B-24. *Lancet* 2000; 355: 848–9.
2. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; 90: 1371–88.
3. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. *Neurology* 2004; 63: 1230–3.
4. Geiger AM, *et al.* Stroke risk and tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 2004; 96: 1528–36.
5. Rosell J, *et al.* Time dependent effects of adjuvant tamoxifen therapy on cerebrovascular disease: results from a randomised trial. *Br J Cancer* 2011; 104: 899–902.

THROMBOEMBOLISM. A case control study,[1] involving 25 cases of deep-vein thrombosis or pulmonary embolism among more than 10 000 women with breast cancer, suggested that current use of tamoxifen was associated with an estimated relative risk of developing idiopathic venous thromboembolism of 7.1 (95% confidence interval 1.5 to 33). Past use of tamoxifen was not associated with a materially increased risk. In a randomised placebo-controlled study, there was an increase in pulmonary emboli in women receiving tamoxifen for cancer prevention (excess of 0.46 cases per 1000 women per year).[2] The fatality rate from pulmonary emboli in tamoxifen recipients was about 17%. In this study, there was also a trend towards more deep-vein thrombosis in tamoxifen recipients. In another controlled study[3] of breast cancer prevention, tamoxifen approximately doubled the risk of developing a major thromboembolic event such as pulmonary embolism, deep-vein thrombosis, or retinal thrombosis. Cerebral sinus thrombosis has also been reported.[4] An analysis[5] of 4 tamoxifen prevention studies also found that venous thromboembolic events were increased in all studies, with a relative risk of 1.9 for those taking tamoxifen compared with placebo. However, another randomised study[6] found only a borderline significantly higher risk of developing venous thromboembolic events in those women allocated to tamoxifen; most of these events were superficial thrombophlebitis. Furthermore, women already at risk for atherosclerosis had a higher risk of venous thromboembolism. While the authors could not exclude a selection bias for healthier subjects in the study, they commented that the prothrombotic effect of tamoxifen may depend on the patient's existing endocrine status, and may be attenuated in those women taking HRT, especially when it is used transdermally.

1. Meier CR, Jick H. Tamoxifen and risk of idiopathic venous thromboembolism. *Br J Clin Pharmacol* 1998; 45: 608–12.
2. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; 90: 1371–88.
3. Duggan C, *et al.* Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. *J Clin Oncol* 2003; 21: 3588–93.
4. Masjuan J, *et al.* Tamoxifen: a new risk factor for cerebral sinus thrombosis. *Neurology* 2004; 62: 334–5.
5. Cuzick J, *et al.* Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003; 361: 296–300.
6. Decensi A, *et al.* Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. *Circulation* 2005; 111: 650–6.

Effects on the eyes. Tamoxifen has been reported to be associated with decreased visual acuity, corneal opacities and cataract, and retinopathy. The latter is sometimes progressive although in most cases it has shown improvement once the drug was stopped.[1] A prospective study in 63 patients taking tamoxifen 20 mg daily found evidence of decreased visual acuity, macular oedema, and retinal opacities in 4, occurring after 10 to 35 months of therapy.[2] A small excess risk of developing cataracts (3.1 extra per year per 1000 women) and of requiring cataract surgery (1.7 per year per 1000 women) was found in women taking tamoxifen for up to 5 years to reduce the risk of breast cancer.[3] Studies *in vitro* have suggested that cataract formation may be due to inhibition of chloride channels in the lens by tamoxifen or its hydroxy metabolite.[4] Retinopathy after high-dose tamoxifen treatment may be associated with crystalline deposition of the drug in the retina.[5]

1. Mihm LM, Barton TL. Tamoxifen-induced ocular toxicity. *Ann Pharmacother* 1994; 28: 740–2.
2. Pavlidis NA, *et al.* Clear evidence that long-term, low-dose tamoxifen treatment can induce ocular toxicity. *Cancer* 1992; 69: 2961–4.
3. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; 90: 1371–88.
4. Zhang JJ, *et al.* Tamoxifen blocks chloride channels: a possible mechanism for cataract formation. *J Clin Invest* 1994; 94: 1690–7.
5. Bourla DH, *et al.* Peripheral retinopathy and maculopathy in high-dose tamoxifen therapy. *Am J Ophthalmol* 2007; 144: 126–8.

Effects on the genito-urinary system. Persistent nocturna priapism was reported in a man receiving tamoxifer 20 mg daily.[1] Symptoms abated within 24 hours of with drawing the drug. Impotence has been reported in met receiving tamoxifen, and has been attributed to a paradox ical oestrogenic effect.[2]

1. Fernando IN, Tobias JS. Priapism in patient on tamoxifen. *Lancet* 1989; i: 436.
2. Collinson MP, *et al.* Two case reports of tamoxifen as a cause o impotence in male subjects with carcinoma of the breast. *Breast* 1993; 2: 48–9.

Effects on the liver. Cholestasis and increased liver enzyme values have been reported on use of tamoxifen in a 75 year-old patient.[1] Enzyme activity rose again on rechal lenge with tamoxifen. Fatal hepatocellular necrosis an agranulocytosis, possibly exacerbated by continuing t take the drug once jaundice developed, has also beer reported;[2] the authors noted that 4 cases of hepatic failure (3 fatal) and 5 cases of hepatitis (1 fatal) had beer reported to the UK CSM. Patients taking tamoxifen may also develop steatohepatitis,[3-7] which must be distin guished from alcohol-induced liver disease. Steatohepatiti is reversible on withdrawal of tamoxifen.[3,5,6] A study ir healthy women who had had hysterectomies found the risk of steatohepatitis to be particularly high among obese women, moderately high among overweight women, an similar to that with placebo in women of normal weight. Bezafibrate has been tried to prevent progression of steato hepatitis and permit continued use of tamoxifen.[9]

For a report of peliosis hepatis and liver haemorrhage in a patient receiving tamoxifen and warfarin, see Anticoa gulants, under Interactions, p. 863.2.

For reference to studies in *animals* suggesting tha tamoxifen has the potential to cause liver cancer, see Carcinogenicity, p. 861.3.

1. Blackburn AM, *et al.* Tamoxifen and liver damage. *BMJ* 1984; 289: 288
2. Ching CK, *et al.* Tamoxifen-associated hepatocellular damage an agranulocytosis. *Lancet* 1992; 339: 940.
3. Pratt DS, *et al.* Tamoxifen-induced steatohepatitis. *Ann Intern Med* 1995 123: 236.
4. Van Hoof M, *et al.* Tamoxifen-induced steatohepatitis. *Ann Intern Me* 1996; 124: 855–6.
5. Ogawa Y, *et al.* Tamoxifen-induced fatty liver in patients with breas cancer. *Lancet* 1998; 351: 725.
6. Oien KA, *et al.* Cirrhosis with steatohepatitis after adjuvant tamoxifen *Lancet* 1999; 353: 36–7.
7. Osman KA, *et al.* Tamoxifen-induced non-alcoholic steatohepatitis where are we now and where are we going? *Expert Opin Drug Safet* 2007; 6: 1–4.
8. Bruno S, *et al.* Incidence and risk factors for non-alcoholi steatohepatitis: prospective study of 5408 women enrolled in Italia tamoxifen chemoprevention trial. *BMJ* 2005; 330: 932–5.
9. Saibara T, *et al.* Bezafibrate for tamoxifen-induced non-alcoholi steatohepatitis. *Lancet* 1999; 353: 1802.

Effects on the ovaries. Ovarian cysts are relatively com mon as an adverse effect in women receiving adjuvan tamoxifen: a study[1] in 95 such women reported the devel opment of ovarian cysts in 6 of 16 (37.5%) who were pre menopausal and in 5 of 79 postmenopausal womer (6.3%). In 2 of the premenopausal women the cysts were complex. Two women underwent laparotomy for persis tent cysts that were found to be benign, and 1 for leio myoma; the cysts in the other 8 women resolved afte withdrawal of tamoxifen. A study of 142 breast cance patients receiving tamoxifen found ovarian cysts in 2 patients after treatment. Cyst development was more com mon in pre-menopausal women, patients with high oes trogen levels, and patients who did not receive high-dos chemotherapy.[2] There is little evidence that tamoxifer increases the risk of ovarian cancer (see Carcinogenicity p. 861.3).

1. Shushan A, *et al.* Ovarian cysts in premenopausal and postmenopausa tamoxifen-treated women with breast cancer. *Am J Obstet Gynecol* 1996 174: 141–4.
2. Mourits MJE, *et al.* Ovarian cysts in women receiving tamoxifen fo breast cancer. *Br J Cancer* 1999; 79: 1761–64.

Effects on the skin and hair. Vasculitis has been reported in patients given tamoxifen.[1,2] Withdrawal of the drug resulted in complete clearance of the lesions;[1,2] in one case, on re-introduction, purpura developed again within a few days.[1] The results suggest that tamoxifen can produce immune-mediated vascular damage.

In another report a patient with white hair developed darkening and repigmentation of the hair after about 2½ years of tamoxifen therapy.[3] Alopecia has also been reported in women given tamoxifen,[4,5] and in older patients the follicle may not recover.[4]

1. Drago F, *et al.* Tamoxifen and purpuric vasculitis. *Ann Intern Med* 1990 112: 965–6.
2. Baptista MZ, *et al.* Tamoxifen-related vasculitis. *J Clin Oncol* 2006; 24 3504–5.
3. Hampson JP, *et al.* Tamoxifen-induced hair colour change. *Br J Dermatol* 1995; 132: 483–4.
4. Gateley CA, Bundred NJ. Alopecia and breast disease. *BMJ* 1997; 314 481.
5. Ayoub J-PM, *et al.* Tamoxifen-induced female androgenetic alopecia in a patient with breast cancer. *Ann Intern Med* 1997; 126: 745–6.

Precautions

All patients being considered for treatment with tamoxifen should be assessed for any increased risk of thromboembolism. Tamoxifen should not be used for treatment of infertility or the prophylaxis of breast cancer in women with a history of thromboembolic events. When used to treat breast cancer in such women, the risks and benefits should be considered; in some patients, especially those given cytotoxic drugs, prophylactic anticoagulation may be justified. Care is also needed during or immediately after major surgery or prolonged immobility; all patients should be given prophylaxis against thrombosis. In patients being treated for infertility, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility and only restarted when the patient is fully mobile. Patients should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness or any pain in the calf of one leg. Tamoxifen should be withdrawn immediately in any patient developing thromboembolism and appropriate treatment given. Treatment should not usually be restarted for infertility therapy but resumption of tamoxifen with prophylactic anticoagulation may be justified in selected patients with breast cancer.

Women treated with tamoxifen should have routine gynaecological monitoring, and any abnormal symptoms such as menstrual irregularities, abnormal vaginal bleeding or discharge, or pelvic pain should be investigated (see also under Carcinogenicity, p. 861.3). Periodic complete blood counts and liver function tests have been suggested.

Abuse. Although the supervised use of tamoxifen for the treatment of gynaecomastia resulting from the abuse of anabolic steroids has been reported[1] it also appears to be widely used without medical supervision. Tamoxifen can be used to treat idiopathic gynaecomastia and gynaecomastia resulting as an adverse effect of nonsteroidal anti-androgens used to treat prostate cancer (see under Breast Disorders, Non-malignant, p. 860.3).

1. de Luis DA, *et al.* Anabolizantes esteroldeos y ginecomastia: revisión de la literatura. *An Med Interna* 2001; **18:** 489–91.

Breast feeding. Tamoxifen was shown to inhibit lactation in 60 puerperal women.[1] Licensed product information recommends that it should not be given to lactating women as it is unknown if tamoxifen appears in breast milk.

1. Masala A, *et al.* Inhibition of lactation and inhibition of prolactin release after mechanical breast stimulation in puerperal women given tamoxifen or placebo. *Br J Obstet Gynaecol* 1978; **85:** 134–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tamoxifen 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 05/09/11)

Pregnancy. Tamoxifen is contra-indicated in pregnancy. Ambiguous genitalia have been reported in an infant exposed to tamoxifen *in utero*, although no causal link was found.[1] Another infant was born with Goldenhar's syndrome (oculoauriculovertebral dysplasia) after exposure to tamoxifen throughout a 26-week pregnancy.[2] The mother had also taken cocaine and marijuana during the first 6 weeks of pregnancy, and a bone scan using technetium (^{99m}Tc) medronate had been performed. The US manufacturer of tamoxifen (*Zeneca, USA*) was aware of 50 pregnancies in patients taking tamoxifen, resulting in 19 normal births, 8 terminations, 13 unknown outcomes and 10 infants with fetal or neonatal abnormalities.[2]

Tamoxifen has also been used to stimulate ovulation in women with luteal phase dysfunction. In one study tamoxifen was given to 40 women, resulting in 14 pregnancies. Although 9 infants were born with no congenital abnormalities, there were 5 spontaneous abortions, which the authors felt was unacceptably high.[3] Another study, using lower doses of tamoxifen (in some cases sequentially with clomifene), reported 32 pregnancies and only 3 spontaneous abortions in 65 treated patients.[4]

1. Tewari K, *et al.* Ambiguous genitalia in infant exposed to tamoxifen in utero. *Lancet* 1997; **350:** 183.
2. Cullins SL, *et al.* Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. *JAMA* 1994; **271:** 1905–6.
3. Ruiz-Velasco V, *et al.* Chemical inducers of ovulation: comparative results. *Int J Fertil* 1979; **24:** 61–64.
4. Wu CH. Less miscarriage in pregnancy following tamoxifen treatment of infertile patients with luteal phase dysfunction as compared to clomiphene treatment. *Early Pregnancy* 1997; **3:** 301–5.

Radiotherapy. There are reports of radiation recall, with erythema at the site of previous radiotherapy, in patients receiving tamoxifen.[1-3]

1. Parry BR. Radiation recall induced by tamoxifen. *Lancet* 1992; **340:** 49.
2. Extermann M, *et al.* Radiation recall in a patient with breast cancer treated for tuberculosis. *Eur J Clin Pharmacol* 1995; **48:** 77–8.
3. Singer EA, *et al.* Tamoxifen-induced radiation recall dermatitis. *Breast J* 2004; **10:** 170–1.

Interactions

There is a risk of increased anticoagulant effect if tamoxifen is given with coumarin anticoagulants. Conversely, use with cytotoxic drugs may increase the risk of thromboembolic events; prophylactic anticoagulation should be considered. In order to avoid bleeding during a possible thrombocytopenic episode, platelet aggregation inhibitors should not be used with tamoxifen. Tamoxifen increases the dopaminergic effect of bromocriptine; bromocriptine increases serum concentrations of tamoxifen and its major metabolite *N*-desmethyltamoxifen (see Pharmacokinetics, below). Use with inhibitors of cytochrome P450 isoenzyme CYP2D6 has been shown to reduce plasma concentrations of endoxifen, a tamoxifen metabolite (see Pharmacokinetics, below); while the clinical relevance is unclear, a reduced effect of tamoxifen cannot be excluded, and use with potent CYP2D6 inhibitors should be avoided if possible.

Tamoxifen is metabolised by CYP3A4 and care is required when it is used with CYP3A4 inducers, as tamoxifen concentrations may be reduced; plasma concentrations of tamoxifen may be increased by use with CYP3A4 inhibitors.

Preparations of sex hormones, especially oestrogens, should not be used with tamoxifen as a mutual decrease in effect is possible. Medroxyprogesterone decreases concentrations of *N*-desmethyltamoxifen, but not of tamoxifen.

Tamoxifen is metabolised by cytochrome P450 isoenzymes, including CYP2D6 (see Pharmacokinetics, below), and drugs which inhibit CYP2D6 can reduce metabolism and potentially increase the risk of breast cancer recurrence. Recommendations regarding the use of these drugs with tamoxifen have been made:[1]

Potent inhibitors should be avoided; these include the SSRIs paroxetine, fluoxetine, bupropion, and duloxetine (see also Antidepressants, below), and other drugs such as perphenazine, pimozide, thioridazine, quinidine, ticlopidine, terbinafine, and cinacalcet.

Weak to moderate inhibitors should be used with caution, especially in patients considered to be CYP2D6 intermediate metabolisers (see Genetic Factors, below). These include the SSRIs sertraline, citalopram, and fluvoxamine, the tricyclic antidepressants clomipramine, doxepin, desipramine, imipramine, amitriptyline, and nortriptyline, as well as other drugs such as chlorpromazine, fluphenazine, haloperidol, amiodarone, amlodipine, felodipine, nicardipine, nifedipine, verapamil, chloroquine, halofantrine, ritonavir, cimetidine, clemastine, diphenylpyraline, hydroxyzine, promethazine, tripelennamine, and celecoxib.

1. Sideras K, *et al.* Coprescription of tamoxifen and medications that inhibit CYP2D6. *J Clin Oncol* 2010; **28:** 2768–76. Correction. *ibid.*: 3543.

Allopurinol. For reference to exacerbation of hepatotoxicity when tamoxifen was given with allopurinol, see p. 603.1.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of tamoxifen in 10 healthy subjects. This was thought to be due to induction of cytochrome P450 isoenzyme CYP3A4 by rifampicin.[1]

1. Kivistö KT, *et al.* Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* 1998; **64:** 648–54.

Anticoagulants. Cases of a potentially life-threatening interaction between tamoxifen and *warfarin*, with marked prolongation of prothrombin times, haematuria, and haematoma, have been reported.[1-3] It has been suggested that in addition to enhancement of the effects of warfarin, competition for the same metabolic enzyme systems might reduce the activity of tamoxifen against tumours,[2] but this remains speculative.

Peliosis hepatis and fatal liver haemorrhage have been reported in a patient who was receiving tamoxifen with warfarin and a liothyronine-levothyroxine preparation.[4]

1. Lodwick R, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1987; **295:** 1141.
2. Tenni P, *et al.* Life threatening interaction between tamoxifen and warfarin. *BMJ* 1989; **298:** 93.
3. Ritchie LD, Grant SMT. Tamoxifen-warfarin interaction: the Aberdeen hospitals drug file. *BMJ* 1989; **298:** 1253.
4. Loomus GN, *et al.* A case of pelliosis hepatis in association with tamoxifen therapy. *Am J Clin Pathol* 1983; **80:** 881–3.

Antidepressants. Some antidepressants, particularly *SSRIs*, may inhibit the bioactivation of tamoxifen via the cytochrome P450 isoenzyme CYP2D6. The metabolism of tamoxifen to an active metabolite, 4-hydroxy-*N*-desmethyltamoxifen (endoxifen), may be inhibited by *paroxetine*, a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6.[1] However, the clinical consequences of this are not fully established. A case-control study[2] found that patients taking tamoxifen with known inhibitors of CYP isoenzymes, including CYP2D6, were no more likely to relapse than those not receiving a CYP inhibitor. However, a retrospective cohort study[3] found that paroxetine use during tamoxifen treatment was associated with an increased risk of death from breast cancer. The increased risk was directly related to the duration of combined use, and supports the hypothesis that irreversible CYP2D6 inhibition by paroxetine can reduce or abolish the survival advantage conferred by long-term tamoxifen treatment in patients with breast cancer. In contrast, no such risk was seen with other antidepressants (*citalopram, fluoxetine, fluvoxamine, sertraline,* and *venlafaxine*), although smaller sample sizes for some may have influenced results. Some consider that potent CYP2D6 inhibitors such as bupropion, paroxetine, and fluoxetine should be avoided in women with breast cancer taking tamoxifen, and antidepressants with a low potential to inhibit CYP2D6 (such as venlafaxine or citalopram) should be considered instead.[4-6] Caution is warranted even with moderate CYP2D6 inhibitors such as duloxetine and sertraline.[6]

For further reference to use of CYPD26 inhibitors with tamoxifen, including a slightly different classification for some of the SSRIs mentioned here, see above.

1. Stearns V, *et al.* Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst* 2003; **95:** 1758–64.
2. Lehmann D, *et al.* Lack of attenuation in the antitumor effect of tamoxifen by chronic CYP isoform inhibition. *J Clin Pharmacol* 2004; **44:** 861–5.
3. Kelly CM, *et al.* Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ* 2010; **340:** c693. Available at: http://www.bmj.com/cgi/reprint/340/feb08_1/c693 (accessed 20/04/10)
4. Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants *via* cytochrome P450 2D6. *J Clin Psychiatry* 2009; **70:** 1688–97.
5. Andersohn F, Willich SN. Interaction of serotonin reuptake inhibitors with tamoxifen. *BMJ* 2010; **340:** c783. Available at: http://www.bmj.com/cgi/section_pdf/340/feb08_3/c783.pdf (accessed 20/04/10)
6. Anonymous. Drug interaction between tamoxifen and antidepressants. *Aust Prescriber* 2011; **34:** 23.

Antineoplastics. *Aminoglutethimide* reduces serum tamoxifen concentrations, possibly by increasing its metabolism.[1] For mention of an increased risk of haemolytic-uraemic syndrome in patients who received therapy with tamoxifen and *mitomycin* see Effects on the Kidneys, under Mitomycin, p. 831.3. Tamoxifen has been reported to affect plasma concentrations of *anastrozole* and *letrozole*, see p. 743.1 and p. 817.3, respectively.

1. Lien EA, *et al.* Decreased serum concentrations of tamoxifen and its metabolites induced by aminoglutethimide. *Cancer Res* 1990; **50:** 5851–7.

Herbal medicines. Some authors have expressed concern that herbs such as *dong quai* (which has been used to relieve hot flushes after chemotherapy for breast cancer), *agnus castus, cimicifuga, ginseng,* and *lupulus* have shown significant oestrogenic activity in studies in *animals* and *in vitro*,[1-3] and might interfere with competitive oestrogen receptor antagonists such as tamoxifen.[1]

1. Boyle FM. Adverse interaction of herbal medicine with breast cancer treatment. *Med J Aust* 1997; **167:** 286.
2. Eagon CL, *et al.* Medicinal botanicals: estrogenicity in rat uterus and liver. *Proc Am Assoc Cancer Res* 1997; **38:** 293.
3. Doyle BJ, *et al.* Estrogenic effects of herbal medicines from Costa Rica used for the management of menopausal symptoms. *Menopause* 2009; **16:** 748–55.

Immunosuppressants. For the results of a study *in vitro* suggesting that tamoxifen might inhibit the metabolism of *tacrolimus* by inhibiting the cytochrome P450 isoenzyme system, see under Interactions of Tacrolimus, p. 1977.3.

Neuromuscular blockers. For reference to prolonged neuromuscular blockade in a patient given *atracurium* while receiving tamoxifen, see p. 2032.2.

Pharmacokinetics

Peak plasma concentrations of tamoxifen occur 4 to 7 hours after an oral dose. It is extensively protein bound. Plasma clearance is reported to be biphasic and the terminal half-life may be up to 7 days. It is extensively metabolised by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6. The major serum metabolite, *N*-desmethyltamoxifen is formed mainly via CYP3A4; it has a half-life at steady state of about 14 days. 4-Hydroxytamoxifen is a minor metabolite. *N*-Desmethyltamoxifen and 4-hydroxytamoxifen are further metabolised (via CYP2D6 and the CYP3A family, respectively) to 4-hydroxy-*N*-desmethyltamoxifen (endoxifen). Several of the metabolites are stated to have similar pharmacological activity to the parent compound, and endoxifen has been proposed as an alternative treatment to avoid differences in metabolism (see Metabolism, p. 864.1). Tamoxifen is excreted slowly in the faeces, mainly as conjugates. Small amounts are excreted in urine. Tamoxifen appears to undergo enterohepatic circulation.

Genetic factors. Tamoxifen is metabolised by the cytochrome P450 isoenzymes, and its metabolites may play a role in its antineoplastic effect. Studies have suggested that

patients with low or absent CYP2D6 activity or who are being treated with CYP2D6 inhibitors have lower concentrations of endoxifen. Patients with CYP2D6*3, *4, *5, and *6 alleles are designated as poor metabolisers, those with *9, *10, *17, *29, and *41 as intermediate metabolisers, and those with *1, *2, and *35 as extensive metabolisers.[1,2] Genetic polymorphism in the enzymes responsible for tamoxifen biotransformation has the potential to affect clinical outcomes. While a small study[3] showed a decreased risk of breast cancer recurrence in patients with the CYP2D6*4 allele when treated with tamoxifen, another[4] found that this allele was an independent predictor of a higher risk of disease relapse and a lower incidence of hot flashes in postmenopausal women with breast cancer. A further study[5] found that carriers of CYP2D6 alleles *4 or *5 showed a greater risk for breast cancer relapse. Furthermore, carriers of the CYP2C19*17 genotype had a more favourable clinical outcome. A retrospective cohort study found that poor metabolisers had an almost twofold increased risk of breast cancer recurrence compared with extensive metabolisers; those with decreased CYP2D6 activity (intermediate and poor metabolisers) also had worse disease-free survival compared with extensive metabolisers, although there was no significant difference in overall survival.[6] The Clinical Pharmacology Subcommittee of the US FDA Advisory Committee for Pharmaceutical Science has advised that availability of genotypic testing be included in licensed product information for tamoxifen.[7,8] Some have commented[8] that it would seem reasonable to confine CYP2D6 testing to situations where it might guide the choice between tamoxifen and an alternative.

It has been suggested[9] that genetic variation in uridine diphosphate glucuronosyltransferase (UGT) enzymes, which are important in the glucuronidation of tamoxifen and its metabolites, may also play a role in interindividual differences in response to the drug.

1. Borges S, *et al.* Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. *Clin Pharmacol Ther* 2006; **80**: 61–74.
2. Goetz MP, *et al.* Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. *Clin Pharmacol Ther* 2008; **83**: 160–6.
3. Wegman P, *et al.* Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. *Breast Cancer Res* 2005; **7**: R284–R290.
4. Goetz MP, *et al.* Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005; **23**: 9312–18.
5. Schroth W, *et al.* Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol* 2007; **25**: 5187–93.
6. Schroth W, *et al.* Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA* 2009; **302**: 1429–36.
7. Young D. Genetics examined in tamoxifen's effectiveness: recurrence warning urged for labeling. *Am J Health-Syst Pharm* 2006; **63**: 2286, 2296.
8. Desta Z, Flockhart DA. Germline pharmacogenetics of tamoxifen response: have we learned enough? *J Clin Oncol* 2007; **25**: 5147–9.
9. Lazarus P, *et al.* Potential role of UGT pharmacogenetics in cancer treatment and prevention: focus on tamoxifen. *Ann N Y Acad Sci* 2009; **1155**: 99–111.

Metabolism. Tamoxifen is extensively metabolised by cytochrome P450 isoenzymes, to active metabolites that include *N*-desmethyltamoxifen, 4-hydroxytamoxifen, and 4-hydroxy-*N*-desmethyltamoxifen (endoxifen).[1,2] *In-vitro* studies suggest that both *N*-desmethyltamoxifen and 4-hydroxytamoxifen are further metabolised to endoxifen.[3] There is growing interest in how genetic polymorphism might influence the efficacy and toxicity of tamoxifen and its metabolites (see Genetic Factors, p. 863.3). Substitution of endoxifen for tamoxifen has been proposed as a treatment option for patients with breast cancer in order to avoid any effects of genetic polymorphisms as well as any interactions with cytochrome P450 isoenzyme CYP2D6 inhibitors (see under Interactions, p. 863.2). The safety, tolerability, and bioavailability of an oral formulation of endoxifen has been evaluated; a daily dose of 4 mg endoxifen citrate has been proposed as being appropriate for breast cancer prevention and therapy.[2]

1. Rochat B. Role of cytochrome P450 activity in the fate of anticancer agents and in drug resistance: focus on tamoxifen, paclitaxel and imatinib metabolism. *Clin Pharmacokinet* 2005; **44**: 349–66.
2. Ahmad A, *et al.* Endoxifen, a new cornerstone of breast cancer therapy: demonstration of safety, tolerability, and systemic bioavailability in healthy human subjects. *Clin Pharmacol Ther* 2010; **88**: 814–7.
3. Desta Z, *et al.* Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. *J Pharmacol Exp Ther* 2004; **310**: 1062–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Crisafeno; Diemon†; Ginarsan; Nolvadex; Rolapt†; Tamoxis; Taxfeno†; Trimetrox†; *Austral.*: Genox; Nolvadex; Tamosin; Tamoxen; *Austria*: Ebefen; Nolvadex; *Belg.*: Doctamoxifene†; Nolvadex; Tamizam; Tamoplex; *Braz.*: Bioxifeno†; Festone; Kessar†; Nolvadex; Tamoxin; Taxofen; Tecnotax; *Canad.*: Apo-Tamox; Nolvadex; Tamofen†; *Chile*: Kessar; Nolvadex; Oncotamox†; Taxus; *China*: De Fu Ling (德孚伶); Tamofen (特莱芬); Xifen (昔芬); *Cz.*: Nolvadex†; Tamoplex; Zitazonium†; *Fin.*: Tadex; Tamexin†; Tamofen; *Fr.*: Nolvadex; *Ger.*: Mandofen†; Nolvadex; Tamokadin†; Tamox†; Tamoxistad†; *Gr.*: Adifen; Defarol; Kessar; Nolvadex; Puretam; Tamoplex; Terimon; Zymoplex; *Hong Kong*: Apo-Tamox; Nolvadex; Novofen†; Zitazonium; *Hung.*: Zitazonium; *India*: Blastofen; Caditam; Cytotam; Eldtam; Mamofen; Moxifen; Neotam; Nolvadex; Oncomox; Oncotam; Tamodex; *Indon.*: Nolvadex†; Tamofen; Tamoplex; Taxen†; *Irl.*: Moxelle; Nolvadex; Soltamox; Tamox; *Israel*: Nolvadex†; Tamofen†; Tamoxi†; *Ital.*: Kessar; Nolvadex; Nomafen; Tamoxene; *Malaysia*: Genox†; Nolvadex; Novofen; Tamoplex; Zitazonium; *Mex.*: Bagotam†; Bilem; Cryoxifeno; Fenobest; Luzamoxin; Nolvadex; Ralsifen-X; Taxus; Tecnofen; *Neth.*: Nolvadex†; Soltamox; *Norw.*: Nolvadex; *NZ*: Genox; Nolvadex†; Tamofen†; *Philipp.*: Cytrolic†; Fenahex; Gynatam; Gyraxen; Kessar†; Medtax; Nolvadex; Tamoplex; Tamoxsta†; Xifen; Zitazonium; *Pol.*: Nolvadex; *Port.*: Mastofen†; Nolvadex; Tamoxan; *Rus.*: Tamifen (Тамифен)†; Zitazonium (Зитазониум); *S.Afr.*: Kessar; Neophedan; Nolvadex; Tamoplex; TamoxiHexal; *Singapore*: Apo-Tamox†; Nolvadex; Novofen; Tamofen†; *Spain*: Nolvadex; Yacesal†; *Swed.*: Nolvadex; *Switz.*: Nolvadex; Tamec; *Thai.*: Bilem; Gynatam†; Mamofen; Moxafen†; Nolvadex; Novofen; Tamoplex; Tuosomin†; Zitazonium; *Turk.*: Nolvadex; Tadex; Tamofen†; Tamoplex; Tamoxifencell; *UAE*: Tamophar; *UK*: Nolvadex†; Soltamox; *USA*: Soltamox; *Venez.*: Gynatam; Nolvadex; Taxus.

Pharmacopoeial Preparations
BP 2014: Tamoxifen Tablets;
USP 36: Tamoxifen Citrate Tablets.

Tegafur *(BAN, USAN, rINN)*

FT-207; Ftorafur; MJF-12264; NSC-148958; Tegafúr; Tégafur; Tegafuras; Tegafūrs; Tegafurum; Tegafuuri; WR-220066; Тегафур.

5-Fluoro-1-(tetrahydro-2-furyl)uracil; 5-Fluoro-1-(tetrahydro-2-furyl)pyrimidine-2,4(1*H*,3*H*)-dione.

$C_8H_9FN_2O_3$=200.2

CAS — 17902-23-7.

ATC — L01BC03.

ATC Vet — QL01BC03.

UNII — 1548R74NSZ.

NOTE. The name S-1 has been used for a mixture of tegafur, gimeracil, and oteracil potassium.

Pharmacopoeias. In *Chin.* and *Jpn.*

Uses and Administration

Tegafur is considered to be an orally active prodrug of fluorouracil (p. 795.3). It has been used in the management of malignant neoplasms including those of the breast, gallbladder, gastrointestinal tract, head and neck, liver, and pancreas. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Tegafur has been given orally in doses up to 1 g/m² daily. It is often given with uracil (UFT; p. 2637.3). Tegafur 300 mg/m² daily, with uracil 672 mg/m² daily, may be given in 3 divided oral doses, together with calcium folinate, in the management of metastatic colorectal cancer. Doses are given for a cycle of 28 days, followed by 7 days without treatment. The drugs should be taken 1 hour before or after meals, and doses modified according to toxicity. Doses of tegafur 1 to 3 g/m² daily for 5 days have been given **intravenously.**

Administration. Tegafur is an orally active prodrug of fluorouracil. Although it has been given as a single agent, it is more often used with drugs that modify its bioavailability and toxicity.[1] These include uracil (p. 2637.3) and gimeracil (5-chloro-2,4-dihydroxypyridine, CDHP, gimestat), which can increase fluorouracil concentrations by inhibition of dihydropyrimidine dehydrogenase, the enzyme responsible for its further catabolism,[1-4] and oteracil (oxonic acid), which inhibits another enzyme, orotate pyrimidine phosphoribosyl transferase, thought to play a role in the gastrointestinal toxicity of fluorouracil and its prodrugs.[2]

UFT consists of tegafur and uracil in the optimal molar ratio 1:4.[1] It is available for the treatment of colorectal cancer (p. 706.3)—for doses, see above. A preliminary analysis of a large study comparing oral UFT and calcium folinate therapy with intravenous fluorouracil and calcium folinate found both regimens to be well tolerated with similar levels of toxicity.[5] It is also used as adjuvant therapy for gastrointestinal and other solid tumours,[6] including being tried in hepatocellular carcinoma;[7] it appears to improve survival in patients with adenocarcinoma of the lung[8] and node-negative breast cancer.[9] The efficacy of tegafur-based adjuvant therapy in Japanese patients with stomach cancer has been reviewed.[10]

A combination of tegafur, gimeracil, and oteracil potassium in the molar ratio 10:4:10 (TS-1, *Taiho Jpn*) has been tried in gastric and colorectal cancers.[2-4,11] Initial results have suggested comparable activity to fluorouracil and calcium folinate in induction regimens but the incidence of diarrhoea and stomatitis was reduced.

1. Adjei AA. A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer. *Br J Clin Pharmacol* 1999; **48**: 265–77.
2. Sakata Y, *et al.* Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34**: 1715–20.
3. Sugimachi K, *et al.* An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. *Oncology* 1999; **57**: 202–10.
4. Onugi H, *et al.* Oral fluoropyrimidine anticancer drug TS-1 for gastric cancer patients with peritoneal dissemination. *Oncol Rep* 2002; **9**: 81 – 15.
5. Smith R, *et al.* UFT plus calcium folinate vs 5-FU plus calcium folinate in colon cancer. *Oncology (Huntingt)* 1999; **13** (suppl 3): 44–7.
6. Tanaka F. UFT (tegafur and uracil) as postoperative adjuvant chemotherapy for solid tumors (carcinoma of the lung, stomach, colon/rectum, and breast): clinical evidence, mechanism of action, and future direction. *Surg Today* 2007; **37**: 923–43.
7. Ishikawa T. Chemotherapy with enteric-coated tegafur/uracil for advanced hepatocellular carcinoma. *World J Gastroenterol* 2008; **14**: 2797–2801.
8. Kato H, *et al.* A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; **350**: 1713 – 21.
9. Noguchi S, *et al.* Postoperative adjuvant therapy with tamoxifen, tegafur plus uracil, or both in women with node-negative breast cancer: a pooled analysis of six randomized controlled trials. *J Clin Oncol* 2005; **23**: 2172–84.
10. Oba K. Efficacy of adjuvant chemotherapy using tegafur-based regimens for curatively resected gastric cancer: update of a meta-analysis. *Int J Clin Oncol* 2009; **14**: 85–9.
11. Shibahara K, *et al.* Retrospective study of S-1 versus tegafur/uracil and leucovorin in patients with metastatic colorectal cancer. *Anticancer Res* 2008; **28**: 1779–83.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p. 797.1.

Bone-marrow depression may be less severe with tegafur but gastrointestinal toxicity is often dose-limiting and central neurotoxicity is more common. Peripheral oedema and dyspnoea occur commonly. Increases in liver function test values are common and there are reports of fatal fulminant hepatitis. Liver function should be monitored in patients with hepatic impairment given tegafur; it should not be given in severe hepatic impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tegafur 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 29/09/11)

Interactions

Tegafur should not be used with drugs that inhibit dihydropyrimidine dehydrogenase; fatalities have occurred in patients given tegafur and sorivudine (see Antivirals under Interactions of Fluorouracil, p. 797.3). For the effect of tegafur with uracil on phenytoin, see p. 544.1.

Pharmacokinetics

Tegafur is well absorbed from the gastrointestinal tract after oral doses. After an intravenous dose it is reported to have a prolonged plasma half-life of 6 to 16 hours. Tegafur appears to be slowly metabolised in the liver to fluorouracil (p. 798.1), and some intracellular conversion to fluorouracil may also occur. Tegafur crosses the blood-brain barrier and is found in the CSF.

References.
1. Etienne-Grimaldi M-C, *et al.* A clinical pharmacokinetic analysis of tegafur-uracil (UFT) plus leucovorin given in a new twice-daily oral administration schedule. *Clin Pharmacokinet* 2007; **46**: 953–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Aisiwan (爱斯万)†; Qi Xing (岐星); *Cz.*: Ftorafur; *Gr.*: Ftorafur; *Hong Kong*: Futraful†; *Hung.*: Ftorafur; *Indon.*: Futraful; *Jpn*: Futraful; *Rus.*: Ftorafur (Фторафур); *Spain*: Utefos; *Ukr.*: Ftorafur (Фторафур).

Multi-ingredient Preparations. *Arg.*: Asofurtal; Fimer; UFT; *Austria*: UFT; *Belg.*: UFT; *Braz.*: UFT; *China*: S-1 (爱斯万); Weikangda (维康达); *Cz.*: Teysuno; UFT†; *Denm.*: Teysuno; UFT; Uftoral†; *Fr.*: UFT; *Ger.*: UFT; *Gr.*: UFT; *Hong Kong*: UFT†; *Hung.*: UFT†; *Irl.*: Teysuno; UFT†; *Israel*: UFT; *Ital.*: UFT; *Jpn*: TS-1; UFT; *Malaysia*: UFT; *Mex.*: UFT; *Neth.*: Teysuno; UFT; *Norw.*: Teysuno; UFT†; *Philipp.*: Tefudex; UFT; *Pol.*: UFT; *Port.*: UFT; *Rus.*: UFT (УФТ); *S.Afr.*: UFT; *Singapore*: TS-One; UFT; *Spain*: UFT†; *Swed.*: Teysuno; UFT†; *Thai.*: TS-One; UFT†; UFUR; *Turk.*: UFT; *UK*: Teysuno; Uftoral†.

Temoporfin (BAN, USAN, rINN)

EF-9; *meso*-Tetrahydroxyphenylchlorin; *meta*-Tetrahydroxyphenylchlorin; mTHPC; Temoporfini; Temoporfina; Témoporfine; Temoporfinum; Темопорфин.

3,3′,3″,3‴-(7,8-Dihydroporphyrin-5,10,15,20-tetrayl)tetraphenol; 7,8-Dihydro-5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin.

$C_{44}H_{32}N_4O_4$=680.8

CAS — 122341-38-2.

ATC — L01XD05.

ATC Vet — QL01XD05.

UNII — FU21S769PF.

Uses and Administration

Temoporfin is a porphyrin derivative. It is used palliatively as a photosensitiser in the photodynamic therapy (see under Porfimer Sodium, p. 849.1) of refractory squamous cell carcinoma of the head and neck (p. 708.1), that cannot be treated with radiotherapy, surgery, or systemic chemotherapy. It is also under investigation in the treatment of various other malignant neoplasms. Temoporfin is given by slow intravenous injection over at least 6 minutes, at a dose of 150 micrograms/kg. This is followed 96 hours later by activation using a laser tuned to a wavelength of 652 nanometres for about 200 seconds, sufficient to supply a dose of 20 J/cm^2. This should take place not less than 90 hours and not more than 110 hours after injection. Treatment may be repeated once after at least 4 weeks if necessary.

Liposomal formulations for topical delivery of temoporfin are under investigation.

References.

1. Kubler AC, *et al.* Photodynamic therapy of primary nonmelanomatous skin tumours of the head and neck. *Lasers Surg Med* 1999; **25**: 60–8.
2. Baas P, *et al.* Photodynamic therapy with *meta*-tetrahydroxyphenylchlorin for basal cell carcinoma: a phase I/II study. *Br J Dermatol* 2001; **145**: 75–8.
3. Kubler AC, *et al.* Treatment of squamous cell carcinoma of the lip using Foscan-mediated photodynamic therapy. *Int J Oral Maxillofac Surg* 2001; **30**: 504–9.
4. Javaid B, *et al.* Photodynamic therapy (PDT) for oesophageal dysplasia and early carcinoma with mTHPC (m-tetrahydroxyphenyl chlorin): a preliminary study. *Lasers Med Sci* 2002; **17**: 51–6.
5. Friedberg JS, *et al.* A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma. *Ann Thorac Surg* 2003; **75**: 952–9.
6. Copper MP, *et al.* Meta-tetra(hydroxyphenyl)chlorin photodynamic therapy in early-stage squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 2003; **129**: 709–11.
7. D'Cruz AK, *et al.* mTHPC-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: a multicenter study of 128 patients. *Head Neck* 2004; **26**: 232–40.
8. Etienne J, *et al.* Photodynamic therapy with green light and m-tetrahydroxyphenyl chlorin for intramucosal adenocarcinoma and high-grade dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2004; **59**: 880–9. Correction. *ibid.*; **60**: 1042.
9. Hopper C, *et al.* mTHPC-mediated photodynamic therapy for early oral squamous cell carcinoma. *Int J Cancer* 2004; **111**: 138–46.
10. Lou PJ, *et al.* Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. *Br J Cancer* 2004; **91**: 441–6.
11. Campbell SM, *et al.* Photodynamic therapy using meta-tetrahydroxyphenylchlorin (Foscan) for the treatment of vulval intraepithelial neoplasia. *Br J Dermatol* 2004; **151**: 1076–80.
12. Naim R. Photodynamische Therapie mit m-THPC (Foscan): Behandlung von Plattenepithelkarzinomen im Kopf-Hals-Bereich. *HNO* 2008; **56**: 490–2.

Adverse Effects and Precautions

Adverse effects of temoporfin include photosensitivity, local inflammatory reactions, and gastrointestinal disturbances. Patients should be advised to avoid direct sunlight or bright indoor light for 15 days, and to protect the injection site from light for at least 3 months if extravasation has occurred.

Porphyria. Licensed product information states that the use of temoporfin is contra-indicated in patients with porphyria.

Interactions

Use of temoporfin with other drugs causing photosensitivity should be avoided as the reaction may be increased; this has been reported with topical fluorouracil.

Pharmacokinetics

Peak plasma concentrations of temoporfin occur about 2 to 4 hours after intravenous infusion. Thereafter, elimination is bi-exponential, with a terminal plasma half-life of about 65 hours. Plasma protein binding is about 85%. *Animal* data indicate that temoporfin is metabolised in the liver and excreted in the faeces via the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Foscan; *Belg.*: Foscan; *Cz.*: Foscan; *Denm.*: Foscan; *Fr.*: Foscan†; *Ger.*: Foscan; *Gr.*: Foscan; *Hung.*: Foscan; *Irl.*: Foscan; *Israel*: Foscan; *Ital.*: Foscan; *Neth.*: Foscan; *Norw.*: Foscan; *Pol.*: Foscan; *Port.*: Foscan; *UK*: Foscan.

Temozolomide (BAN, USAN, rINN)

CCRG-81045; M&B-39831; NSC-362856; Sch-52365; Temotsolomidi; Temozolomid; Temozolomida; Témozolomide; Temozolomidum; Темозоломид.

3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxamide.

$C_6H_6N_6O_2$=194.2

CAS — 85622-93-1.

ATC — L01AX03.

ATC Vet — QL01AX03.

UNII — YF1K15M17Y.

Pharmacopoeias. In *US.*

USP 36: (Temozolomide). A white to light pink or light tan powder. Sparingly soluble in water; practically insoluble in toluene; soluble in dimethyl sulfoxide.

Uses and Administration

Temozolomide is a prodrug that is converted to MTIC (see Pharmacokinetics, p. 866.1), the active metabolite of dacarbazine (p. 776.1). MTIC acts as an alkylating agent. Temozolomide is licensed for the treatment of malignant gliomas (below) such as glioblastoma multiforme and anaplastic astrocytoma, and metastatic malignant melanoma (below).

Temozolomide may be given orally or intravenously. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

In adult patients with *newly diagnosed* **glioblastoma multiforme**, temozolomide is given initially with focal radiotherapy (the *concomitant phase*) in an oral or intravenous dose of 75 mg/m^2 daily for 42 days. Treatment may be interrupted or stopped depending on toxicity. Complete blood counts should be monitored weekly. Four weeks after completing the concomitant phase, temozolomide *monotherapy* is begun at an oral or intravenous dose of 150 mg/m^2 once daily for 5 days of a 28-day cycle. In cycle 2, the dose is increased to 200 mg/m^2 for 5 days, if toxicity allows. If the dose cannot be increased in cycle 2, it should not be increased in subsequent cycles. The dose used at cycle 2 is then given every 28 days, toxicity allowing. Up to 6 cycles of temozolomide monotherapy may be given.

The usual oral dose for *recurrent or progressive* malignant gliomas in adults previously untreated with chemotherapy is 200 mg/m^2 once daily for 5 days, repeated every 28 days. In patients who have received previous courses of chemotherapy the initial oral or intravenous dose is 150 mg/m^2 once daily for 5 days, for the first cycle of therapy, but may be increased to 200 mg/m^2 for subsequent courses if there is no haematological toxicity.

An oral dose of 200 mg/m^2 once daily for 5 days every 28 days is also used for metastatic **malignant melanoma**.

Administration. References[1,2] to the use of temozolomide in dose-dense regimens, designed to maximise exposure to the drug and consequent efficacy. In contrast to the original 5-day regimen (150 to 200 mg/m^2 daily for 5 days of a 28-day cycle) used in glioma, these have included 75 mg/m^2 daily for 6 to 7 weeks[1] (this is now recommended by licensed product information for the initial phase of glioma treatment) and regimens in which 150 mg/m^2 was given for 5 or 7 days of a 14-day cycle, or 100 mg/m^2 for 21 days of a 28-day cycle.[1] However, the increased dose intensity may be associated with increased adverse effects and the clinical benefits are still uncertain.

1. Wick W, *et al.* New (alternative) temozolomide regimens for the treatment of glioma. *Neuro Oncol* 2009; **11**: 69–79.
2. Neyns B, *et al.* Dose-dense temozolomide regimens: antitumor activity, toxicity, and immunomodulatory effects. *Cancer* 2010; **116**: 2868–77.

Administration in children. In the UK, temozolomide may be given to children aged 3 years or older for the treatment of malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, that recurs or progresses after standard therapy. It is given orally in the same dose as that used for adults (see Uses and Administration, above).

Malignant neoplasms. Temozolomide has been studied[1-9] particularly in the management of malignant neoplasms of the brain (p. 701.2). In the UK, guidance has been issued[10] on its use in patients with recurrent progressive malignant glioma who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of adverse effects). A systematic review[11] concluded that temozolomide is an effective primary therapy for newly diagnosed glioblastoma multiforme; it prolongs survival and delays progression. For recurrent disease, data from a single study indicate that it delays progression but does not affect overall survival. Another review[12] concluded that although there was good evidence for the use of temozolomide in both high- and low-grade gliomas, value could not be shown for other brain tumours, including metastases.

1. Dinnes J, *et al.* A rapid and systematic review of the effectiveness of temozolomide for the treatment of recurrent malignant glioma. *Br J Cancer* 2002; **86**: 501–5.
2. Wick W, *et al.* One week on/one week off: a novel active regimen of temozolomide for recurrent glioblastoma. *Neurology* 2004; **62**: 2113–15.
3. Levin N, *et al.* Chemotherapy as initial treatment in gliomatosis cerebri: results with temozolomide. *Neurology* 2004; **63**: 354–6.
4. Agarwala SS, *et al.* Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol* 2004; **22**: 2101–7.
5. Stupp R, *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352**: 987–96.
6. Athanassiou H, *et al.* Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol* 2005; **23**: 2372–7.
7. Tosoni A, *et al.* Is protracted low-dose temozolomide feasible in glioma patients? *Neurology* 2006; **66**: 427–9.
8. Wick A, *et al.* Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. *J Clin Oncol* 2007; **25**: 3357–61.
9. Sher DJ, *et al.* The added value of concurrently administered temozolomide versus adjuvant temozolomide alone in newly diagnosed glioblastoma. *J Neurooncol* 2008; **88**: 43–50.
10. NICE. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (issued April 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/temozolomideguidance.pdf (accessed 30/07/08)
11. Hart MG, *et al.* Temozolomide for high grade glioma. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2008 (accessed 24/07/09).
12. Tilleul P, *et al.* Guide de prescription et de bon usage du témozolomide dans les tumeurs cérébrales. *Bull Cancer* 2009; **96**: 579–89.

MELANOMA. Temozolomide has been studied[1-3] as a treatment for advanced metastatic melanoma (p. 714.3). A phase III study compared the overall survival-time in 305 patients treated with either oral temozolomide or intravenous dacarbazine in standard doses for up to 12 cycles of therapy. Temozolomide was found to be at least equivalent to dacarbazine in these patients, and there were no major differences in adverse effects.[2] However, median survival-times were short in both groups (7.7 months and 6.4 months respectively). Another phase III study comparing temozolomide alone or with interferon alfa in 282 patients also found modest median survival-times of 8.4 and 9.7 months respectively.[4] Studies in *animals* have investigated isolated limb infusion of temozolomide, plus hyperthermia, for regional therapy of melanoma of the extremities.[5]

1. Bleehen NM, *et al.* Cancer research campaign phase II trial of temozolomide in metastatic melanoma. *J Clin Oncol* 1995; **13**: 910–13.
2. Middleton MR, *et al.* Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000; **18**: 158–66.
3. Quirt I, *et al.* Temozolomide for the treatment of metastatic melanoma: a systematic review. *Oncologist* 2007; **12**: 1114–23.
4. Kaufmann R, *et al.* Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: a randomized, phase III, multicenter study from the Dermatologic Cooperative Oncology Group. *J Clin Oncol* 2005; **23**: 9001–7.
5. Ko SH, *et al.* Optimizing a novel regional chemotherapeutic agent against melanoma: hyperthermia-induced enhancement of temozolomide cytotoxicity. *Clin Cancer Res* 2006; **12**: 289–97.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. Myelosuppression is common with temozolomide and is dose-limiting. Blood counts should be obtained before the start of treatment and monitored throughout. The nadir of cell counts usually occurs 21 to 28 days after treatment, with recovery within the next 1 to 2 weeks. Patients over 70 years of age are thought to be more susceptible to severe myelosuppression. Prolonged pancytopenia may result in aplastic anaemia, and fatalities have been reported. Opportunistic infections can occur; pneumocystis pneumonia has been reported in patients also given radiotherapy or corticosteroids, or during a longer dosing regimen of temozolomide. Prophylaxis against pneumocystis pneumonia should be given to all patients receiving temozolomide with radiotherapy, regardless of lymphocyte count.

Nausea and vomiting are very common; antiemetic therapy may be given before or during treatment. Other common adverse effects include constipation, diarrhoea, anorexia, alopecia, fatigue, headache, rashes, convulsions, and insomnia or somnolence. Anxiety, depression, confusion, dizziness, hemiparesis, aphasia, dysphagia, peripheral neuropathy, paraesthesia, neurological and/or speech disorders, tremor, and concentration or memory impairment can occur, as can visual field defects, blurred vision, diplopia, hearing impairment, or tinnitus. Deafness has been reported. Vascular disorders such as haemorrhage, deep venous thrombosis, and peripheral oedema can occur; pulmonary embolism has been reported. Other commonly reported adverse effects include dyspnoea, coughing, dry skin, pruritus, arthralgia and/or myalgia, urinary incontinence, fever, pain, and dysgeusia. Liver enzyme values can

increase, and hyperglycaemia may occur. Cushingoid disorders have occurred uncommonly. Hypersensitivity reactions, including rare cases of anaphylaxis, can occur. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported rarely. Cases of interstitial pneumonitis have also been reported. Temozolomide has carcinogenic, mutagenic, and teratogenic potential. Use in pregnancy should be avoided, and men should be advised not to father a child for up to 6 months after receiving the final dose; sperm preservation before treatment should be considered as temozolomide may cause irreversible infertility.

Carcinogenicity. Antineoplastic drugs such as alkylating agents are associated with the development of secondary malignancies (see Carcinogenicity, p. 726.2). Myelodysplastic syndrome and myeloid leukaemia have been reported in patients treated with regimens containing temozolomide. Three patients with glioma developed malignant lymphoma after treatment with temozolomide.[1]

1. Neyns B, *et al.* Non-Hodgkin's lymphoma in patients with glioma treated with temozolomide. *J Clin Oncol* 2008; **26**: 4518–19. Correction. *ibid.* 2009; **27**: 3070.

Effects on the lungs. After completing 2 cycles of temozolomide therapy for glioblastoma multiforme, an 88-year-old man presented with a 4-week history of fever, weakness, shortness of breath, and non-productive cough. Auscultation of the lungs revealed inspiratory crackles without wheezing or rub. Drug-associated organising pneumonitis was suspected, and temozolomide therapy was stopped. Prednisolone was started, with prophylaxis against *Pneumocystis jirovecii*, and the patient improved dramatically.[1] Others have subsequently reported temozolomide-associated hypersensitivity pneumonitis.[2]

1. Maldonado F, *et al.* Temozolomide-associated organizing pneumonitis. *Mayo Clin Proc* 2007; **82**: 771–3.
2. Koschel D, *et al.* Hypersensitivity pneumonitis associated with the use of temozolomide. *Eur Respir J* 2009; **33**: 931–4.

Hepatitis. Hepatitis B reactivation has been associated with the use of temozolomide plus radiotherapy.[1,2] In one case, corticosteroid treatment may have played a role in reactivation,[1] and in another case, which was fatal, hepatotoxicity from valproic acid or temozolomide itself could have contributed.[2]

1. Chheda MG, *et al.* Hepatitis B reactivation during glioblastoma treatment with temozolomide: a cautionary note. *Neurology* 2007; **68**: 955–6.
2. Grewal J, *et al.* Fatal reactivation of hepatitis B with temozolomide. *N Engl J Med* 2007; **356**: 1591–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies temozolomide 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 28/09/11)

Interactions

Valproic acid decreases oral clearance of temozolomide by about 5%; the clinical significance is unknown.

Pharmacokinetics

Temozolomide is rapidly and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 0.5 to 1.5 hours after a dose. Food reduces the rate and extent of absorption. Temozolomide readily crosses the blood-brain barrier and can be detected in the CSF. The plasma elimination half-life is about 1.8 hours. Plasma protein binding is about 10 to 20%. Temozolomide undergoes spontaneous hydrolysis to its active metabolite 5-(3-methyl-triazen-1-yl)-imidazole-4-carboxamide (MTIC), which is then further hydrolysed to 5-amino-imidazole-4-carboxamide (AIC) and methylhydrazine. Temozolomide is largely eliminated by the kidneys, about 5 to 10% as unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dralitem; Temodal; Temola; Tezulina; Tocitrap; Zolom; *Austral.*: Temodal; *Austria*: Temodal; *Belg.*: Temodal; *Braz.*: Temodal; *Canad.*: Temodal; *Chile*: Dralitem; Temodal; *China*: Diqing (帝清); Temodal (泰道); *Cz.*: Onkmoeck; Temodal; Temomedac; Temostad; *Denm.*: Onkmoeck; Temodal; Temomedac; *Fin.*: Temodal; *Fr.*: Temodal; *Ger.*: Temodal; Temomedac; Temozo-cell; *Gr.*: Temodal; Temomedac; *Hong Kong*: Temodal; *Hung.*: Temodal; *India*: Emzolam; Gliotem; Glioz; *Indon.*: Temodal; *Irl.*: Temodal; Temomedac; *Israel*: Temo; Temodal; *Ital.*: Temodal; *Malaysia*: Temodal; *Mex.*: Temodal; *Neth.*: Blastomat; Nogron; Ridoca; Temodal; Temomedac; *Norw.*: Temodal; *NZ*: Temaccord; Temodal; *Philipp.*: Temodal; Temozam; *Pol.*: Temodal; Temomedac; *Port.*: Temodal; Temomedac; *Rus.*: Temodal (Темодал); Temomid (Темомид); *S.Afr.*: Temodal; *Singapore*: Temodal; *Spain*: Temodal; Temomedac; *Swed.*: Temodal; Temomedac; *Switz.*: Temodal; *Thai.*: Temodal; *Turk.*: Temodal; *UK*: Temodal; *Ukr.*: Temodal (Темодал); *USA*: Temodar; *Venez.*: Temodal.

Temsirolimus *(BAN, USAN, rINN)*

CCI-779; Temsirolimusum; Темсиролимус.

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone 4′[2,2-bis(hydroxymethyl)propionate].

$C_{56}H_{87}NO_{16}$=1030.3

CAS — 162635-04-3.

ATC — L01XE09.

ATC Vet — QL01XE09.

UNII — 624KN6GM2T.

Incompatibility. The formulation of temsirolimus injection contains polysorbate 80, which increases the rate of extraction of the plasticiser di-2-ethylhexylphthalate (DEHP) from PVC. In order to minimise exposure to DEHP, the infusion should be given in glass, polyolefin, or polyethylene containers, through non-DEHP giving sets with an in-line polyethersulfone filter of not greater than 5 micrometres.

Uses and Administration

Temsirolimus is an ester analogue of sirolimus (p. 1970.2) that is used for the treatment of advanced renal cell carcinoma and relapsed and/or refractory mantle cell lymphoma. It is given intravenously, diluted in 250 mL sodium chloride 0.9% and infused over 30 to 60 minutes, preferably via an infusion pump.

For **renal cell carcinoma**, temsirolimus 25 mg is given once weekly. Treatment should be interrupted and the dose reduced if toxicity occurs. US licensed product information recommends withholding the dose if the absolute neutrophil count falls below 1000 cells/mm³, or the platelet count falls below 75 000 cells/mm³, or if grade 3 toxicity occurs. Once these have resolved to grade 2 or less, temsirolimus may be restarted with the dose reduced by 5 mg weekly, to a dose no lower than 15 mg weekly.

Use of strong inhibitors or inducers of CYP3A4 may increase or decrease exposure to sirolimus, the active metabolite of temsirolimus. If no alternative is available, US licensed product information suggests dose adjustments for renal cell carcinoma patients. A reduction of temsirolimus to 12.5 mg weekly should be considered if it is given with a strong CYP3A4 inhibitor. Once the inhibitor is stopped, a washout period of about 1 week should be allowed before temsirolimus is increased back to the original dose. A dose increase of temsirolimus to 50 mg weekly should be considered if it is given with a strong CYP3A4 inducer; once the inducer is stopped, temsirolimus should be decreased to the original dose.

In the UK, temsirolimus is also licensed for **mantle cell lymphoma**; the recommended dose is 175 mg once weekly for 3 weeks followed by 75 mg once weekly thereafter. Treatment should be interrupted and the dose reduced for absolute neutrophil counts below 1000 cells/mm³ and/or platelet counts below 50 000 cells/mm³. Once these counts have returned to these levels or higher, temsirolimus may be restarted with the weekly dose reduced in the following way:

- last dose 175 mg, reduce to 75 mg
- last dose 75 mg, reduce to 50 mg
- last dose 50 mg, reduce to 25 mg

If neutrophil and platelet counts are not maintained at or above these levels on the new dose, then treatment should be withheld and the next lower dose given once the counts have recovered. Inhibitors and inducers of CYP3A4 should be avoided in patients given temsirolimus for mantle cell lymphoma.

Temsirolimus treatment may continue until disease progression or toxicity occurs.

For doses in patients with hepatic impairment see below.

References.

1. Hudes G, *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; **356**: 2271–81.
2. Simpson D, Curran MP. Temsirolimus: in advanced renal cell carcinoma. *Drugs* 2008; **68**: 631–8.
3. Boni JP, *et al.* Intravenous temsirolimus in cancer patients: clinical pharmacology and dosing considerations. *Semin Oncol* 2009; **36** (suppl 3): S18–S25.
4. Dancey JE, *et al.* Evaluating temsirolimus activity in multiple tumors: a review of clinical trials. *Semin Oncol* 2009; **36** (suppl 3): S46–S58.
5. Thompson Coon J, *et al.* Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation. *Health Technol Assess* 2010; **14**: 1–208.
6. Ravaud A, *et al.* Inhibiteurs de mTOR: temsirolimus et évérolimus dans le traitement du cancer du rein. *Bull Cancer* 2010; **97**: 45–51.
7. Stock C, *et al.* Temsirolimus. *Recent Results Cancer Res* 2010; **184**: 189–97.
8. Borders EB, *et al.* Mammalian target of rapamycin: biological function and target for novel anticancer agents. *Am J Health-Syst Pharm* 2010; **67**: 2095–2106.
9. Hoy SM, McKeage K. Temsirolimus: in relapsed and/or refractory mantle cell lymphoma. *Drugs* 2010; **70**: 1819–29.

Administration in hepatic impairment. Temsirolimus is mainly metabolised in the liver, and should be used with caution in patients with hepatic impairment. In the treatment of renal cell carcinoma, UK licensed product information considers that no dose adjustment is required for mild or moderate hepatic impairment (Child-Pugh class A or B). For severe impairment (Child-Pugh class C) and a baseline platelet count ≥100 000 cells/mm³, a reduced dose of temsirolimus 10 mg intravenously once weekly is recommended. Temsirolimus is contra-indicated for treatment of mantle cell lymphoma in patients with moderate or severe hepatic impairment.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Temsirolimus is metabolised to sirolimus; for adverse effects of sirolimus, see p. 1971.2. Additional adverse effects reported with temsirolimus include lymphopenia, myalgia, hypocalcaemia, anorexia, asthenia, nail disorders, dry skin, pruritus, and conjunctivitis. Cataracts have occurred in patients given temsirolimus with interferon alfa. Effects on the nervous system include insomnia, anxiety, depression, dysgeusia, paraesthesia, dizziness, and ageusia. Although hepatotoxicity has not been reported with temsirolimus, raised liver transaminase concentrations are common.

Hypersensitivity reactions to temsirolimus may be life-threatening; symptoms include anaphylaxis, dyspnoea, flushing, and chest pain. Antihistamines should be given about 30 minutes before the start of the infusion. If the patient develops a hypersensitivity reaction, the infusion should be stopped and the patient observed for 30 to 60 minutes. If appropriate, treatment may be restarted about 30 minutes after a further dose of an antihistamine and/or an H_2-antagonist. The infusion may be restarted at a slower infusion rate (up to 60 minutes) and completed within 6 hours of preparation. Cases of fatal bowel perforation have occurred; patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhoea, and/or acute abdomen. Patients with CNS tumours and/or those given anticoagulants may be at increased risk of developing intracranial bleeding, which may be fatal.

Serum glucose, cholesterol, and triglycerides should be monitored before and during treatment with temsirolimus.

Effects on the lungs. Eight out of 22 patients given temsirolimus developed pulmonary abnormalities compatible with drug-induced pneumonitis. Dyspnoea and dry cough were the most common symptoms, although 4 patients were asymptomatic. The risk of developing pulmonary toxicity is increased in those with abnormal pretreatment pulmonary function, or a history of lung disease.[1] A retrospective review[2] found that 29% of patients developed radiographically diagnosed temsirolimus-related pneumonitis; radiographic changes were not necessarily associated with symptoms. The onset of drug-related pneumonitis occurred within the first 8 weeks of temsirolimus treatment in 60% of patients.

1. Duran I, *et al.* Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer* 2006; **42**: 1875–80.
2. Maroto JP, *et al.* Drug-related pneumonitis in patients with advanced renal cell carcinoma treated with temsirolimus. *J Clin Oncol* 2011; **29**: 1750–6.

Interactions

Both temsirolimus and its main active metabolite, sirolimus, are metabolised by cytochrome P450 isoenzyme CYP3A4, and inducers or inhibitors of CYP3A4 may affect exposure, see Interactions, under Sirolimus, p. 1972.1. If the use of alternative drugs is not feasible, dose adjustments of temsirolimus may be necessary, see Uses and Administration, above.

References.

1. Boni J, *et al.* Pharmacokinetic profile of temsirolimus with concomitant administration of cytochrome P450-inducing medications. *J Clin Pharmacol* 2007; **47**: 1430–9.
2. Boni JP, *et al.* Differential effects of ketoconazole on exposure to temsirolimus following intravenous infusion of temsirolimus. *Br J Cancer* 2008; **98**: 1797–1802.

Pharmacokinetics

Temsirolimus is mainly metabolised by cytochrome P450 isoenzyme CYP3A4 to 5 metabolites; sirolimus is the main active metabolite. The mean half-life of temsirolimus is about 17 hours. Exposure to sirolimus may be much greater than that of temsirolimus, due principally to the longer half-life of sirolimus (see p. 1972.1). Elimination is mainly in faeces; about 5% is recovered in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Torisel; *Austral.*: Torisel; *Austria*: Torisel; *Belg.*: Torisel; *Braz.*: Torisel; *Canad.*: Torisel; *Chile*: Torisel; *Cz.*: Torisel; *Denm.*: Torisel; *Fr.*: Torisel; *Ger.*: Torisel; *Gr.*: Torisel; *Hong Kong*: Torisel; *Hung.*: Torisel; *Irl.*: Torisel; *Israel*: Torisel; *Ital.*: Torisel; *Malaysia*: Torisel; *Neth.*: Torisel; *Norw.*: Torisel; *Philipp.*: Torisel; *Pol.*: Torisel; *Port.*: Torisel; *Rus.*: Torisel (Торизел); *Singapore*: Torisel; *Spain*: Torisel; *Swed.*: Torisel; *Switz.*: Torisel; *Thai.*: Torisel; *Turk.*: Torisel; *UK*: Torisel; *USA*: Torisel.

Teniposide *(BAN, USAN, rINN)*

ETP; NSC-122819; Teniposid; Téniposide; Teniposidi; Teniposido; Tenipósido; Teniposidum; VM-26; Тенипозид.

(5*S*,5a*R*,8a*S*,9*R*)-5,8,8a,9-Tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-(4,6-*O*-thenylidene-β-D-glucopyranosyloxy)isobenzofuro[5,6-*f*][1,3]benzodioxol-6(5a*H*)-one.

$C_{32}H_{32}O_{13}S$=656.7

CAS — 29767-20-2.

ATC — L01CB02.

ATC Vet — QL01CB02.

UNII — 957E6438QA.

Stability. Precipitation occurred repeatedly in preparations for infusion containing teniposide 200 micrograms/mL in either glucose 5% or sodium chloride 0.9% injection, although previously such preparations had been used uneventfully.[1] Dilution of teniposide solutions to 100 micrograms/mL or less reduced the frequency of the problem, which could not be attributed to a change in formulation and remained unexplained.

1. Strong DK, Morris LA. Precipitation of teniposide during infusion. *Am J Hosp Pharm* 1990; 47: 512,518.

Uses and Administration

Teniposide is an antineoplastic agent with general properties similar to those of etoposide (p. 790.2). It is given as monotherapy or part of a combination regimen for refractory non-Hodgkin's lymphoma (p. 696.3), and with other antineoplastic agents in the treatment of refractory acute lymphoblastic leukaemia (p. 692.3). Teniposide is also used in solid tumours including neuroblastoma (p. 716.2), and has been used in retinoblastoma (p. 717.2).

Teniposide is given by slow intravenous infusion over at least 30 to 60 minutes, as a solution of up to 1 mg/mL in sodium chloride 0.9% or glucose 5%. Dosage regimens vary.

For non-Hodgkin's **lymphoma**, the following monotherapy regimens have been used:

- 30 mg/m² daily for 10 days
- 30 mg/m² daily every five days
- 50 to 100 mg/m² once weekly

Doses in combination regimens have generally been given once weekly, at 60 to 70 mg/m².

In the treatment of refractory acute lymphoblastic **leukaemia**, the following combination regimens have been used:

- 165 mg/m² twice weekly for 8 to 9 doses, with cytarabine
- 250 mg/m² weekly for 4 to 8 weeks, with vincristine and prednisone

For **neuroblastoma**, doses as a single agent range from 130 to 180 mg/m² once weekly.

Adverse Effects, Treatment, and Precautions

As for Etoposide, p. 791.2. There is some evidence that teniposide may be a more potent mutagen and carcinogen than etoposide.

Breast feeding. US licensed product information states that it is unknown whether teniposide is excreted in human milk. It has been suggested[1] that breast feeding be withheld for 30 to 48 hours after a dose.

1. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Hypersensitivity. Haemolytic anaemia and acute renal failure with tubular necrosis has been reported in a patient who developed an antibody to teniposide.[1] As with etoposide (p. 791.3) hypersensitivity or infusion reactions occur, sometimes with the first dose, and may be severe;[2,3] the frequency may be as high as 13% in neuroblastoma patients.[2] Although it has been suggested that hypersensitivity reactions might be due to the polyoxyl castor oil in the injection vehicle,[2] studies *in vitro* suggest that it is the drug rather than the vehicle that is responsible.[3]

1. Habibi B, *et al.* Immune hemolytic anemia and renal failure due to teniposide. *N Engl J Med* 1982; 306: 1091–3.
2. Siddall SJ, *et al.* Anaphylactic reactions to teniposide. *Lancet* 1989; i: 394.
3. Carstensen H, *et al.* Teniposide-induced hypersensitivity reactions in children. *Lancet* 1989; ii: 55.

Pregnancy. A 32-year-old woman was diagnosed with Burkitt's lymphoma at 22 weeks of gestation. She was treated with combination chemotherapy, including doxorubicin, vincristine, teniposide, cyclophosphamide, and prednisolone; courses were given every 2.5 or 3 weeks depending on haematological recovery, for a total of 6 courses. At 35 weeks, she was given intrathecal methotrexate for a total of 7 doses, and bleomycin for a total of 4 doses. The infant was healthy, fully developed, with no physical abnormalities, and had a normal heart, and a normal blood count.[1]

1. Lowenthal RM, *et al.* Normal infant after combination chemotherapy including teniposide for Burkitt's lymphoma in pregnancy. *Med Pediatr Oncol* 1982; 10: 165–9.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Salicylic acid, sulfamethizole, and tolbutamide may affect the protein binding of teniposide, potentially increasing free teniposide in plasma and resulting in toxicity; caution is advised when giving any of these drugs with teniposide.

Antiepileptics. Clearance of teniposide was markedly increased by *phenytoin* or *phenobarbital*; the resultant decrease in systemic exposure to the antineoplastic might reduce its efficacy, and increased dosage would be needed in patients receiving these drugs to guarantee equivalent exposure.[1]

1. Baker DK, *et al.* Increased teniposide clearance with concomitant anticonvulsant therapy. *J Clin Oncol* 1992; 10: 311–15.

Ciclosporin. Use of ciclosporin with teniposide has been reported[1] to produce a decrease in the clearance of the latter, with increased terminal half-life, peak plasma concentrations, and toxicity.

1. Toffoli G, *et al.* Cyclosporin A as a multidrug-resistant modulator in patients with renal cell carcinoma treated with teniposide. *Br J Cancer* 1997; 75: 715–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vumon; *Austral.*: Vumon; *Austria*: Vumon†; *Braz.*: Vumon; *Canad.*: Vumon; *Chile*: Vumon†; *China*: Bang Lai (邦萊); Vumon (卫萌); *Gr.*: Vumon; *Hong Kong*: Vumon†; *Mex.*: Vumon; *Neth.*: Vumon; *NZ*: Vumon; *Pol.*: Vumon; *Port.*: Vumon†; *S.Afr.*: Vumon†; *Spain*: Vumon†; *USA*: Vumon.

Testolactone *(USAN, rINN)* ⊗

1-Dehydrotestololactone; NSC-23759; SQ-9538; Testolactona; Testolactonum; Testolaktor; Testolaktoni; Тестолактон.

D-Homo-17a-oxaandrosta-1,4-diene-3,17-dione.

$C_{19}H_{24}O_3$=300.4

CAS — 968-93-4.

UNII — 6J9BLA949Q.

Pharmacopoeias. In *US*.

USP 36: (Testolactone). A white to off-white, practically odourless, crystalline powder. Soluble 1 in 4050 of water; soluble in alcohol and in chloroform; slightly soluble in benzyl alcohol; insoluble in ether and in petroleum spirit. Store in airtight containers.

Profile

Testolactone is a derivative of testosterone (see p. 2305.1). It is reported to be an aromatase inhibitor that reduces peripheral oestrogen synthesis but has no significant androgenic activity. It has been given orally in the palliative treatment of advanced breast cancer in postmenopausal women (p. 702.1).

It is unsuitable for men with breast cancer.

Peripheral neuropathies have occurred in patients given testolactone; gastrointestinal disturbances, pain or oedema of the extremities, hypertension, malaise, maculopapular erythema, and glossitis have also been reported.

Congenital adrenal hyperplasia. For mention of the use of testolactone with flutamide to block androgenic effects in congenital adrenal hyperplasia, see p. 1603.2.

Precocious puberty. Encouraging results have been reported using testolactone in the treatment of 5 girls with precocious puberty (p. 2254.1) due to the McCune-Albright syndrome.[1] Testolactone is an aromatase inhibitor and blocks the synthesis of oestrogens from androgens. Long-term therapy (for up to 5 years) was associated with continued benefit in many patients; however, signs of puberty were not always completely suppressed, in some cases perhaps because of difficulties in maintaining the dosage regimen.[2] Encouraging results were also obtained using testolactone with spironolactone in the treatment of familial precocious puberty in boys, although neither agent was successful when used alone.[3] Again, signs of a reduced response to longer-term therapy have occurred; in this case control was restored by addition of a gonadorelin analogue.[4] Another study[5] in 10 boys who were treated for at least 6 years with spironolactone and testolactone, with deslorelin added at the onset of secondary central precocious puberty, found normalisation in growth rate and bone maturation, and improvements in predicted adult height.

1. Feuillan PP, *et al.* Treatment of precocious puberty in the McCune-Albright syndrome with the aromatase inhibitor testolactone. *N Engl J Med* 1986; 315: 1115–19.
2. Feuillan PP, *et al.* Long term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1993; 77: 647–51.
3. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; 320: 496–502.
4. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; 76: 151–5.
5. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; 84: 175–8.

Preparations

Pharmacopoeial Preparations

USP 36: Testolactone Tablets.

Thalidomide *(BAN, USAN, rINN)*

E-217; K-17; NSC-66847; Talidomid; Talidomida; Talidomidi; Thalidomidum; Талидомид.

2-Phthalimidoglutarimide.

$C_{13}H_{10}N_2O_4$=258.2

CAS — 50-35-1.

ATC — L04AX02.

ATC Vet — QL04AX02.

UNII — 4Z8R6ORS6L.

Pharmacopoeias. In *US*.

USP 36: (Thalidomide). A white to off-white powder. Sparingly soluble in water, in dehydrated alcohol, in acetone, in butyl acetate, in ethyl acetate, in glacial acetic acid, and in methyl alcohol; practically insoluble in chloroform, in ether, and in benzene; very soluble in dimethylformamide, in dioxan, and in pyridine. Store in airtight containers. Protect from light.

Stability. An extemporaneously prepared oral suspension of thalidomide 20 mg/mL was reported to be stable for at least 35 days when stored in amber plastic bottles under refrigeration (3 degrees to 5 degrees). The contents of capsules (*Thalomid; Celgene, USA*) were suspended in a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (*Paddock, USA*). Appropriate precautions should be taken during preparation and handling, because of the risks associated with this drug.[1]

1. Kraft S, *et al.* Stability of an extemporaneously prepared thalidomide suspension. *Am J Health-Syst Pharm* 2012; 69: 56–8.

Uses and Administration

Thalidomide has immunomodulating, anti-inflammatory, and anti-angiogenic activities. It should always be given under appropriately supervised and controlled conditions because of the teratogenic risks and other potential adverse effects (see Adverse Effects and Precautions, p. 869.2). Thalidomide is given orally. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Thalidomide is used in the treatment of **multiple myeloma** (see Malignant Neoplasms, p. 868.3). In disease that is refractory to standard therapies, it is given as monotherapy in an initial oral dose of 200 mg once daily. The dose may be increased by 100 mg at weekly intervals up to a maximum dose of 400 mg daily, as tolerated. Thalidomide may be used with melphalan and prednisone in patients with newly diagnosed multiple myeloma who are over 65 years of age or ineligible for high-dose chemotherapy; thalidomide in a dose of 200 mg daily is given continuously for a maximum of 12 treatment cycles of 6 weeks each. Thalidomide may also be used with dexamethasone in the treatment of patients with newly diagnosed multiple myeloma. Thalidomide 200 mg is given once daily, with dexamethasone 40 mg given orally on days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle. Four cycles of a thalidomide and dexamethasone regimen may be used as induction therapy before high-dose chemotherapy with autologous stem cell rescue.

Thalidomide is also used for the treatment of acute cutaneous manifestations of moderate to severe type 2 (erythema nodosum leprosum) **lepra reactions** (see Leprosy, p. 188.3), but should not be given as monotherapy if moderate to severe neuritis is present; in such cases, corticosteroid therapy should also be given and continued

until neuritis improves. Thalidomide may also be used for maintenance therapy for prevention and suppression of the cutaneous manifestations of recurrent type 2 lepra reactions. It is of no value in type 1 lepra reactions. It may be given orally in usual initial doses of 100 to 300 mg once daily. In severe cases up to 400 mg daily may be given. The dose should be reduced gradually by 50 mg every 2 to 4 weeks once a satisfactory response has been achieved. An alternative regimen is to start treatment with 100 mg once daily, and if symptoms are not controlled, increase the dose by increments of 100 mg at weekly intervals up to a maximum of 400 mg once daily.

Thalidomide should preferably be given at bedtime and at least 1 hour after the evening meal.

Thalidomide has been used in several other conditions whose aetiology may involve the immune system, such as treatment and prevention of graft-versus-host disease, treatment and prevention of recurrent aphthous stomatitis in severely and terminally immunocompromised patients, treatment of the clinical manifestations of both tuberculous and non-tuberculous mycobacterial infection, treatment of myelodysplastic syndrome and treatment of HIV-associated wasting syndrome, Kaposi's sarcoma, and Crohn's disease. It has also been used in the treatment of primary brain malignancies. Thalidomide is being investigated in some other malignancies.

Guidelines on the clinical use of thalidomide.

1. Powell RJ, Gardner-Medwin JMM. Guideline for the clinical use and dispensing of thalidomide. *Postgrad Med J* 1994; **70**: 901–4.
2. Lary JM, *et al.* The return of thalidomide: can birth defects be prevented? *Drug Safety* 1999; **21**: 161–9.
3. Zeldis JB, *et al.* S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. *Clin Ther* 1999; **21**: 319–30. Further information available at: http://www.thalomid.com/steps_program.aspx (accessed 27/05/08)
4. Chave TA, *et al.* All-Wales Dermatology Audit Committee. Thalidomide usage in Wales: the need to follow guidelines. *Br J Dermatol* 2001; **144**: 310–15.

Action. The mechanism of action of thalidomide is not completely understood, although investigations have shown that it has anti-inflammatory and immunomodulating effects, including inhibition of the synthesis of tumour necrosis factor (TNF)-α. However, this inhibition is incomplete and selective, and increased plasma-TNF-α concentrations have been seen in some patient groups. Other immunomodulatory and anti-inflammatory properties include inhibition of leucocyte chemotaxis into the site of inflammation and reduction of phagocytosis by polymorphonuclear leucocytes. Thalidomide also appears to modulate interleukins, although results of investigations into its effect on specific interleukins and interferon gamma have so far been equivocal. Effects on CD4+ cells and variable effects on other mediators of intercellular reactions have also been implicated. Thalidomide also inhibits angiogenesis, which may have implications in solid tumours and other diseases.

General references to the mechanism of action and uses of thalidomide.[1-8]

1. Schuler U, Ehninger G. Thalidomide: rationale for renewed use in immunological disorders. *Drug Safety* 1995; **12**: 364–9.
2. Calabrese L, Fleischer AB. Thalidomide: current and potential clinical applications. *Am J Med* 2000; **108**: 487–95.
3. Peuckmann V, *et al.* Potential novel uses of thalidomide: focus on palliative care. *Drugs* 2000; **60**: 273–92.
4. Franks ME, *et al.* Thalidomide. *Lancet* 2004; **363**: 1802–11.
5. Rajkumar SV. Thalidomide: tragic past and promising future. *Mayo Clin Proc* 2004; **79**: 899–903.
6. Joglekar S, Levin M. The promise of thalidomide: evolving indications. *Drugs Today* 2004; **40**: 197–204.
7. Bessmertny O, Pham T. Thalidomide use in pediatric patients. *Ann Pharmacother* 2002; **36**: 521–5.
8. Teo SK. Properties of thalidomide and its analogues: implications for anticancer therapy. *AAPS J* 2005; **7**: E14–E19.

Behçet's syndrome. Thalidomide was effective for the treatment of oral and genital ulceration and follicular lesions in a randomised, double-blind, placebo-controlled study[1] in 96 male patients with Behçet's syndrome (p. 1601.1). It was also noted that the development of new oral and genital ulcers was prevented, although relapses may occur on cessation of therapy. Thalidomide has also been reported[2,3] to be of benefit for severe oral and genital ulceration in children with Behçet's syndrome unresponsive to other treatments. Thalidomide also improved symptoms in a woman with Behçet's syndrome who had recurrent perforating intestinal ulcers.[4]

1. Hamuryudan V, *et al.* Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998; **128**: 443–50.
2. Shek LP-C, *et al.* Thalidomide responsiveness in an infant with Behçet's syndrome. *Pediatrics* 1999; **103**: 1295–7.
3. Kari JA, *et al.* Behçet's disease in UK children: clinical features and treatment including thalidomide. *Rheumatology (Oxford)* 2001; **40**: 933–8.
4. Sayarlioglu M, *et al.* Treatment of recurrent perforating intestinal ulcers with thalidomide in Behçet's disease. *Ann Pharmacother* 2004; **38**: 808–11.

Cachexia. For the use of thalidomide in HIV-associated wasting, see HIV-associated Complications, below, and in cancer-related cachexia, see Malignant Neoplasms, below.

Gastrointestinal bleeding. Thalidomide has been used to control refractory bleeding in patients with gastrointestinal vascular malformations including angiodysplasia. Studies in small groups of patients have shown reductions in the number and size of angiodysplasias and in transfusion requirements. Doses of 50 to 200 mg orally daily have generally been used.[1-3] At least 8 weeks of treatment may be needed for a beneficial effect; the optimum duration of therapy is unknown but thalidomide has been continued for up to 6 months.[1] However, adverse effects may limit its use.[1,3]

1. Kamalaporn P, *et al.* Thalidomide for the treatment of chronic gastrointestinal bleeding from angiodysplasias: a case series. *Eur J Gastroenterol Hepatol* 2009; **21**: 1347–50.
2. Ge Z-Z, *et al.* Efficacy of thalidomide for refractory gastrointestinal bleeding from vascular malformation. *Gastroenterology* 2011; **141**: 1629–37.
3. Garrido A, *et al.* Thalidomide in refractory bleeding due to gastrointestinal angiodysplasias. *Rev Esp Enferm Dig* 2012; **104**: 69–71.

Graft-versus-host disease. A review[1] of studies investigating the use of thalidomide in chronic graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p. 1937.1) concluded that although thalidomide appeared to be of benefit in some patients unresponsive to other treatments, doses greater than 200 mg daily are poorly tolerated in most patients. Giving thalidomide as prophylaxis led to poor survival, possibly through interfering with development of tolerance. Thalidomide was not of benefit when given as treatment for newly diagnosed disease.

1. Flowers MED, Martin PJ. Evaluation of thalidomide for treatment or prevention of chronic graft-versus-host disease. *Leuk Lymphoma* 2003; **44**: 1141–6.

HIV-associated complications. It has been proposed that thalidomide's inhibitory activity against TNF-α may explain its anti-HIV effect. However, there are conflicting reports as both decreased and increased TNF-α levels, as well as unchanged levels, have been seen in HIV-patients.[1] Nevertheless, thalidomide has shown some promise as a therapeutic agent for some AIDS-related diseases. It is an effective treatment for severe ulceration of the mouth (p. 1814.2), oropharynx, and oesophagus in patients with HIV-infection.[2-5] Of concern though is the finding that modest increases in plasma HIV RNA levels have been seen in some patients, which correlated with increases in TNF-α levels.[2,4] Thalidomide has also been tried with some success in HIV-infected patients with prurigo nodularis,[6] alopecia areata[7] (p. 1682.3), and hypertrophic genital herpes[8] (p. 955.2). It has also proved to be of benefit in HIV-associated wasting[9] (p. 959.1), and has shown promise in high doses for the treatment of AIDS-related Kaposi's sarcoma[10] (p. 718.1). Thalidomide was also of benefit in 3 patients with severe idiopathic HIV-associated colitis.[11]

1. Ravot E, *et al.* New uses for old drugs in HIV infection: the role of hydroxyurea, cyclosporin and thalidomide. *Drugs* 1999; **58**: 953–63.
2. Jacobson JM, *et al.* Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. *N Engl J Med* 1997; **336**: 1487–93.
3. Ramirez-Amador VA, *et al.* Thalidomide as therapy for human immunodeficiency virus-related oral ulcers: a double-blind placebo-controlled clinical trial. *Clin Infect Dis* 1999; **28**: 892–4.
4. Jacobson JM, *et al.* Thalidomide for the treatment of esophageal aphthous ulcers in patients with human immunodeficiency virus infection. *J Infect Dis* 1999; **180**: 61–7.
5. Shetty K. Thalidomide in the management of recurrent aphthous ulcerations in patients who are HIV-positive: a review and case reports. *Spec Care Dentist* 2005; **25**: 236–41.
6. Maurer T, *et al.* Thalidomide treatment for prurigo nodularis in human immunodeficiency virus-infected subjects: efficacy and risk of neuropathy. *Arch Dermatol* 2004; **140**: 845–9.
7. Baranda L, *et al.* Severe and unresponsive HIV-associated alopecia areata successfully treated with thalidomide. *Acta Derm Venereol* 2005; **85**: 277–8.
8. Holmes A, *et al.* Thalidomide therapy for the treatment of hypertrophic herpes simplex virus-related genitalis in HIV-infected individuals. *Clin Infect Dis* 2007; **44**: e96–e99. Available at: http://www.journals.uchicago.edu/doi/abs/10.1086/517513 (accessed 18/01/08)
9. Reyes-Terán G, *et al.* Effects of thalidomide on HIV-associated wasting syndrome: a randomized, double-blind, placebo-controlled trial. *AIDS* 1996; **10**: 1501–7.
10. Little RF, *et al.* Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2000; **18**: 2593–2602.
11. Johnson L, *et al.* Thalidomide treatment for refractory HIV-associated colitis: a case series. *Clin Infect Dis* 2008; **47**: 133–6.

Inflammatory bowel disease. Small open-label studies[1-3] have shown efficacy of thalidomide in patients with refractory Crohn's disease (see under Inflammatory Bowel Disease, p. 1811.3). In many of those patients already receiving corticosteroids the dosage could be reduced and in some corticosteroids could be stopped completely. Reduction of TNF-α and interleukin-12 by thalidomide may be responsible for its clinical effects in Crohn's disease.[4] Thalidomide has also been reported[5] to be of benefit in children and young adults with intractable inflammatory bowel disease (both Crohn's disease and ulcerative colitis).

1. Ehrenpreis ED, *et al.* Thalidomide therapy for patients with refractory Crohn's disease: an open-label trial. *Gastroenterology* 1999; **117**: 1271–7.
2. Vasiliauskas EA, *et al.* An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn's disease. *Gastroenterology* 1999; **117**: 1278–87.
3. Bariol C, *et al.* Early studies on the safety and efficacy of thalidomide for symptomatic inflammatory bowel disease. *J Gastroenterol Hepatol* 2002; **17**: 135–9.
4. Bauditz J, *et al.* Thalidomide reduces tumour necrosis factor α and interleukin 12 production in patients with chronic active Crohn's disease. *Gut* 2002; **50**: 196–200.
5. Lazzerini M, *et al.* Efficacy and safety of thalidomide in children and young adults with intractable inflammatory bowel disease: long-term results. *Aliment Pharmacol Ther* 2007; **25**: 419–27.

Kaposi's sarcoma. See under HIV-associated complications, above and under Malignant Neoplasms, below.

Lupus erythematosus. Thalidomide has been found to be of benefit in lupus erythematosus, including chronic discoid lupus erythematosus,[1,2] lupus erythematosus profundus,[3,4] SLE[5] (p. 1613.3), and cutaneous lupus erythematosus.[6-11] The beneficial effect of thalidomide on cutaneous lupus erythematosus may be partly mediated through protection against UV-induced inflammation.[11]

1. Knop J, *et al.* Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol* 1983; **108**: 461–6.
2. Brocard A, *et al.* Lupus érythémateux chronique: traitement par thalidomide. *Ann Dermatol Venereol* 2005; **132**: 853–6.
3. Burrows NP, *et al.* Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. *Br J Dermatol* 1991; **125**: 62–7.
4. Wienert S, *et al.* Facetten des Lupus erythematodes: Pannikulitis mit gutem Ansprechen auf Thalidomid. *J Dtsch Dermatol Ges* 2008; **6** 214–16.
5. Bessis D, *et al.* Thalidomide for systemic lupus erythematosus. *Lancet* 1992; **339**: 549–50.
6. Atra E, Sato EI. Treatment of the cutaneous lesions of systemic lupus erythematosus with thalidomide. *Clin Exp Rheumatol* 1993; **11**: 487–93.
7. Stevens RJ, *et al.* Thalidomide in the treatment of the cutaneous manifestations of lupus erythematosus: experience in sixteen consecutive patients. *Br J Rheumatol* 1997; **36**: 353–9.
8. Duong DJ, *et al.* American experience with low-dose thalidomide therapy for severe cutaneous lupus erythematosus. *Arch Dermatol* 1999; **135**: 1079–87.
9. Pelle MT, Werth VP. Thalidomide in cutaneous lupus erythematosus. *Am J Clin Dermatol* 2003; **4**: 379–87.
10. Cuadrado MJ, *et al.* Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med* 2005; **118**: 246–50.
11. Cummins DL, Gaspari AA. Photoprotection by thalidomide in patients with chronic cutaneous and systemic lupus erythematosus: discordant effects on minimal erythema dose and sunburn cell formation. *Br J Dermatol* 2004; **151**: 458–64.

Malignant neoplasms. Thalidomide has shown benefit in the treatment of patients with multiple myeloma (p. 699.2).[1] In relapsed or refractory disease, a review[2] of uncontrolled studies showed that thalidomide monotherapy may achieve complete or partial responses in about 29% of patients, and found at 12 months after starting therapy an overall survival rate of about 60% and event-free survival of about 35%. The response improves when dexamethasone is added, increasing the complete or partial response rate to about 46% without a significant increase in toxicity.[3] The combination of thalidomide and dexamethasone has also been used in newly-diagnosed patients, with response rates of at least 63% reported.[4,5] This combination may be used as induction therapy before autologous haematopoietic stem cell transplantation.[4] After transplantation, thalidomide has been studied for maintenance therapy and found to reduce the risk for disease progression, but the effect on overall survival has been mixed.[7] It has been suggested that the lowest effective maintenance dose is 50 mg orally daily, that therapy should be given for 1 year or less to limit the risk of significant toxicity, and that thalidomide should not be used in patients with FISH-defined poor-risk cytogenetics; however, the situation for elderly patients is less clear.[7] Improved response rates have been found when thalidomide was added to cycles of melphalan and prednisone in newly-diagnosed elderly patients (when transplantation is generally unsuitable), extending survival-time by about 20% (about 6 to 7 months).[8]

Thalidomide has also been tried in the treatment of several non-plasma cell malignancies with variable results.[9] It has shown promise in patients with recurrent high-grade gliomas[10] (p. 701.2) and is under investigation for non-AIDS-related Kaposi's sarcoma[11,12] (p. 718.1), metastatic melanoma[13] (p. 714.3), myelofibrosis with myeloid metaplasia,[14-16] and androgen-independent prostate cancer[17,18] (p. 712.3).

Thalidomide has shown some benefit in the treatment of cancer-related cachexia (see under Megestrol, p. 2289.3) in patients with pancreatic cancer.[19]

1. Palumbo A, *et al.* Thalidomide for treatment of multiple myeloma: 10 years later. *Blood* 2008; **111**: 3968–77.
2. Glasmacher A, *et al.* A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. *Br J Haematol* 2006; **132**: 584–93.
3. von Lilienfeld-Toal M, *et al.* A systematic review of phase II trials of thalidomide/dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma. *Eur J Haematol* 2008; **81**: 247–52.
4. Rajkumar SV, *et al.* Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 2006; **24**: 431–6.

5. Rajkumar SV, *et al.* Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J Clin Oncol* 2008; **26**: 2171–7.
6. Ludwig H, *et al.* Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood* 2009; **113**: 3435–42.
7. Ludwig H, *et al.* International Myeloma Working Group. IMWG consensus on maintenance therapy in multiple myeloma. *Blood* 2012; **119**: 3003–15.
8. Fayers PM, *et al.* Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood* 2011; **118**: 1239–47.
9. Kumar S, *et al.* Thalidomid: current role in the treatment of non-plasma cell malignancies. *J Clin Oncol* 2004; **22**: 2477–88. Correction. *ibid.*; 2973. [title]
10. Fine HA, *et al.* Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. *J Clin Oncol* 2000; **18**: 708–15.
11. Ben M'barek L, *et al.* A retrospective analysis of thalidomide therapy in non-HIV-related Kaposi's sarcoma. *Dermatology* 2007; **215**: 202–5.
12. Rubegni P, *et al.* Thalidomide in the treatment of Kaposi's sarcoma. *Dermatology* 2007; **215**: 240–4.
13. Danson S, *et al.* Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. *J Clin Oncol* 2003; **21**: 2551–7.
14. Mesa RA, *et al.* Durable responses to thalidomide-based drug therapy for myelofibrosis with myeloid metaplasia. *Mayo Clin Proc* 2004; **79**: 883–9.
15. Marchetti M, *et al.* Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: a phase II trial. *J Clin Oncol* 2004; **22**: 424–31.
16. Thomas DA, *et al.* Thalidomide therapy for myelofibrosis with myeloid metaplasia. *Cancer* 2006; **106**: 1974–84.
17. Figg WD. The 2005 Leon L Goldberg Young Investigator Award Lecture: Development of thalidomide as an angiogenesis inhibitor for the treatment of androgen-independent prostate cancer. *Clin Pharmacol Ther* 2006; **79**: 1–8.
18. Cox MC, *et al.* The use of thalidomide in androgen-independent prostate cancer. *Urol Oncol* 2006; **24**: 246–9.
19. Gordon JN, *et al.* Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005; **54**: 540–5.

Mouth ulceration. See under Behçet's syndrome p. 868.1 and under HIV-associated complications, p. 868.2.

Oesophageal ulceration. Thalidomide has been shown to be of benefit in the treatment of idiopathic oesophageal ulcers in patients with AIDS (see under HIV-associated complications, p. 868.2). Thalidomide has also been reported to have healed an oesophageal ulcer refractory to other treatments in an immunocompetent patient,[1] and in an immunocompromised patient after liver transplant.[2]

1. Ollivier S, *et al.* Idiopathic giant oesophageal ulcer in an immunocompetent patient: the efficacy of thalidomide treatment. *Gut* 1999; **45**: 463–4.
2. Atiq M, *et al.* Successful treatment with thalidomide in a liver transplant recipient with giant esophageal ulcers. *Liver Transpl* 2006; **12**: 987–8.

Rheumatic disorders. Beneficial responses to thalidomide have been reported in the treatment of refractory rheumatoid arthritis[1] and adult-onset Still's disease.[2] Thalidomide also improved symptoms in 2 children with systemic onset juvenile rheumatoid arthritis, in whom other therapy, including etanercept, had been ineffective.[3] Efficacy was also shown in a further 11 children with refractory disease who were able to reduce their use of prednisone.[4]

1. Gutiérrez-Rodríguez O, *et al.* Treatment of refractory rheumatoid arthritis—the thalidomide experience. *J Rheumatol* 1989; **16**: 158–63.
2. Stambe C, Wicks IP. TNFα and response of treatment-resistant adult-onset Still's disease to thalidomide. *Lancet* 1998; **352**: 544–5.
3. Lehman TJA, *et al.* Thalidomide therapy for recalcitrant systemic onset juvenile rheumatoid arthritis. *J Pediatr* 2002; **140**: 125–7.
4. Lehman TJ, *et al.* Thalidomide for severe systemic onset juvenile rheumatoid arthritis: a multicenter study. *J Pediatr* 2004; **145**: 856–7.

Sarcoidosis. Case reports[1-5] of thalidomide in the treatment of sarcoidosis suggest that it might be of benefit.

1. Carlesimo M, *et al.* Treatment of cutaneous and pulmonary sarcoidosis with thalidomide. *J Am Acad Dermatol* 1995; **32**: 866–9.
2. Baughman RP, *et al.* Thalidomide for chronic sarcoidosis. *Chest* 2002; **122**: 227–32.
3. Walter MC, *et al.* Successful treatment of muscle sarcoidosis with thalidomide. *Acta Myol* 2003; **22**: 22–5.
4. Nguyen YT, *et al.* Treatment of cutaneous sarcoidosis with thalidomide. *J Am Acad Dermatol* 2004; **50**: 235–41.
5. Hammond ER, *et al.* Thalidomide for acute treatment of neurosarcoidosis. *Spinal Cord* 2007; **45**: 802–3.

Skin disorders. Thalidomide has shown efficacy in several severe dermatological disorders refractory to conventional therapies.[1,2] A review[3] of studies of thalidomide in the treatment of severe type 2 (erythema nodosum leprosum) lepra reactions concluded that it is an effective alternative to corticosteroid therapy. It has also been investigated in other severe skin disorders and beneficial responses have been reported in erythema multiforme[4,5] (p. 1684.3), pruritus associated with uraemia,[6] Langerhans-cell histiocytosis[7] (p. 692.1), epidermolysis bullosa and its variants,[8-10] prurigo nodularis,[11,12] pyoderma gangrenosum[13,14] (p. 1688.3), and Schnitzler's syndrome.[15] Thalidomide has been reported[16] to be of benefit in the treatment of erythema nodosum-like lesions attributed to immune reconstitution inflammatory syndrome that developed in a patient after initiation of antibacterial therapy for Whipple's disease.

1. Wu JJ, *et al.* Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* 2005; **153**: 254–73.
2. Faver IR, *et al.* Thalidomide for dermatology: a review of clinical uses and adverse effects. *Int J Dermatol* 2005; **44**: 61–7.
3. Walker SL, *et al.* The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev* 2007; **78**: 197–215.
4. Bahmer FA, *et al.* Thalidomide treatment of recurrent erythema multiforme. *Acta Derm Venereol (Stockh)* 1982; **62**: 449–50.
5. Moisson YF, *et al.* Thalidomide for recurrent erythema multiforme. *Br J Dermatol* 1992; **126**: 92–3.
6. Silva SRB, *et al.* Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. *Nephron* 1994; **67**: 270–3.
7. McClain KL, Kozinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2007; **48**: 44–9.
8. Goulden V, *et al.* Linear prurigo simulating dermatitis artefacta in dominant dystrophic epidermolysis bullosa. *Br J Dermatol* 1993; **129**: 443–6.
9. Ozanic Bulic S, *et al.* Thalidomide in the management of epidermolysis bullosa pruriginosa. *Br J Dermatol* 2005; **152**: 1332–4.
10. Strauss RM, *et al.* A child with laryngo-onychocutaneous syndrome partially responsive to treatment with thalidomide. *Br J Dermatol* 2006; **155**: 1283–6.
11. Ferrándiz C, *et al.* Sequential combined therapy with thalidomide and narrow-band (TL01) UVB in the treatment of prurigo nodularis. *Dermatology* 1997; **195**: 359–61.
12. Lan C-CE, *et al.* Treatment of idiopathic prurigo nodularis in Taiwanese patients with low-dose thalidomide. *J Dermatol* 2007; **34**: 237–42.
13. Federman GL, Federman DG. Recalcitrant pyoderma gangrenosum treated with thalidomide. *Mayo Clin Proc* 2000; **75**: 842–4.
14. Koca E, *et al.* Successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum. *Neth J Med* 2006; **64**: 422–4.
15. Worm M, Kolde G. Schnitzler's syndrome: successful treatment of two patients using thalidomide. *Br J Dermatol* 2003; **148**: 601–2.
16. Lagier J-C, *et al.* Successful treatment of immune reconstitution inflammatory syndrome in Whipple's disease using thalidomide. *J Infect* 2010; **60**: 79–82.

Adverse Effects and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Thalidomide was withdrawn from use as a hypnotic in the early 1960s after it was discovered that it produced teratogenic effects when given in early pregnancy. These effects, which could develop after a single dose, involved mainly malformations of the limbs and defects of the ears, eyes, and internal organs. Death at or shortly after birth was also common. Further abnormalities and problems, including effects on the CNS, developed in later life.

Thalidomide was reintroduced in 1998 for use as an immunomodulator but because of its severe teratogenic effects, it should not be used in women of child-bearing potential, or if such use is absolutely essential then stringent contraceptive measures must be used, including the simultaneous use of 2 reliable forms of contraception for at least 4 weeks before, during, and for 4 weeks after, thalidomide therapy. A pregnancy test must be carried out before starting thalidomide treatment (preferably within 24 hours, and no more than 3 days before), and regular tests carried out during treatment. If pregnancy occurs during thalidomide therapy the drug must be stopped immediately and the patient given appropriate evaluation and counselling. As thalidomide is present in semen, male patients receiving thalidomide should use barrier methods of contraception even after successful vasectomy if their partner is of child-bearing potential. Patients should not donate blood or sperm during thalidomide therapy, or for 4 weeks after stopping.

The other major adverse effect of thalidomide is peripheral neuropathy, which can be severe and irreversible, and dose modifications should be considered. If there is no loss of function (grade 1), the patient should be monitored and doses reduced if symptoms worsen. If function deteriorates but daily living activities are not compromised (grade 2), the dose should be reduced or treatment interrupted and the patient monitored; treatment should be discontinued if there is no improvement, or it may be restarted if neuropathy resolves. Treatment should be discontinued when the neuropathy interferes with daily activities (grade 3) or is disabling (grade 4).

Venous thromboembolism has been reported in a significant number of patients receiving thalidomide for multiple myeloma, particularly in those also receiving chemotherapeutic drugs, including dexamethasone. Arterial thromboembolic events, including myocardial infarction and stroke, have also occurred, especially in patients with pre-existing risk factors for these; thromboprophylaxis should be considered, particularly in the first few months of treatment (see Effects on the Cardiovascular System, below).

Thalidomide is a centrally active hypnotic sedative and frequently causes drowsiness and somnolence; affected patients should not drive or operate machinery. Other common adverse effects include constipation, dizziness, and orthostatic hypotension. Hypersensitivity reactions have occurred. An erythematous macular rash may develop, usually 2 to 10 days after initiation of therapy. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported, and therefore thalidomide should be stopped if a rash develops and only restarted after appropriate clinical evaluation. Thalidomide therapy should not be resumed if the rash is exfoliative, purpuric, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. Neutropenia and an increase in the viral load in HIV-infected patients have also been reported; thalidomide therapy should not be started in neutropenic patients. Bradycardia, heart failure, renal failure, seizures, worsening of Parkinson's disease symptoms, and hearing impairment or deafness, have also been reported. Patients with a high tumour burden before treatment are at increased risk of tumour lysis syndrome.

Although human data for breast feeding while taking thalidomide are lacking, licensed product information recommends that it should be avoided in view of the potential for serious adverse effects in the infant.

Reviews.
1. Günzler V. Thalidomide in human immunodeficiency virus (HIV) patients: a review of safety considerations. *Drug Safety* 1992; **7**: 116–34.
2. Clark TE, *et al.* Thalomid(thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Safety* 2001; **24**: 87–117.
3. Grover JK, *et al.* The adverse effects of thalidomide in relapsed and refractory patients of multiple myeloma. *Ann Oncol* 2002; **13**: 1636–40.
4. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. *J Support Oncol* 2003; **1**: 194–205.
5. Dimopoulos MA, Eleutherakis-Papaiakovou V. Adverse effects of thalidomide administration in patients with neoplastic diseases. *Am J Med* 2004; **117**: 508–15.
6. Uhl K, *et al.* Thalidomide use in the US: experience with pregnancy testing in the S.T.E.P.S. programme. *Drug Safety* 2006; **29**: 321–9.

Effects on the blood. Thrombocytopenia has been reported in patients given thalidomide for multiple myeloma.[1,2]

1. Duyvendak M, *et al.* Thalidomide-associated thrombocytopenia. *Ann Pharmacother* 2005; **39**: 1936–9.
2. Prasad HK, *et al.* Isolated thrombocytopenia induced by thalidomide in a patient with multiple myeloma: case report and review of literature. *Am J Hematol* 2007; **82**: 855–7.

Effects on the cardiovascular system. Use of thalidomide in patients with malignant neoplastic disease has been associated with an increased risk of **venous** thromboembolic events such as deep-vein thrombosis. There were 27 spontaneous reports of thromboembolic events in the first 18 months of thalidomide returning to the US market in July 1998; 26 of these were in patients with malignancies.[1] A review[2] of thromboembolic events associated with thalidomide identified 67 such reports from a total of 2075 adverse events reported to the FDA between October 1998 and June 2001; a further 29 cases were identified from clinical study data. Deep-vein thrombosis occurred in 48 of these patients, pulmonary embolism in 25, and 23 developed both. The most common primary diagnoses among these patients were multiple myeloma and renal cell carcinoma. However, it should be noted that patients with cancer are known to be at increased risk of venous thromboembolism and some chemotherapeutic regimens may further increase this risk. The contribution of thalidomide to the development of venous thromboembolism remains to be fully evaluated in controlled studies. Further reviews[3,4] of reports of venous thromboembolism associated with thalidomide concluded that the incidence of venous thromboembolism in patients with multiple myeloma is higher when thalidomide is given with chemotherapeutic drugs such as dexamethasone, melphalan, or doxorubicin.

Patients given thalidomide have also been reported to be at increased risk of **arterial** thromboembolic events such as myocardial infarction and stroke. This risk appeared to be greatest in the first 5 months of treatment, and most patients who had such effects had pre-existing thromboembolic risk factors. It is recommended that measures should be taken to reduce modifiable risk factors such as hypertension, hyperlipidaemia, and smoking in those given thalidomide, and that candidates for thalidomide treatment be given appropriate thromboprophylaxis at least for the first 5 months, especially those with thromboembolic risk factors additional to their underlying pathology.[5]

Studies suggest that prophylactic use of a low-molecular-weight heparin (enoxaparin),[6] low-dose aspirin,[7] or low-dose warfarin[8] may reduce the incidence of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapeutic drugs. A comparison of these 3 drugs in patients who did not have any other clear indication for prophylaxis showed them to be equally effective in reducing serious thromboembolic events, acute cardiovascular events, and sudden death.[9]

Bradycardia has been associated with thalidomide therapy in some patients, although symptoms may be managed by a reduction in dose.[10,11] See also under Effects on the Endocrine System, p. 870.1.

1. Clark TE, *et al.* Thalomid(thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Safety* 2001; **24**: 87–117.
2. Bennett CL, *et al.* Thalidomide-associated deep vein thrombosis and pulmonary embolism. *Am J Med* 2002; **113**: 603–6.
3. Bennett CL, *et al.* Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. *JAMA* 2006; **296**: 2558–60.
4. Rajkumar SV. Thalidomide therapy and deep venous thrombosis in multiple myeloma. *Mayo Clin Proc* 2005; **80**: 1549–51.
5. Celgene, Fr. Thalidomide Celgene(thalidomide) et effets indésirables thromboemboliques artériels et veineux (issued May 2011). Available at: http://www.afssaps.fr/var/afssaps_site/storage/original/application/e9fe25485f5b263201af9b1395909881.pdf (accessed 12/05/11)

6. Zangari M, *et al.* Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. *Br J Haematol* 2004; 126: 715–21.
7. Baz R, *et al.* The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc* 2005; 80: 1568–74.
8. Ikhlaque N, *et al.* Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis. *Am J Hematol* 2006; 81: 420–2.
9. Palumbo A, *et al.* Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol* 2011; 29: 986–93.
10. Coutsouvelis J, Corallo CE. Thalidomide-induced bradycardia and its management. *Med J Aust* 2004; 180: 366–7.
11. Fahdi IE, *et al.* Bradycardia during therapy for multiple myeloma with thalidomide. *Am J Cardiol* 2004; 93: 1052–5.

Effects on the endocrine system. Amenorrhoea has been reported[1,2] in women taking thalidomide for severe dermatological conditions; menses resumed 2 to 3 months after stopping thalidomide.[2]

Hypothyroidism has been associated with thalidomide use in patients with multiple myeloma,[3,4] and it was suggested[3] that some adverse effects of thalidomide, such as bradycardia and constipation, may be manifestations of hypothyroidism.

Severe hyperglycaemia has been reported[5] in a 70-year-old man 4 weeks after starting thalidomide for multiple myeloma. Plasma-glucose concentrations returned to normal after treatment with insulin and an oral antidiabetic and he continued with thalidomide therapy.

1. Passeron T, *et al.* Thalidomide-induced amenorrhoea: two cases. *Br J Dermatol* 2001; 144: 1292–3.
2. Francès C, *et al.* Transient secondary amenorrhea in women treated by thalidomide. *Eur J Dermatol* 2002; 12: 63–5.
3. Badros AZ, *et al.* Hypothyroidism in patients with multiple myeloma following treatment with thalidomide. *Am J Med* 2002; 112: 412–13.
4. de Savary N, *et al.* Severe hypothyroidism after thalidomide treatment. *J R Soc Med* 2004; 97: 443.
5. Pathak RD, *et al.* Thalidomide-associated hyperglycemia and diabetes: case report and review of literature. *Diabetes Care* 2003; 26: 1322–3.

Effects on the gastrointestinal tract. Bowel perforation requiring surgery has been reported[1] in 3 patients taking thalidomide for malignant neoplasms. A fourth case of acute abdominal pain and suspected bowel perforation is also described but the patient died of a cardiac arrest before surgery.

1. McClay H, Cervi P. Thalidomide and bowel perforation: four cases in one hospital. *Br J Haematol* 2008; 140: 360–1.

Effects on the liver. Hepatitis has been reported[1] in a 58-year-old woman taking thalidomide for end-stage plasma cell leukaemia. In another report of hepatotoxicity,[2] a 76-year-old woman with multiple myeloma being treated with thalidomide and dexamethasone developed jaundice and acute increases in liver enzymes, which returned to normal when thalidomide was stopped. Fatal fulminant hepatic failure with encephalopathy that appeared to be associated with thalidomide developed in a 64-year-old woman being treated for multiple myeloma.[3]

1. Fowler R, Imrie K. Thalidomide-associated hepatitis: a case report. *Am J Hematol* 2001; 66: 300–2.
2. Hanje AJ, *et al.* Thalidomide-induced severe hepatotoxicity. *Pharmacotherapy* 2006; 26: 1018–22.
3. Hamadani M, *et al.* Thalidomide-induced fulminant hepatic failure. *Mayo Clin Proc* 2007; 82: 638.

Effects on the lungs. Interstitial pneumonitis,[1] including interstitial pneumonia,[2] has been reported in patients taking *thalidomide* for multiple myeloma. There have also been reports of dyspnoea in women taking thalidomide for ovarian cancer; resolution of symptoms occurred on drug withdrawal and some patients were able to continue therapy when reintroduced at a reduced dose.[3]

There have also been reports of respiratory toxicity associated with *pomalidomide* therapy for multiple myeloma.[4] One patient abruptly developed dyspnoea, pyrexia, and chills about 4 months after starting pomalidomide plus dexamethasone treatment; lung infiltrates consistent with pneumonitis were noted. Pomalidomide was stopped and symptoms resolved quickly with corticosteroid treatment. Treatment was later restarted with a reduced dose of pomalidomide without recurrence of symptoms. Another patient developed dyspnoea 16 months after starting pomalidomide plus dexamethasone treatment. Symptoms resolved when treatment was withdrawn but recurred with 2 further rechallenges, one using a lower dose of pomalidomide.

1. Onozawa M, *et al.* Thalidomide-induced interstitial pneumonitis. *J Clin Oncol* 2005; 23: 2425–6.
2. Sasaki M, *et al.* Thalidomide may induce interstitial pneumonia preferentially in Japanese patients. *Eur J Haematol* 2009; 82: 73–4.
3. Gordinier ME, Dizon DS. Dyspnea during thalidomide treatment for advanced ovarian cancer. *Ann Pharmacother* 2005; 39: 962–5.
4. Geyer BL, *et al.* Acute lung toxicity related to pomalidomide. *Chest* 2011; 140: 529–33.

Effects on mental function. Symptoms of dementia appeared in a patient who had been taking thalidomide for about 2 months for the treatment of multiple myeloma.[1] Dementia later resolved completely within 48 hours of stopping thalidomide.

1. Morgan AE, *et al.* Reversible dementia due to thalidomide therapy for multiple myeloma. *N Engl J Med* 2003; 348: 1821–2.

Effects on the nervous system. Peripheral neuropathy is a major adverse effect of thalidomide therapy, although the underlying mechanisms, risk factors, and optimum management are still not clear.[1] One prospective study[2] in patients with cutaneous lupus erythematosus or SLE concluded that the cumulative dose of thalidomide had no effect on the incidence of peripheral neuropathy, whereas results from a retrospective study[3] in patients with SLE or multiple myeloma showed that the risk of developing neurotoxicity as well as severity of symptoms did correlate with cumulative dose. However, the latter study[3] examined a range of doses and found that this correlation was most significant at cumulative doses over 20 g but either absent or equivocal at lower doses, which might explain the discrepancies in results between studies using different doses. Two further studies[4,5] in patients with multiple myeloma concluded that neurotoxicity was associated with duration of treatment of greater than 6 to 12 months rather than dose-intensity or total cumulative dose. Conversely, another study,[6] also in multiple myeloma patients, found electrophysiologic evidence of peripheral neuropathy in two-thirds of patients as early as 4 months from the start of treatment, and in all of them by 7 months; many patients also had clinical symptoms.

Central neurotoxicity has also been reported[7] in a patient who developed encephalopathy after receiving thalidomide monotherapy for multiple myeloma over 21 months.

1. Apiel SC, Zochodne DW. Thalidomide neuropathy: too much or too long? *Neurology* 2004; 62: 2158–9.
2. Briani C, *et al.* Thalidomide neurotoxicity: prospective study in patients with lupus erythematosus. *Neurology* 2004; 62: 2288–90.
3. Cavaletti G, *et al.* Thalidomide sensory neurotoxicity: a clinical and neurophysiologic study. *Neurology* 2004; 62: 2291–3.
4. Tosi P, *et al.* Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *Eur J Haematol* 2005; 74: 212–16.
5. Mileshkin L, *et al.* Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring. *J Clin Oncol* 2006; 24: 4507–14.
6. Plasmati R, *et al.* Neuropathy in multiple myeloma treated with thalidomide: a prospective study. *Neurology* 2007; 69: 573–81.
7. Sohlbach K, *et al.* Encephalopathy in a patient after long-term treatment with thalidomide. *J Clin Oncol* 2006; 24: 4942–4.

Effects on sexual function. Dose-related sexual dysfunction, including loss of libido, loss of penile rigidity, and premature ejaculation, was associated with thalidomide use in 2 male patients.[1] Erectile dysfunction has been reported[2] in 6 patients within 4 weeks of starting thalidomide therapy.

1. Pouaha J, *et al.* Thalidomide and sexual dysfunction in men. *Br J Dermatol* 2002; 146: 1112–13.
2. Murphy PT, O'Donnell JR. Thalidomide induced impotence in male hematology patients: a common but ignored complication? *Haematologica* 2007; 92: 1440.

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a 62-year-old woman about 5 weeks after starting thalidomide for the treatment of a glioblastoma. Although she was taking several other drugs, including dexamethasone, thalidomide was considered responsible since its use had the closest temporal relationship to the adverse effect. Toxic epidermal necrolysis has also been reported[2] in a 64-year-old patient 24 days after starting thalidomide and dexamethasone for myeloma. It was suggested that there might be an adverse interaction between thalidomide and dexamethasone. Thalidomide had previously been studied[3] for the *treatment* of toxic epidermal necrolysis, but the study was prematurely terminated because of significantly higher mortality in the thalidomide group; the causes of death were those usually attributed to the disease itself. Thalidomide had been chosen as an investigative drug because it is a potent inhibitor of TNF-α, which has been implicated in the pathogenesis of this condition. However, the authors noted that there was a tendency for plasma concentrations of TNF-α to increase after treatment with thalidomide compared with the placebo group, and postulated that thalidomide might paradoxically enhance TNF-α production in these patients.

Exacerbation of psoriasis by thalidomide, reported, in 2 patients might also have been due to an increase in TNF-α production.[4,5]

In an open-label study in 87 patients with multiple myeloma[6] comparing thalidomide given as monotherapy or given with dexamethasone, minor to moderate skin eruptions were noted in about 45% of patients in each group, and included morbilliform, seborrhoeic, maculopapular, and non-specific dermatitis. Three patients receiving thalidomide and dexamethasone developed severe skin reactions (exfoliative erythroderma, erythema multiforme, or toxic epidermal necrolysis) that required treatment to be stopped.

1. Horowitz SB, Stirling AL. Thalidomide-induced toxic epidermal necrolysis. *Pharmacotherapy* 1999; 19: 1177–80.
2. Rajkumar SV, *et al.* Life-threatening toxic epidermal necrolysis with thalidomide therapy for myeloma. *N Engl J Med* 2000; 343: 972–3.
3. Wolkenstein P, *et al.* Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; 352: 1586–9.
4. Dobson CM, Parslew RA. Exacerbation of psoriasis by thalidomide in Behçet's syndrome. *Br J Dermatol* 2003; 149: 432–3.
5. Varma K, Finlay AY. Exacerbation of psoriasis by thalidomide in a patient with erythema multiforme. *Br J Dermatol* 2006; 154: 789–90.
6. Hall VC, *et al.* Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003; 48: 548–52.

Migraine. Migraine attacks were associated with thalidomide use in a 36-year-old man.[1]

1. García-Albea E, *et al.* Jaqueca típica y talidomida. *Med Clin (Barc)* 1993; 100: 557.

Mutagenicity. Reports of the birth of 3 malformed infants to parents who had themselves been exposed to thalidomide *in utero*[1,2] provoked fears that thalidomide may be a mutagen. However, the limb malformations seen in the infants were not typical of mutagenesis[3] and the teratogenic effect of thalidomide was likely to be associated with interference with angiogenesis in the fetus rather than mutation.[4] Review[5] of the evidence up to 1998 concluded that there was no scientific basis for the hypothesis that thalidomide is a mutagen and birth defects appeared to be no more common in children born to thalidomide-affected parents than in the population as a whole. Further support for the counter-argument came in 2002 from a Swedish retrospective study in which malformations or functional anomalies consistent with thalidomide embryopathy were not found in 64 children born to 34 parents with thalidomide embryopathy.[6]

1. McBride WG. Thalidomide may be a mutagen. *BMJ* 1994; 308: 1635–6.
2. Tenconi R, *et al.* Amniotic band sequence in child of thalidomide victim. *BMJ* 1994; 309: 1442.
3. Read AP. Thalidomide may be a mutagen. *BMJ* 1994; 308: 1636.
4. D'Amato RJ, *et al.* Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994; 91: 4082–5.
5. Smithells D. Does thalidomide cause second generation birth defects? *Drug Safety* 1998; 19: 339–41.
6. Strömland K, *et al.* Offspring of male and female parents with thalidomide embryopathy: birth defects and functional anomalies. *Teratology* 2002; 66: 115–21.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thalidomide 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 28/09/11)

Interactions

The sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine has been reported to be enhanced by thalidomide. Use with other drugs that have the potential to cause peripheral neuropathy should be undertaken cautiously.

Antineoplastics. There may be an increased risk of deep-vein thrombosis from the use of thalidomide with *doxorubicin* (see p. 785.3). See also Effects on the Cardiovascular System, p. 869.3.

For the effect of thalidomide on the metabolism of *irinotecan*, see under Interactions of Irinotecan, p. 814.2.

Corticosteroids. For reference to a possible interaction between thalidomide and *dexamethasone*, see under Effects on the Skin, above.

Hormonal contraceptives. Thalidomide does *not* alter the metabolism of ethinylestradiol and norethisterone,[1,2] and so the efficacy of oral contraceptives should not be affected by thalidomide therapy. Nevertheless, 2 reliable forms of contraception should always be used simultaneously when taking thalidomide (see Adverse Effects and Precautions, p. 869.2), bearing in mind that the reliability of hormonal contraceptives may be compromised by drugs other than thalidomide (see p. 2242.3).

1. Trapnell CB, *et al.* Thalidomide does not alter the pharmacokinetics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* 1998; 64: 597–602.
2. Scheffler MR, *et al.* Thalidomide does not alter estrogen-progesterone hormone single-dose pharmacokinetics. *Clin Pharmacol Ther* 1999; 65: 483–90.

Interferons. Neurological toxicity was reported[1] in 4 of 13 patients in a phase II study of thalidomide and interferon alfa-2a used together in the treatment of renal cell carcinoma. It was suggested that the membrane-destabilising properties of both drugs could have produced such serious toxicity since it exceeded that expected from either drug alone. A fifth patient had a Stevens-Johnson reaction that was also attributed to the combination. The study was halted as a result of these serious adverse effects.

Severe bone marrow depression has been reported[2] in a patient given thalidomide with peginterferon alfa-2b that was also attributed to the combined effect of the 2 drugs.

1. Nathan PD, *et al.* Unexpected toxicity of combination thalidomide and interferon alfa-2a treatment in metastatic renal cell carcinoma. *J Clin Oncol* 2002; **20**: 1429–30.
2. Gómez-Rangel JD, *et al.* Pegylated-interferon induced severe bone marrow hypoplasia in a patient with multiple myeloma receiving thalidomide. *Am J Hematol* 2003; **74**: 290–1.

Pharmacokinetics

Thalidomide is slowly absorbed from the gastrointestinal tract; peak plasma concentrations occur within about 3 to 6 hours of an oral dose. It crosses the placenta and is distributed into the semen. The exact metabolic route and fate of thalidomide is unknown, although it appears to undergo non-enzymatic hydrolysis in plasma. The elimination half-life is about 5 to 7 hours.

References.

1. Aweeka F, *et al.* Pharmacokinetics and pharmacodynamics of thalidomide in HIV patients treated for oral aphthous ulcers: ACTG protocol 251. *J Clin Pharmacol* 2001; **41**: 1091–7.
2. Wohl DA, *et al.* Safety, tolerability, and pharmacokinetic effects of thalidomide in patients infected with human immunodeficiency virus: AIDS Clinical Trials Group 267. *J Infect Dis* 2002; **185**: 1359–63.
3. Teo SK, *et al.* Clinical pharmacokinetics of thalidomide. *Clin Pharmacokinet* 2004; **43**: 311–27.
4. Kamikawa R, *et al.* The pharmacokinetics of low-dose thalidomide in Japanese patients with refractory multiple myeloma. *Biol Pharm Bull* 2006; **29**: 2331–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Thalomid; *Canad.*: Thalomid; *Chile*: Inmunoprin; *India*: Oncothal; Thalix; *Jpn*: Thaled; *Mex.*: Inmunoprin; Talizer; *NZ*: Thalomid; *Philipp.*: Thalix; *UK*: Talidex; *USA*: Thalomid.

Pharmacopoeial Preparations
USP 36: Thalidomide Capsules.

Thiotepa *(BAN, rINN)*

NSC-6396; TESPA; Thiophosphamide; Thiotépa; Thiotepum; Tiotepa; Triethylenethiophosphoramide; TSPA; WR-45312; Tiotrena.

Phosphorothioic tri(ethyleneamide); Tris(aziridin-1-yl)phosphine sulphide.

$C_6H_{12}N_3PS$=189.2

CAS — 52-24-4.

ATC — L01AC01.

ATC Vet — QL01AC01.

UNII — 905Z5W3GKH.

Pharmacopoeias. In *Br., Chin., Fr., Jpn,* and *US.*

BP 2014: (Thiotepa). Fine white, crystalline flakes. M.p. 52 degrees to 57 degrees. Freely soluble in water, in alcohol, and in chloroform. Store at 2 degrees to 8 degrees. At higher temperatures it polymerises and becomes inactive.

USP 36: (Thiotepa). Fine white, crystalline flakes, having a faint odour. M.p. 52 degrees to 57 degrees. Soluble 1 in 13 of water, 1 in about 8 of alcohol, 1 in about 2 of chloroform, and 1 in about 4 of ether. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Incompatibility. Lyophilised thiotepa 1 mg/mL in glucose 5% was incompatible when mixed with solutions of cisplatin or minocycline hydrochloride.[1]

1. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53**: 1041–5.

Stability. A solution of a lyophilised thiotepa preparation 500 micrograms/mL in glucose 5% was considered to be stable (less than 10% loss of thiotepa) for 8 hours at both 4 degrees and 23 degrees.[1] After 24 hours losses ranged between about 10 and 17%. A higher thiotepa concentration (5 mg/mL) was stable for 3 days at 23 degrees and 14 days at 4 degrees. Another study found that solutions containing 1 or 3 mg/mL of thiotepa in sodium chloride 0.9% were stable for 24 hours at 25 degrees and 48 hours at 8 degrees, but solutions containing 0.5% thiotepa needed to be used immediately.[2]

1. Xu QA, *et al.* Stability of thiotepa (lyophilized) in 5% dextrose injection at 4 and 23 degreesC. *Am J Health-Syst Pharm* 1996; **53**: 2728–30.
2. Murray KM, *et al.* Stability of thiotepa (lyophilized) in 0.9% sodium chloride injection. *Am J Health-Syst Pharm* 1997; **54**: 2588–91.

Uses and Administration

Thiotepa is an ethyleneimine compound whose antineoplastic effect is related to its alkylating action. It has generally been replaced by cyclophosphamide (p. 771.1) or other drugs. It is not a vesicant and may be given by all parenteral routes, as well as directly into tumour masses.

Thiotepa has been given parenterally in the palliative treatment of various solid tumours, including those of breast and ovary (p. 702.1 and p. 711.2). It may also be given intravenously with other antineoplastic drugs, with or without total body irradiation, as a conditioning therapy before autologous or allogeneic haematopoietic progenitor cell transplantation (HPCT). Instillations of thiotepa may be used in the adjuvant treatment of superficial tumours of the bladder (p. 700.2) and in the control of malignant effusions (p. 700.1). It has also been given intrathecally to patients with malignant meningeal disease, and has been used, in the form of eye drops, as an adjunct to the surgical removal of pterygium, to prevent recurrence (see p. 831.2). Thiotepa has also been used in the treatment of condylomata acuminata (p. 1689.3).

Thiotepa is given in a variety of dosage schedules for the **palliative treatment** of various solid tumours. In general, initial doses to suit the individual patient are followed by maintenance doses given at intervals of 1 to 4 weeks. Blood counts are recommended before and during therapy and should continue for at least 3 weeks after stopping. Thiotepa should not be given if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p. 730.3) and treatment should be stopped if the white cell count falls rapidly. Dosage should be reduced in patients with lesser degrees of leucopenia.

Intramuscular and intravenous dosage regimens vary considerably; several regimens have used courses of 15 mg daily for 4 days. In the USA a licensed dose of 300 to 400 micrograms/kg may be given intravenously at 1- to 4-week intervals. A solution containing 1 mg/mL in sterile water has been tried intrathecally in doses of up to 10 mg given on alternate days, for up to 4 doses (see also Administration, below).

The following doses, given by intravenous infusion over 2 to 4 hours, are recommended for use as **conditioning therapy:**

- for haematological diseases:
  - 125 to 300 mg/m² daily, given as a single infusion, for 2 to 4 days before *autologous* HPCT to a maximum cumulative dose of 900 mg/m² for the entire conditioning treatment, *or*
  - 185 to 481 mg/m² daily, given in one or two infusions, for 1 to 3 days before *allogeneic* HPCT to a maximum cumulative dose of 555 mg/m² for the entire conditioning treatment
- for solid tumours:
  - 120 to 250 mg/m² daily, given in one or two infusions, for 2 to 5 days before autologous HPCT to a maximum cumulative dose of 800 mg/m² for the entire conditioning treatment

For doses of thiotepa given as conditioning therapy in children, see below.

In the treatment of **bladder cancer** thiotepa in doses up to 60 mg may be instilled in 30 to 60 mL of sterile water or sodium chloride 0.9% into the bladder of a patient previously dehydrated for 8 to 12 hours, and retained if possible for 2 hours. The instillation may be repeated weekly for up to 4 weeks. Similar instillations have been given at intervals of 1 to 2 weeks, for up to 8 instillations in the prophylaxis of recurrence after surgical removal of bladder cancer. Single doses of 90 mg in 100 mL of sterile water have also been used prophylactically. For **malignant effusions**, doses of up to 60 mg of thiotepa in 20 to 60 mL of sterile water may be instilled after aspiration; in the USA the licensed dose is 600 to 800 micrograms/kg, a dose similar to that suggested for injection directly into tumours. Thiotepa for local use may be mixed with solutions of procaine and adrenaline.

Thiotepa 0.05% in sterile Ringer's solution has been instilled as eye drops every 3 hours for up to 6 weeks after surgical removal of **pterygium** in order to reduce the likelihood of recurrence.

A dose of 60 mg in a gel has been instilled weekly into the urethra for the treatment of **condylomata acuminata** (genital warts). Topical application of thiotepa has also been used for condylomata.

Administration. Neurotoxicity of intrathecal chemotherapy has been variously attributed to preservatives, volume, osmolality, and pH of the preparation; common practice is to prepare intrathecal chemotherapy with preservative-free diluent and limit the volume of the final solution, usually to 5 mL. A study evaluated pH and osmolality for thiotepa intrathecal solutions (in various diluents) at concentrations commonly used in practice: 1, 2, and 5 mg/mL. The concentration of thiotepa or the diluent used did not significantly change the pH of the injection; however, osmolality was generally lower than the physiological range of the CSF.[1]

1. de Lemos ML, *et al.* Evaluation of osmolality and pH of various concentrations of methotrexate, cytarabine, and thiotepa prepared in normal saline, sterile water for injection, and lactated Ringer's solution for intrathecal administration. *J Oncol Pharm Pract* 2009; **15**: 45–52.

Administration in children. Thiotepa may be given with other antineoplastic drugs, with or without total body irradiation, to children as a conditioning therapy before autologous or allogeneic haematopoietic progenitor cell transplantation (HPCT). The following doses, given by intravenous infusion over 2 to 4 hours, are recommended:

- for haematological diseases: 125 to 250 mg/m² daily, given in one or two infusions, for 1 to 3 days before *allogeneic* HPCT to a maximum cumulative dose of 375 mg/m² for the entire conditioning treatment
- for solid tumours: 150 to 350 mg/m² daily, given as a single infusion, for 2 to 3 days before *autologous* HPCT to a maximum cumulative dose of 1050 mg/m² for the entire conditioning treatment

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression may be delayed; the nadir of white cell and platelet counts may occur up to 30 days after thiotepa has been stopped. Bone-marrow depression has been reported after intravesical as well as parenteral use, and has occasionally been prolonged or fatal.

Gastrointestinal disturbances, fatigue, weakness, headache and dizziness, hypersensitivity reactions, blurred vision and conjunctivitis may occur. Amenorrhoea and impaired fertility have also been reported. Local irritation, and rarely frank chemical or haemorrhagic cystitis may follow intravesical instillation. Depigmentation of periorbital skin has occurred after the use of thiotepa eye drops. As with other alkylating agents, thiotepa is potentially mutagenic, teratogenic, and carcinogenic.

Thiotepa should be given with extreme care, if at all, to patients with pre-existing impairment of hepatic, renal, or bone-marrow function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies thiotepa 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 28/09/11)

Pharmacokinetics

The absorption of thiotepa from the gastrointestinal tract is incomplete and unreliable; variable absorption also occurs from intramuscular injection sites. Absorption through serous membranes such as the bladder and pleura occurs to some extent. After intravenous doses it is rapidly cleared from plasma, with an elimination half-life of about 2.4 hours. It is extensively metabolised: triethylenephosphoramide (TEPA), the primary metabolite, and some of the other metabolites have cytotoxic activity and are eliminated more slowly than the parent compound. It is excreted in the urine: less than 2% of a dose is reported to be present as unchanged drug or its primary metabolite.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Tepadina; *Cz.*: Tepadina; *Denm.*: Tepadina; *Ger.*: Tepadina; *Gr.*: Thioplex; *Irl.*: Tepadina; *Ital.*: Thioplex; *Neth.*: Ledertepa; Tepadina; *Norw.*: Tepadina; *Pol.*: Tepadina; *Port.*: Tepadina; *Spain*: Tepadina; *UK*: Tepadina; *USA*: Thioplex.

Pharmacopoeial Preparations
BP 2014: Thiotepa Injection;
USP 36: Thiotepa for Injection.

Tioguanine *(BAN, rINN)*

NSC-752; 6-TG; 6-Thioguanine; Thioguanine (USAN); Tioguaniini; Tioguanin; Tioguanina; Tioguaninum; WR-1141; Тиогуанин.

2-Aminopurine-6(1*H*)-thione; 2-Amino-6-mercaptopurine; 2-Aminopurine-6-thiol.

$C_5H_5N_5S$=167.2

CAS — 154-42-7 (anhydrous tioguanine); 5580-03-0 (tioguanine hemihydrate).

ATC — L01BB03.

ATC Vet — QL01BB03.

UNII — FTK8U1GZNX (thioguanine); WIX31ZPX66 (anhydrous thioguanine).

Pharmacopoeias. In *Br., Chin.,* and *US.*

BP 2014: (Tioguanine). A pale yellow, crystalline powder. Practically insoluble in water, in alcohol, and in chloroform; dissolves in dilute solutions of alkali hydroxides.

USP 36: (Thioguanine). It is anhydrous or contains one-half molecule of water of hydration. A pale yellow, odourless or practically odourless, crystalline powder. Insoluble in water and in chloroform; soluble 1 in 7700 of alcohol; freely

soluble in dilute solutions of alkali hydroxides. Store in airtight containers.

Uses and Administration

Tioguanine is an analogue of the naturally occurring purine, guanine, and is an antimetabolite antineoplastic with actions and uses similar to those of mercaptopurine (p. 821.1). It appears to cause fewer gastrointestinal reactions but cross-resistance exists so that patients who do not respond to one are unlikely to respond to the other.

Tioguanine is given *orally*, usually with other antineoplastics, in the induction and consolidation of remissions in acute myeloid leukaemia (p. 693.1). It has also been used in other malignancies including acute lymphoblastic leukaemia (p. 692.3) and chronic myeloid leukaemia (p. 694.2). *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Doses of between 100 and 200 mg/m² daily have been given at various stages of treatment for short term cycles. A dose of 2 mg/kg daily increased after 4 weeks to 3 mg/kg daily if there is no response and toxicity allows, may be given in those rare cases when single agent therapy is considered appropriate.

Blood counts should be made frequently, particularly during induction and when tioguanine is given with other antineoplastics. Therapy should be withdrawn at the first sign of severe bone-marrow depression. Tioguanine is not recommended for maintenance or similar long-term continuous therapy because of the high risk of hepatotoxicity (see Effects on the Liver, below).

Tioguanine has been given *intravenously* as the sodium salt.

Administration in children. Tioguanine is given orally in the treatment of acute childhood leukaemias in the same doses as those used for adults (see Uses and Administration, above).

Administration in the elderly. UK licensed product information states that tioguanine has been used in elderly patients with acute leukaemia at the same doses as those used for younger patients, and that there are no dosage recommendations based on age alone. US licensed product information states that dose selection for elderly patients should be made cautiously, in view of the greater possibility of decreased hepatic, renal, or cardiac function, and suggests that initial doses be at the lower end of the dosing range.

Administration in hepatic or renal impairment. UK licensed product information states that reduced doses should be considered in patients with hepatic or renal impairment, but makes no specific dose recommendations. US licensed product information makes no recommendations for dose adjustment in hepatic or renal impairment, aside from advising caution in elderly patients who might have reduced hepatic or renal function (see Administration in the Elderly, above).

Psoriasis. A report of the use of tioguanine, in oral doses ranging from 20 mg twice weekly to 120 mg daily, in the management of patients with refractory psoriasis.[1] Dramatic improvement occurred in 14 of 18 patients, but a further 2 were unable to tolerate the drug. Myelosuppression was the principal toxic effect and it was suggested that thiopurine methyltransferase activity could be measured as a basis to determine initial dosage and the risk of toxicity. For the conventional management of psoriasis see p. 1688.1.

1. Mason C, Krueger GG. Thioguanine for refractory psoriasis. *J Am Acad Dermatol* 2001; **44**: 67–72.

Adverse Effects, Treatment, and Precautions

As for Mercaptopurine, p. 821.2.

In some patients, gastrointestinal reactions are reported to be less frequent than with mercaptopurine.

Effects on the blood. For the view that it may be possible to predict those individuals likely to have severe bone-marrow depression with tioguanine based on measurement of the activity of thiopurine methyltransferase or the concentration of tioguanine nucleotide, see under Azathioprine, p. 1946.2.

Effects on the liver. The use of tioguanine has been limited by reports of hepatic veno-occlusive disease attributed to the drug.[1-4] The manufacturer (*GlaxoSmithKline*) has stated that, in most cases, liver toxicity is reversible upon withdrawal of chemotherapy. A comparison with mercaptopurine in the maintenance treatment of children with acute lymphoblastic leukaemia found that of 95 patients who developed veno-occlusive disease, 82 were receiving tioguanine, representing about 11% of all patients assigned to the drug.[5] In addition, although tioguanine was associated with fewer CNS relapses, patients in the tioguanine arm were more likely to develop fatal infections.

Centrilobular hepatic necrosis has also been reported; reports are confounded by the use of high doses of tioguanine, other antineoplastics, oral contraceptives, and chronic alcohol abuse.

1. Gill RA, *et al.* Hepatic veno-occlusive disease caused by 6-thioguanine. *Ann Intern Med* 1982; **96**: 58–60.
2. Krivoy N, *et al.* Reversible hepatic veno-occlusive disease and 6-thioguanine. *Ann Intern Med* 1982; **96**: 788.
3. Kao NL, Rosenblate HJ. 6-Thioguanine therapy for psoriasis causing toxic hepatic venoocclusive disease. *J Am Acad Dermatol* 1993; **28**: 1017–18.
4. Romagosa R, *et al.* Treatment of psoriasis with 6-thioguanine and hepatic venoocclusive disease. *J Am Acad Dermatol* 2002; **47**: 970–2.
5. Vora A, *et al.* Medical Research Council/National Cancer Research Network Childhood Leukaemia Working Party. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006; **368**: 1339–48.

Handling and disposal. For reference to a method for the destruction of tioguanine in wastes, see Mercaptopurine, p. 821.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tioguanine 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 29/09/11)

Interactions

Unlike mercaptopurine (p. 821.3), normal doses of tioguanine may be used with allopurinol.

Several cases of portal hypertension with hepatic nodular regenerative hyperplasia have been reported in patients who received tioguanine with busulfan (see p. 756.1).

It has been suggested that daunorubicin might enhance the hepatotoxicity of tioguanine (see p. 779.3).

Pharmacokinetics

Tioguanine is incompletely and variably absorbed from the gastrointestinal tract; on average about 30% of a dose is absorbed after oral doses. It is rapidly activated in the body by intracellular conversion to its nucleotide, thioguanylic acid and its thioguanosine phosphate derivatives. With repeated doses increasing amounts of the nucleotide are incorporated into DNA. Very little unchanged tioguanine has been detected circulating in the blood but the half-life of the nucleotide in the tissues is prolonged. Tioguanine is inactivated mainly by methylation to aminomethylthiopurine; small amounts are deaminated to thioxanthine, and may go on to be oxidised by xanthine oxidase to thiouric acid, but inactivation is essentially independent of xanthine oxidase and is not affected by inhibition of the enzyme.

It is excreted in the urine almost entirely as metabolites; only negligible amounts of tioguanine have been detected. Tioguanine does not appear to cross the blood-brain barrier to a significant extent; very little is found in CSF after normal clinical doses. It crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lanvis; ***Austral.***: Lanvis; ***Belg.***: Lanvis; ***Braz.***: Lanvis; ***Canad.***: Lanvis; ***Chile***: Lanvis; ***Cz.***: Lanvis; ***Fr.***: Lanvis; ***Gr.***: Lanvis; ***Hong Kong***: Lanvis; ***Irl.***: Lanvis; ***Israel***: Lanvis; ***Malaysia***: Lanvis; ***Neth.***: Lanvis; ***NZ***: Lanvis; ***Pol.***: Lanvis; ***S.Afr.***: Lanvis; ***Swed.***: Lanvis; ***Switz.***: Lanvis; ***Thai.***: Lanvis; ***Turk.***: Lanvis; ***UK***: Lanvis†; ***USA***: Tabloid†.

Pharmacopoeial Preparations
BP 2014: Tioguanine Tablets;
USP 36: Thioguanine Tablets.

Tipifarnib *(USAN, rINN)*

R-115777; Tipifarnibum; Типифарниб.
(+)-6-[(*R*)-Amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone.
$C_{27}H_{22}Cl_2N_4O$=489.5
CAS — 192185-72-1.
UNII — MAT637500A.

NOTE. The name Zarnestra has been used as a trade mark for tipifarnib.

Profile

Tipifarnib is a farnesyl transferase inhibitor that is under investigation for the treatment of acute myeloid leukaemia.

References.
1. Zhang S, *et al.* Pharmacokinetics of tipifarnib after oral and intravenous administration in subjects with advanced cancer. *J Clin Pharmacol* 2006; **46**: 1116–27.
2. Siegel-Lakhal WS, *et al.* Clinical and pharmacologic study of the farnesyltransferase inhibitor tipifarnib in cancer patients with normal or mildly or moderately impaired hepatic function. *J Clin Oncol* 2006; **24**: 4558–64.
3. Perez-Ruixo JJ, *et al.* Exposure-toxicity relationships for tipifarnib in cancer patients. *Br J Clin Pharmacol* 2007; **64**: 219–32.
4. Martinelli G, *et al.* Farnesyltransferase inhibition in hematologic malignancies: the clinical experience with tipifarnib. *Clin Adv Hematol Oncol* 2008; **6**: 303–10.
5. Harousseau JL, *et al.* FIGHT-AML-301 Investigators. A randomized phase 3 study of tipifarnib compared with best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia in patients 70 years or older. *Blood* 2009; **114**: 1166–73.
6. Epling-Burnette PK, Loughran TP. Suppression of farnesyltransferase activity in acute myeloid leukemia and myelodysplastic syndrome: current understanding and recommended use of tipifarnib. *Expert Opin Invest Drugs* 2010; **19**: 689–98.

Tirapazamine *(USAN, rINN)*

SR-4233; Tirapazamina; Tirapazaminum; Win-59075; Тирапазамин.
3-Amino-1,2,4-benzotriazine 1,4-dioxide.
$C_7H_6N_4O_2$=178.2
CAS — 27314-97-2.
UNII — 1UD32YRS9G.

Profile

Tirapazamine is reported to be reduced in hypoxic cells to an active anion that causes DNA strand breaks. It sensitises hypoxic tumour cells to the cytotoxic activity of other drugs. It is under investigation for its cytotoxic actions, alone or with cisplatin or radiotherapy. Adverse effects reported with tirapazamine include nausea and vomiting, diarrhoea, rashes, muscle cramps and fatigue; myelosuppression is said to be rare.

Reviews.
1. Gandara DR, *et al.* Tirapazamine: prototype for a novel class of therapeutic agents targeting tumor hypoxia. *Semin Oncol* 2002; **29** (suppl 4): 102–9.
2. Marcu L, Olver I. Tirapazamine: from bench to clinical trials. *Curr Clin Pharmacol* 2006; **1**: 71–9.
3. Reddy SB, Williamson SK. Tirapazamine: a novel agent targeting hypoxic tumor cells. *Expert Opin Invest Drugs* 2009; **18**: 77–87.

Tivozanib *(USAN, rINN)*

AV-951 (tivozanib hydrochloride); KI-8951; Tivozanibum; Тивозаниб.
1-[2-Chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl]-3-(5-methyl-1,2-oxazol-3-yl)urea.
$C_{22}H_{19}ClN_4O_5$=454.9
CAS — 475108-18-0.
UNII — 172030934T.

Profile

Tivozanib is an orally active tyrosine kinase inhibitor that targets vascular epidermal growth factor receptors 1, 2, and 3. It is under investigation for the treatment of renal cell carcinoma and other solid tumours.

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

References.
1. De Luca A, Normanno N. Tivozanib, a pan-VEGFR tyrosine kinase inhibitor for the potential treatment of solid tumors. *IDrugs* 2010; **13**: 636–45.

Topotecan Hydrochloride

(BANM, USAN, pINNM)

Hidrocloruro de topotecán; Nogitecan Hydrochloride; SKF 104864A; SKFS-104864-A; Topotecán, hidrocloruro de Topotécane, Chlorhydrate de; Topotecani Hydrochloridum Topotekaanihydrokloridi; Topotekanhydroklorid; Топотекана Гидрохлорид.
(*S*)-10-Dimethylaminomethyl-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2*b*]quinoline-3,14(4*H*,12*H*)-dione hydrochloride.
$C_{23}H_{23}N_3O_5$,HCl=457.9
CAS — 123948-87-8 (topotecan); 119413-54-6 (topotecan hydrochloride).
ATC — L01XX17.
ATC Vet — QL01XX17.
UNII — 956S425ZCY.

Incompatibility. Topotecan hydrochloride was found to degrade to 88.7% of its original concentration over 24 hours when mixed with ticarcillin sodium or potassium clavulanate. It was also found to be incompatible with dexamethasone sodium phosphate and fluorouracil.

When mixed with mitomycin solution an immediate colour change took place and concentrations of mitomycin fell by 15 to 20% over 4 hours. The pH of the mixtures remained constant at 3.3 to 3.5.

1. Mayron D, Gennaro AR. Stability and compatibility of topotecan hydrochloride with selected drugs. *Am J Health-Syst Pharm* 1999; 56: 875–81.

Uses and Administration

Like irinotecan (p. 812.3), topotecan is a semisynthetic derivative of the alkaloid camptothecin that exerts its antineoplastic activity by inhibition of topoisomerase I. It is used in the treatment of metastatic carcinoma of the ovary refractory to other therapy (see p. 711.2) and in relapsed small cell lung cancer (p. 710.2) after standard therapy. Topotecan is given with cisplatin in the treatment of metastatic, recurrent, or persistent carcinoma of the cervix (p. 704.2) that is not amenable to curative treatment with surgery and/or radiation therapy. Topotecan is also under investigation in the management of myelodysplastic syndromes.

Topotecan is given as the hydrochloride but doses are expressed in terms of the base. Topotecan hydrochloride 1.09 mg is equivalent to about 1 mg of topotecan. Topotecan may be given orally or intravenously. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* When given by intravenous infusion, topotecan is diluted in sodium chloride 0.9% or glucose 5%; a final concentration of between 25 and 50 micrograms/mL is specified in the UK.

In **ovarian** and **small cell lung cancer**, topotecan hydrochloride may be given *intravenously* in an initial dose equivalent to topotecan 1.5 mg/m², infused over 30 minutes, on days 1 to 5 of a 21-day course. A minimum of 4 courses should be given, in the absence of tumour progression, and provided that blood counts and haemoglobin have recovered adequately (see also Bone-marrow Depression, p. 730.3). If severe neutropenia occurs in any course, or if the platelet count falls below 25 000 cells/mm³, the dose in the subsequent courses may be reduced by 250 micrograms/m² to 1.25 mg/m² daily, and subsequently to 1 mg/m² daily if necessary. Alternatively, in the event of severe neutropenia, a granulocyte colony-stimulating factor may be given from day 6 of the course, 24 hours after topotecan dosage is complete. If severe toxicity recurs once the dose has been reduced to 1 mg/m² withdrawal of topotecan may be required. Dosage should also be reduced in patients with renal impairment (see below).

Topotecan may also be given *orally* for small cell lung cancer. The recommended dose is 2.3 mg/m² once daily for 5 consecutive days, repeated every 21 days. If neutropenia occurs, or if the platelet count falls below 25 000 cells/mm³, or for patients with severe diarrhoea, the daily dose should be reduced by 400 micrograms/m²(to 1.9 mg/m² daily, and subsequently to 1.5 mg/m² daily if necessary) for subsequent courses.

In **cervical cancer**, topotecan is given in an intravenous dose of 750 micrograms/m², infused over 30 minutes, on days 1, 2, and 3 of a 21-day course; cisplatin 50 mg/m² is given by intravenous infusion after topotecan on day 1. Dosage adjustments for subsequent courses are specific for each drug; for cisplatin, see p. 766.2. If severe neutropenia occurs, or if the platelet count falls below 25 000 cells/mm³, the topotecan dose should be reduced to 600 micrograms/m², and subsequently to 450 micrograms/m² if necessary. Alternatively, in the event of severe febrile neutropenia, granulocyte colony-stimulating factor may be given from day 4 of the course, 24 hours after completion of the topotecan infusion.

References.
1. Long HJ, *et al.* Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 2005; 23: 4626–33.
2. Randall-Whitis LM, Monk BJ. Topotecan in the management of cervical cancer. *Expert Opin Pharmacother* 2007; 8: 227–36.
3. Eckardt JR, *et al.* Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007; 25: 2086–92. Correction. *ibid.*; 3387.
4. Nicum SJ, O'Brien ME. Topotecan for the treatment of small-cell lung cancer. *Expert Rev Anticancer Ther* 2007; 7: 795–801.
5. O'Brien M, *et al.* Recent advances with topotecan in the treatment of lung cancer. *Oncologist* 2007; 12: 1194–204.
6. Ackermann S, *et al.* Topotecan in cervical cancer. *Int J Gynecol Cancer* 2007; 17: 1215–23.
7. Peng LH, *et al.* Topotecan for ovarian cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 08/05/08).
8. Sehouli J, Oskay-Özcelik G. Current role and future aspects of topotecan in relapsed ovarian cancer. *Curr Med Res Opin* 2009; 25: 639–51.
9. Lorusso D, *et al.* Review role of topotecan in gynaecological cancers: current indications and perspectives. *Crit Rev Oncol Hematol* 2010; 74: 163–74.
10. Loveman E, *et al.* The clinical effectiveness and cost-effectiveness of topotecan for small cell lung cancer: a systematic review and economic evaluation. *Health Technol Assess* 2010; 14: 1–204.
11. Paton F, *et al.* Topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix. *Health Technol Assess* 2010; 14 (suppl 1): 55–62.

Administration. In an attempt to reduce haematological toxicity, various schedule modifications of topotecan have been investigated, one of the most commonly studied being a regimen of intravenous topotecan 4 mg/m² over 30 minutes, once weekly for 3 weeks, followed by a week of rest.[1] A pharmacokinetic study found this dose to be well tolerated in patients with advanced solid tumours, although clinical efficacy was not assessed.[1] A study compared the conventional schedule of topotecan (see Uses and Administration, above), at a reduced dose of 1.25 mg/m² on days 1 to 5 of a 21-day cycle, with a weekly schedule of 4 mg/m² on days 1, 8 and 15 of a 28-day cycle in patients with platinum-resistant ovarian cancer.[2] Haematological toxicity was less with the weekly regimen. Slightly lower efficacy in terms of response rates and progression-free survival was seen with the weekly regimen, although these differences were not statistically significant, and there was no notable differences in overall survival between the two regimens. The authors concluded that weekly topotecan is a viable treatment option in this setting, allowing therapy to be geared towards goals of management.[2]

1. Curtis KK, *et al.* A phase I study to characterize the safety, tolerability, and pharmacokinetics of topotecan at 4 mg/m² administered weekly as a 30-minute intravenous infusion in patients with cancer. *J Clin Pharmacol* 2010; 50: 268–75.
2. Sehouli J, *et al.* Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol* 2011; 29: 242–8.

Administration in renal impairment. Licensed product information for *intravenous* topotecan recommends the following for patients with **ovarian** or **small cell lung cancer** according to creatinine clearance (CC):
- mild renal impairment (CC 40 to 60 mL/minute): no dosage adjustment
- moderate renal impairment (CC 20 to 39 mL/minute): 750 micrograms/m² daily for 5 consecutive days

For patients with small cell lung cancer given *oral* topotecan, the following is suggested:
- mild renal impairment (CC 50 to 80 mL/minute): no dosage adjustment
- moderate renal impairment (CC 30 to 49 mL/minute): 1.8 mg/m² once daily for 5 consecutive days

Data are insufficient to make dose recommendations in patients with severe renal impairment.

In patients with **cervical cancer**, treatment with topotecan and cisplatin should only be started in those with a serum creatinine of 1.5 mg or less per 100 mL.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Neutropenia is very common with topotecan and is usually dose-limiting. The nadir of white cell count usually occurs about 9 to 12 days after a dose. Febrile neutropenia, sepsis, and neutropenic colitis can occur; fatalities have been reported. Thrombocytopenia, anaemia, and leucopenia also occur commonly. Topotecan should not be given to those patients with pre-existing bone-marrow depression, and blood counts should be monitored regularly. Gastrointestinal disturbances and anorexia are also common with topotecan, and may be severe; oral topotecan is associated with severe diarrhoea.

Interstitial lung disease has been reported, and can be fatal; underlying risk factors include pulmonary fibrosis, lung cancer, thoracic radiation, and use of other drugs toxic to the lungs or of colony-stimulating factors. Patients should be monitored for signs and symptoms such as cough, fever, dyspnoea, or hypoxia, and treatment should be stopped if interstitial lung disease is suspected.

Other adverse effects include fatigue and weakness, alopecia, malaise, pruritus, pyrexia, and hyperbilirubinaemia. Hypersensitivity reactions including rashes have been reported; anaphylaxis, angioedema, and urticaria may occur rarely.

Licensed product information recommends that topotecan should not be given to patients with severe hepatic or renal impairment, due to a lack of data in these patients. Its use in breast feeding is contra-indicated for the same reason. Topotecan has been reported to produce fetal death and malformations in *animals*.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies topotecan 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 26/08/11)

Interactions

For a report of topotecan reducing the clearance of docetaxel, see Antineoplastics, p. 782.2.

Greater myelosuppression is seen when topotecan is used with other cytotoxic drugs, which may require dosage reductions of either drug. However, with platinum drugs, there is a sequence-dependent interaction: giving a platinum drug on the first day of topotecan dosage requires lower doses of each, compared with giving it on the fifth day.

Granulocyte colony-stimulating factor can prolong the duration of neutropenia if given with topotecan, so if used, it should not be started until, 24 hours after topotecan dosage is complete.

Ciclosporin has been reported to increase exposure to topotecan.

Pharmacokinetics

Topotecan is rapidly absorbed after oral doses; peak plasma concentrations occur after about 1 to 2 hours. The oral bioavailability is about 40%. Food does not appreciably affect topotecan pharmacokinetics. Topotecan is widely distributed after intravenous doses. Plasma protein binding is about 35%. The drug undergoes reversible hydrolysis of the lactone ring to the inactive hydroxy acid form; only small amounts are demethylated in the liver. A significant proportion of a dose is excreted in urine. The terminal half-life has been reported to be 2 to 3 hours for the intravenous formulation, and 3 to 6 hours for the oral formulation.

References.
1. Herben VMM, *et al.* Clinical pharmacokinetics of topotecan. *Clin Pharmacokinet* 1996; 31: 85–102.
2. Mould DR, *et al.* Population pharmacokinetic and adverse event analysis of topotecan in patients with solid tumors. *Clin Pharmacol Ther* 2002; 71: 334–48.
3. Herben VM, *et al.* Urinary and fecal excretion of topotecan in patients with malignant solid tumours. *Cancer Chemother Pharmacol* 2002; 50: 59–64.
4. Léger F, *et al.* Factors affecting pharmacokinetic variability of oral topotecan: a population artalysis. *Br J Cancer* 2004; 90: 343–7.
5. Schalquevich P, *et al.* Population pharmacokinetic analysis of topotecan in pediatric cancer patients. *Clin Cancer Res* 2007; 13: 6703–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asotecan; Hycamtin; Potekam; Tisogen; Topokebir; ***Austral.***: Hycamtin; ***Austria***: Hycamtin; ***Belg.***: Hycamtin; ***Braz.***: Evotecan; Hycamtin; Toporan; ***Canad.***: Hycamtin; ***Chile***: Hycamtin; ***China***: Ai Tuo (艾妥); Aoluona (奥罗那); Bo En (卜恩); Hycamtin (和美新); Jin Xi Su (金喜素); Sheng Cheng (胜诚); Xinze (欣泽); ***Cz.***: Hycamtin; Potactasol; ***Denm.***: Hycamtin; ***Fin.***: Hycamtin; ***Fr.***: Hycamtin; Potactasol; ***Ger.***: Hycamtin; ***Gr.***: Hycamtin; ***Hong Kong***: Hycamtin; ***Hung.***: Hycamtin; Viatopin†; ***India***: Cantop; Topotel; ***Irl.***: Hycamtin; Potactasol; ***Israel***: Hycamtin; Potactasol; ***Ital.***: Hycamtin; ***Mex.***: Toranex; ***Neth.***: Hycamtin; Potactasol; ***Norw.***: Hycamtin; Potactasol; ***Philipp.***: Hycamtin; Topotel; ***Pol.***: Hycamtin; Potactasol; ***Port.***: Hycamtin; Potactasol; ***Rus.***: Hycamtin (Гикамтин); Verotekan (Веротекан); ***S.Afr.***: Hycamtin; ***Singapore***: Hycamtin; ***Spain***: Hycamtin; ***Swed.***: Hycamtin; ***Switz.***: Hycamtin; ***Thai.***: Hycamtin; Topotel; ***Turk.***: Hycamtin; ***UK***: Hycamtin; Potactasol; ***Ukr.***: Hycamtin (Гикамтин); ***USA***: Hycamtin.

Toremifene Citrate (BANM, USAN, rINNM) ⊗

Citrato de toremifeno; FC-1157a; Toremifen Sitrat; Torémifène, Citrate de; Toremifeni Citras; Toremifeno, citrato de; Торемифена Цитрат.

2-[*p*-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy]-*N*,*N*-dimethylethylamine citrate.

$C_{26}H_{28}ClNO.C_6H_8O_7$=598.1

CAS — 89778-26-7 (toremifene); 89778-27-8 (toremifene citrate).

ATC — L02BA02.

ATC Vet — QL02BA02.

UNII — 2498Y7B3QT.

Uses and Administration

Toremifene is a selective oestrogen receptor modulator with properties similar to those of tamoxifen (p. 860.2). It is used in the treatment of metastatic breast cancer (p. 702.1) in postmenopausal women with oestrogen-receptor positive tumours.

Toremifene is given orally as the citrate, but doses are calculated in terms of the base; 88.4 mg of toremifene citrate is equivalent to about 60 mg of toremifene. A dose of toremifene 60 mg once daily is used.

Toremifene is also under investigation for the prevention of prostate cancer in men with high-grade intraepithelial neoplasia, as well as for the treatment of adverse effects related to androgen deprivation therapy.

References.
1. Wiseman LR, Goa KL. Toremifene: a review of its pharmacological properties and clinical efficacy in the management of advanced breast cancer. *Drugs* 1997; 54: 141–60.
2. Holli K, *et al.* Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. *J Clin Oncol* 2000; 18: 3487–94.
3. Taneja SS, *et al.* Toremifene—a promising therapy for the prevention of prostate cancer and complications of androgen deprivation therapy. *Expert Opin Invest Drugs* 2006; 15: 293–305.
4. Smith MR, *et al.* Toremifene increases bone mineral density in men receiving androgen deprivation therapy for prostate cancer: interim analysis of a multicenter phase 3 clinical study. *J Urol (Baltimore)* 2008; 179: 152–5.
5. Smith MR, *et al.* Toremifene improves lipid profiles in men receiving androgen-deprivation therapy for prostate cancer: interim analysis of a multicenter phase III study. *J Clin Oncol* 2008; 26: 1824–9.
6. Lewis JD, *et al.* Excellent outcomes with adjuvant toremifene or tamoxifen in early stage breast cancer. *Cancer* 2010; 116: 2307–15.
7. Yamamoto Y, *et al.* Clinical usefulness of high-dose toremifene in patients relapsed on treatment with an aromatase inhibitor. *Breast Cancer* 2010; 17: 254–60.
8. Smith MR, *et al.* Toremifene to reduce fracture risk in men receiving androgen deprivation therapy for prostate cancer. *J Urol (Baltimore)* 2010; 184: 1316–21.

Mastalgia. For reports of efficacy with toremifene in the management of mastalgia, see under Danazol, p. 2265.1.

Adverse Effects and Precautions

As for Tamoxifen Citrate, p. 861.2. Increased sweating occurs very commonly with toremifene.

Use of toremifene is contra-indicated in patients with pre-existing endometrial hyperplasia, or in those with severe thromboembolic disease or severe hepatic impairment. Toremifene has been shown to prolong the QT interval in a dose-dependent manner. Its use is therefore contra-indicated in patients with QT prolongation, electrolyte disturbances (especially uncorrected hypokalaemia), or in those with bradycardia, heart failure, or a history of arrhythmias. Toremifene should also be used with caution in those with conditions such as myocardial ischaemia, as treatment may lead to an increased risk for ventricular arrhythmias such as torsade de pointes and cardiac arrest; if cardiac arrhythmia occurs during therapy, toremifene should be stopped and an ECG should be performed. Patients with bone metastases should be monitored for signs and symptoms of hypercalcaemia.

Breast feeding. Licensed product information states that toremifene is excreted in the milk of *rats*, and that bodyweight gain of the rat offspring was seen during lactation. It is unknown whether the drug is excreted in human milk, and use is contra-indicated during breast feeding. It has been suggested[1] that breast feeding be withheld for a minimum of 25 to 30 days after a dose.

1. *et al.*, eds. *Drugs during pregnancy and lactation: treatment options and risk assessment.* 2nd ed. London: Elsevier, 2007.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies toremifene 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 05/09/11)

Interactions

Toremifene is metabolised by cytochrome P450 isoenzyme CYP3A4, and potent enzyme-inducing drugs such as phenytoin, phenobarbital and carbamazepine, can increase toremifene metabolism, thereby lowering the serum concentration; dose adjustment of toremifene may be needed. Conversely, azole antifungals and macrolide antibacterials may theoretically inhibit toremifene metabolism by inhibiting the isoenzyme.

Toremifene should not be used with drugs that prolong the QT interval, such as antiarrhythmics, antipsychotics (such as phenothiazines, pimozide, sertindole, haloperidol, and sultopride), certain antimicrobials (such as moxifloxacin, erythromycin, pentamidine, and antimalarials, particularly halofantrine), certain antihistamines (terfenadine, astemizole, mizolastine) and other drugs such as cisapride, vincamine, bepridil, and diphemanil.

Use with drugs that decrease renal calcium excretion, such as thiazide diuretics, may increase the incidence of hypercalcaemia. Use with coumarin anticoagulants should be avoided as there is a risk of increased bleeding time.

Antibacterials. *Rifampicin* was found to decrease plasma concentrations of toremifene in 9 subjects. This was thought to be due to induction of cytochrome P450 isoenzyme CYP3A4 by rifampicin.[1]

1. Kivistö KT, *et al.* Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clin Pharmacol Ther* 1998; 64: 648–54.

Pharmacokinetics

Toremifene citrate is well absorbed from the gastrointestinal tract and peak plasma concentrations of toremifene occur within 3 hours. Food intake may delay peak plasma concentrations by up to 2 hours but has no effect on the extent of absorption. Plasma concentration declines biexponentially; the mean distribution half-life is about 4 hours and the elimination half-life is about 5 days. It is extensively bound to plasma proteins, mainly albumin. Toremifene is metabolised principally by the cytochrome P450 isoenzyme CYP3A4. The main metabolite is *N*-demethyltoremifene, which is reported to have similar anti-oestrogenic activity but weaker anti-tumour activity than toremifene; it is even more extensively bound to plasma proteins. Minor metabolites of toremifene include (deaminohydroxy)-toremifene, 4-hydroxytoremifene, and *N,N*-didemethyltoremifene; concentrations of these are considered to be too low to have biological effects. Toremifene undergoes enterohepatic circulation and is eliminated mainly in the faeces as metabolites. About 10% is excreted in the urine.

Reviews.
1. Taras TL, *et al.* Clinical pharmacokinetics of toremifene. *Clin Pharmacokinet* 2000; 39: 327–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fareston; ***Austria***: Fareston; ***Belg.***: Fareston†; ***China***: Fareston (法乐通); ShuRui (枢瑞); ***Cz.***: Fareston; ***Fin.***: Fareston; ***Fr.***: Fareston; ***Ger.***: Fareston†; ***Gr.***: Fareston; ***Hung.***: Fareston; ***Irl.***: Fareston; ***Ital.***: Fareston; ***Mex.***: Fareston†; ***Neth.***: Fareston; ***NZ***: Fareston; ***Pol.***: Fareston; ***Port.***: Fareston; ***Rus.***: Fareston (Фаерстон); ***S.Afr.***: Fareston; ***Spain***: Fareston†; ***Swed.***: Fareston; ***Switz.***: Fareston†; ***Thai.***: Fareston; ***Turk.***: Fareston; ***UK***: Fareston; ***Ukr.***: Fareston (Фаерстон); ***USA***: Fareston.

Tositumomab *(rINN)*

B-1; Tositumomabum; Тозитумомаб.

Immunoglobulin G2a anti-(human antigen CD 20) (mouse monoclonal clone B1R1 γ2a-chain), disulfide with mouse monoclonal clone B1R1 λ_a-chain, dimer.

CAS — 192391-48-3.

UNII — 0343IGH41U.

Uses and Administration

Tositumomab is an anti-B1 monoclonal antibody that is directed against the CD20 antigen found on the surface of B lymphocytes. It is radiolabelled with iodine-131 (p. 2225.3) for the treatment of patients with CD20 antigen-expressing, relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma (p. 696.3), and including those patients who have disease refractory to rituximab.

The regimen consists of a dosimetric step, followed 7 to 14 days later by a therapeutic step. The dosimetric step consists of 450 mg of tositumomab given intravenously in 50 mL sodium chloride 0.9% over 60 minutes. Tositumomab 35 mg radiolabelled with iodine-131 is then given intravenously in 30 mL sodium chloride 0.9% over 20 minutes. This is followed by whole body imaging to determine whether biodistribution is acceptable, and to allow calculation of the therapeutic dose of radiolabelled tositumomab. In the therapeutic step, tositumomab 450 mg is given again, and followed by the calculated dose of radiolabelled tositumomab.

The rate of infusion may be halved for mild to moderate infusional toxicity, and stopped if this is severe; the infusions may be restarted at half the rate once toxicity resolves. Patients are pretreated with thyroid protective agents at least 24 hours before the first radiolabelled dose of tositumomab; treatment is continued until 2 weeks after the radiolabelled therapeutic dose. Analgesics and antihistamines are also given orally 30 minutes before doses of tositumomab.

References.
1. Kaminski MS, *et al.* Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol* 2001; 19: 3918–28.
2. Wahl RL. The clinical importance of dosimetry in radioimmunotherapy with tositumomab and iodine I 131 tositumomab. *Semin Oncol* 2003; 30 (suppl): 31–8.
3. Davies AJ, *et al.* Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2004; 22: 1469–79.
4. Vose JM. Bexxar: novel radioimmunotherapy for the treatment of low-grade and transformed low-grade non-Hodgkin's lymphoma. *Oncologist* 2004; 9: 160–72.
5. Horning SJ, *et al.* Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol* 2005; 23: 712–19.
6. Kaminski MS, *et al.* ^{131}I-Tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med* 2005; 352: 441–9.
7. Fisher RI, *et al.* Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. *J Clin Oncol* 2005; 23: 7565–73.
8. Dosik AD, *et al.* Subsequent therapy can be administered after tositumomab and iodine I-131 tositumomab for non-Hodgkin lymphoma. *Cancer* 2005; 106: 616–22.
9. Davies AJ. A review of tositumomab and I^{131} tositumomab radioimmunotherapy for the treatment of follicular lymphoma. *Expert Opin Biol Ther* 2005; 5: 577–88.
10. Smith S, Sweetenham JW. Iodine 131 tositumomab in the treatment of non-Hodgkin's lymphoma. *Future Oncol* 2007; 3: 255–62.
11. Cheung MC, *et al.* Members of the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. ^{131}I-Tositumomab in lymphoma. *Curr Oncol* 2009; 16: 32–47.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 721.1, p. 730.2, and p. 732.2.

Infusion reactions suggestive of a cytokine release syndrome, and other hypersensitivity reactions including anaphylaxis, have been reported with tositumomab. Prolonged and severe neutropenia, thrombocytopenia, and anaemia occur commonly; full blood counts should be monitored weekly for up to 12 weeks. Other adverse effects include gastrointestinal disturbances, dehydration, abdominal pain, pleural effusion, and increased susceptibility to infection. Delayed adverse effects such as the development of secondary malignancies, leukaemia, or myelodysplastic syndrome may occur. Patients receiving the radiolabelled regimen may be susceptible to hypothyroidism and pretreatment with thyroid blocking drugs is recommended (see Uses and Administration, above); levels of thyroid-stimulating hormone should be measured before treatment and annually thereafter.

Hypersensitivity. A report of successful use of tositumomab in a patient who had repeated infusion reactions to rituximab[1] suggests a possible lack of cross-sensitivity between the 2 anti-CD20 antibodies.

1. Hayslip J, Fenning R. Safe administration of iodine-131 tositumomab after repeated infusion-related reactions to rituximab. *Oncologist* 2007; 12: 338–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Bexxar; ***USA***: Bexxar.

Trabectedin *(BAN, USAN, rINN)*

Ecteinascidin-743; ET-743; NSC-648766; Trabectedina; Trabectédine; Trabectedinum; Трабектедин.

(1′*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-6′,8,14-Trihydroxy-7′,9-dimethoxy-4,10,23-trimethyl-19-oxo-3′,4′,6,7,12,13,14,16-octahydrospiro[6,16-(epithiopropanooxymethano)-7,13-imino-6a*H*-1,3-dioxolo[7,8]isoquino[3,2-*b*][3]benzazocine-20,1′(2′*H*)-isoquinolin]-5-yl acetate.

$C_{39}H_{43}N_3O_{11}S$=761.8

CAS — 114899-77-3.

ATC — L01CX01.

ATC Vet — QL01CX01.

UNII — ID0YZQ2TCP.

Uses and Administration

Trabectedin is a novel DNA-binding agent derived from the marine tunicate, *Ecteinascidia turbinata*. It is used for the treatment of advanced soft-tissue sarcomas, after failure of anthracyclines or ifosfamide, or in patients for whom these drugs are unsuitable. It is also licensed for use with liposomal doxorubicin in the treatment of relapsed platinum-sensitive ovarian cancer.

For treatment of **soft-tissue sarcomas**, the recommended dose is 1.5 mg/m², given as an intravenous infusion over 24 hours.

For the treatment of **ovarian cancer** trabectedin is given in a dose of 1.1 mg/m² as an intravenous infusion over 3 hours immediately following an infusion of pegylated liposomal doxorubicin 30 mg/m².

Treatment may be repeated at 3-week intervals as long as clinical benefit persists, provided haematological, hepatic, and renal function parameters are met. If these baseline criteria are not met, treatment must be delayed for up to 3 weeks, until the criteria are met. If severe toxicity occurs at any time between cycles, the dose for subsequent cycles must be reduced (see Administration in Subsequent Cycles, p. 875.1).

If trabectedin is given via a central venous line, which is the preferred method, the dose should be diluted in at least 50 mL of sodium chloride 0.9% or glucose 5%. If central access is unfeasible, and it is given peripherally, the dose should be diluted in at least 1 litre of diluent. Dexamethasone 20 mg is given intravenously 30 minutes before treatment with trabectedin (or before liposomal doxorubicin in patients treated for ovarian cancer), to reduce nausea and hepatotoxicity.

References.
1. van Kesteren C, *et al.* Yondelis (trabectedin, ET-743): the development of an anticancer agent of marine origin. *Anticancer Drugs* 2003; 14: 487–502.
2. D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. *Expert Opin Invest Drugs* 2003; 12: 1843–53.
3. Beumer JH, *et al.* Hepatotoxicity and metabolism of trabectedin: a literature review. *Pharmacol Res* 2005; 51: 391–8.
4. Fayette J, *et al.* ET-743: a novel agent with activity in soft tissue sarcomas. *Oncologist* 2005; 10: 827–32.
5. Schöffski P, *et al.* Trabectedin (ET-743): evaluation of its use in advanced soft-tissue sarcoma. *Futurr Oncol* 2007; 3: 381–92.
6. Schöffski P, *et al.* Clinical impact of trabectedin (ecteinascidin-743) in advanced/metastatic soft tissue sarcoma. *Expert Opin Pharmacother* 2008; 9: 1609–18.
7. Boudou L, *et al.* Trabectedin for the management of soft-tissue sarcoma. *Expert Rev Anticancer Ther* 2009; 9: 727–37.
8. Chuk MK, *et al.* Trabectedin. *Oncologist* 2009; 14: 794–9. Correction. *ibid.*: 949.
9. Ganjoo KN, Patel SR. Trabectedin: an anticancer drug from the sea. *Expert Opin Pharmacother* 2009; 10: 2735–43.
10. Carter NJ, Keam SJ. Trabectedin: a review of its use in soft tissue sarcoma and ovarian cancer. *Drugs* 2010; 70: 355–76.

Administration in hepatic impairment. Licensed product information states that there are no studies of trabectedin in hepatic impairment and data are unavailable to recommend doses in these patients. However, since systemic exposure is likely to be increased in these patients, thus increasing the risk of hepatotoxicity, caution is advised and dose adjustments may be needed. Trabectedin should not be given to patients with hyperbilirubinaemia.

Administration in renal impairment. Licensed product information for trabectedin states that no dose adjustments are needed when used as monotherapy in patients with mild or moderate renal impairment, but that trabectedin should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) as no data are available for this population. For similar reasons, combination therapy is not recommended in those with creatinine clearance less than 60 mL/min.

Administration in subsequent cycles. Initial criteria for administration of trabectedin are:
- absolute neutrophil count: at least 1500 cells/mm³
- platelet count: at least 100 000 cells/mm³
- bilirubin: less than or equal to upper limit of normal (ULN)
- alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase: less than or equal to 2.5 X ULN
- albumin: 25 mg/mL or more
- creatine phosphokinase: less than or equal to 2.5 X ULN
- haemoglobin: 9 g/dL
- creatinine clearance: at least 30 mL/minute for monotherapy or 60 mL/minute for combination therapy with liposomal doxorubicin

These baseline criteria must also be met before re-treating the patient in subsequent cycles. If serious toxicity occurs between cycles, e.g neutropenia of less than 500 cells/mm³ lasting more than 5 days or associated with fever or infection, thrombocytopenia below 25 000 cells/mm³, bilirubin above the ULN or alkaline phosphatase > 2.5 X ULN, or increase in aminotransferases above 2.5 X ULN for monotherapy or 5 X ULN for combination therapy, then subsequent doses must be reduced as follows:
- for **soft-tissue sarcoma** the dose of trabectedin is reduced from 1.5 mg/m² to 1.2 mg/m² initially, and then to 1 mg/m² if necessary. If severe toxicity still continues, stopping treatment should be considered
- for **ovarian cancer**, the initial dose of 1.1 mg/m² is reduced to 900 micrograms/m² (with a reduction in liposomal doxorubicin dose to 25 mg/m²), and then to 750 micrograms/m² (with liposomal doxorubicin 20 mg/m²). Again, consideration should be given to stopping treatment if further reduction is necessary

Once a dose has been reduced for toxicity, re-escalation in subsequent cycles is inadvisable.

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2. Neutropenia, thrombocytopenia, anaemia, and leucopenia are very common with trabectedin; febrile neutropenia often occurs. Full blood counts should be performed at baseline, weekly for the first 2 cycles, and then once between cycles thereafter. Dose reductions may be needed in those with haematological toxicity. Hepatobiliary disorders are also very common, and include hyperbilirubinaemia and alterations in liver function tests, which are mostly transient. Patients with liver disease should be closely monitored, and trabectedin should not be given to those with hyperbilirubinaemia.

Other very common adverse effects include gastrointestinal disturbances, anorexia, headache, and fatigue. Antiemetic prophylaxis with dexamethasone should be given to all patients. Peripheral sensory neuropathy, paraesthesia, dysgeusia, dizziness, pyrexia, and oedema are common, as are dyspnoea, cough, alopecia, myalgia, arthralgia, dehydration, hypokalaemia, hypotension, and flushing. Injection site reactions can occur, and the use of a central line is recommended.

Deaths associated with trabectedin treatment have often involved a combination of adverse events including pancytopenia, febrile neutropenia, and in some cases sepsis, hepatic involvement, renal failure, and rhabdomyolysis.

Trabectedin may cause serious birth defects if given during pregnancy, although data are limited. Women and men of fertile age are advised to use effective contraception during treatment, and for 3 and 5 months, respectively, after stopping treatment. Breast feeding is contra-indicated due to lack of data, and should be avoided for the duration of treatment and for 3 months after therapy is stopped.

Extravasation. A report[1] of severe local tissue inflammation and necrosis in 2 patients, associated with extravasation of trabectedin from central venous access devices. Both patients had full thickness injuries that required surgical debridement of affected skin, subcutaneous tissue, and pectoral muscle, suggesting that trabectedin should be considered a vesicant.

1. Theman TA, *et al.* Recognition of a new chemotherapeutic vesicant: trabectedin (ecteinascidin-743) extravasation with skin and soft tissue damage. *J Clin Oncol* 2009; 27: e198–e200.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trabectedin 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 28/09/11)

Interactions

Trabectedin is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme (such as azole antifungals, macrolide antibacterials, or ritonavir) may increase blood concentrations of trabectedin. Equally, inducers of CYP3A4 (such as rifampicin, phenobarbital, and St John's wort) may decrease systemic exposure to trabectedin. Trabectedin is a substrate of P-glycoprotein, and use with P-glycoprotein inhibitors (such as ciclosporin and verapamil) may alter trabectedin pharmacokinetics, although the clinical significance of this interaction has not been established. Alcohol and other hepatotoxic drugs should be avoided during trabectedin treatment due to possible potentiation of hepatotoxicity. Use with live attenuated vaccines is not recommended, and use with yellow fever vaccine is specifically contra-indicated. For the effect of trabectedin on phenytoin, see p. 544.1.

Pharmacokinetics

Trabectedin is extensively distributed in the tissues. Plasma protein binding is about 94 to 98%. It is metabolised in the liver, mainly by cytochrome P450 isoenzyme CYP3A4. The terminal half-life is about 180 hours. Trabectedin is excreted mainly in the faeces, with a small amount in the urine, of which less than 1% is unchanged drug.

References.
1. Beumer JH, *et al.* Metabolism of trabectedin (ET-743, Yondelis) in patients with advanced cancer. *Cancer Chemother Pharmacol* 2007; 59: 825–37.
2. Perez-Ruixo JJ, *et al.* Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis) in cancer patients. *Clin Pharmacokinet* 2007; 46: 867–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Yondelis; ***Austria***: Yondelis; ***Belg.***: Yondelis; ***Canad.***: Yondelis; ***Chile***: Yondelis; ***Cz.***: Yondelis; ***Denm.***: Yondelis; ***Fr.***: Yondelis; ***Ger.***: Yondelis; ***Gr.***: Yondelis; ***Hung.***: Yondelis; ***Irl.***: Yondelis; ***Israel***: Yondelis; ***Ital.***: Yondelis; ***Neth.***: Yondelis; ***Norw.***: Yondelis; ***Pol.***: Yondelis; ***Port.***: Yondelis; ***Rus.***: Yondelis (Йонделис); ***Singapore***: Yondelis; ***Spain***: Yondelis; ***Swed.***: Yondelis; ***Switz.***: Yondelis; ***Thai.***: Yondelis; ***UK***: Yondelis.

Trabedersen *(BAN, rINN)*

AP-12009; TGF-β2 antisense oligonucleotide; Trabédersen; Trabedersén; Trabedersenum; Transforming growth factor-β2-specific phosphorothioate antisense oligodeoxynucleotide; Трабедерсен.

2′-Deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-2′-deoxy-*P*-thioadenylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thiocytidylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thioadenylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-*P*-thiothymidylyl-(3′→5′)-2′-deoxy-*P*-thioguanylyl-(3′→5′)-2′-deoxyadenosine.

CAS — 925681-61-4.

NOTE. The name Oncomun has been used as a trade mark for trabedersen.

Profile

Trabedersen is an antisense oligonucleotide that specifically suppresses the production of transforming growth factor-beta-2, an immunosuppressive protein produced by tumour cells. It is under investigation for the treatment of high-grade glioma (see Malignant Neoplasms of the Brain, p. 701.2) and other neoplasms such as pancreatic cancer.

Trametinib *(USAN, pINN)*

GSK-1120212; Tramétinib; Trametinibum; Траметиниб.

N-(3-[3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl]phenyl)acetamide.

$C_{26}H_{23}FIN_5O_4$=615.4

CAS — 871700-17-3.

UNII — 33E86K87QN.

Trametinib Dimethyl Sulfoxide *(USAN, pINNM)*

GSK-1120212B.

$C_{26}H_{23}FIN_5O_4.C_2H_6OS$=693.5

CAS — 1187431-43-1.

UNII — BSB9VJ5TUT.

Profile

Trametinib is an inhibitor of mitogen-activated extracellular kinases (MEK 1 and 2) that is used in the treatment of unresectable or metastatic melanoma (p. 714.3) with BRAF V600E or V600K mutations; it should not be used in patients who have previously been treated with a BRAF inhibitor. It is given as the compound trametinib dimethyl sulfoxide but doses are expressed as the non-solvated base; 2 mg of trametinib is equivalent to about 2.25 mg trametinib dimethyl sulfoxide. The usual oral dose is equivalent to 2 mg once daily; tablets should be swallowed whole and taken on an empty stomach. A missed dose should not be taken within 12 hours of the next dose. Doses may need to be withheld or reduced if toxicity occurs. Where dose adjustment is required, reductions are made in steps of 500 micrograms. Treatment is continued until disease progression or unacceptable toxicity occurs. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Commonly reported adverse effects with trametinib are skin reactions such as rash, dry skin, and pruritus, paronychia, lymphoedema, hypertension, haemorrhage, and gastrointestinal disturbances, particularly diarrhoea. Severe skin toxicity, cardiomyopathy, interstitial lung disease, retinal pigment epithelial detachment, and retinal vein occlusion have also occurred. Trametinib should be avoided during pregnancy and women of child-bearing potential should use contraception during and for 4 months after treatment.

References.
1. Wright CJ, McCormack PL. Trametinib: first global approval. *Drugs* 2013; 73: 1245–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***USA***: Mekinist.

Trastuzumab *(BAN, USAN, rINN)*

Anticuerpo monoclonal HER2; HER-2 Monoclonal Antibody; rhuMAb HER2; Trastutsumabi; Trastuzumabum; Трастузумаб.

Immunoglobulin G1 (human-mouse monoclonal rhuMab HER2 γ1-chain anti-human $p185^{c\text{-}erbB2}$ receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer.

CAS — 180288-69-1.

ATC — L01XC03.

ATC Vet — QL01XC03.

UNII — P188ANX8CK.

Trastuzumab Emtansine *(USAN, rINN)*

Ado-trastuzumab Emtansine; PRO-132365; RG-3502; T-DM1; Trastuzumab-DM1; Trastuzumab Emtansina; Trastuzumab-

MCC-DM1; Trastuzumabum Emtansinum; Трастузумаб Эмтанзин.
CAS — 1018448-65-1.
UNII — SE2KH7T06F.

NOTE. Trastuzumab emtansine contains trastuzumab covalently linked to the microtubule inhibitory drug DM1, via the stable thioether linker MCC (4-[*N*-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex.

Trastuzumab and trastuzumab emtansine are not interchangeable.

Uses and Administration

Trastuzumab is a humanised monoclonal antibody directed against a cell surface protein produced by the human epidermal growth factor receptor 2 (HER2) gene. HER2 protein is overexpressed in about one-third of all breast cancers. Trastuzumab is used in the treatment of breast cancer (p. 702.1) with such characteristics. It is also used with combination chemotherapy in HER2-positive metastatic gastric cancer (p. 706.1). Trastuzumab emtansine (also called ado-trastuzumab emtansine) consists of trastuzumab conjugated to DM1, a maytansine derivative and cytotoxic microtubule inhibitor. It is used in the treatment of metastatic HER2-positive breast cancer.

Note that trastuzumab and trastuzumab emtansine are not interchangeable.

Trastuzumab is generally given in either a weekly or 3-weekly infusion schedule. Doses should be added to 250 mL of sodium chloride 0.9% for intravenous infusion. The initial dose is given over 90 minutes and subsequent doses may be given over 30 to 90 minutes. Alternatively, for some indications, it may be given subcutaneously once every 3 weeks; injection sites should be alternated between thighs, and the dose injected over 2 to 5 minutes. Preparations for subcutaneous injection contain recombinant human hyaluronidase and are not suitable for intravenous use.

- Weekly infusion schedule: 4 mg/kg initially, followed after 1 week by a maintenance dose of 2 mg/kg at weekly intervals.
- 3-Weekly infusion schedule: 8 mg/kg initially, followed after 3 weeks by a maintenance dose of 6 mg/kg once every 3 weeks.
- 3-Weekly subcutaneous schedule: 600 mg once every 3 weeks (no loading dose is required).

In metastatic breast cancer, trastuzumab may be given alone or with a taxane or an aromatase inhibitor. It is given in either a weekly or 3-weekly schedule, and continued until disease progression.

In the adjuvant treatment of early breast cancer, trastuzumab may be given in a weekly schedule with docetaxel or paclitaxel for 12 weeks, starting after 4 cycles of the AC regimen (doxorubicin and cyclophosphamide). Alternatively, weekly trastuzumab may be given with docetaxel and carboplatin for 18 weeks. One week after the completion of either of these treatment courses, trastuzumab may be continued at 6 mg/kg by infusion every 3 weeks. A 3-weekly trastuzumab regimen may also be given as adjuvant monotherapy after multimodal therapy including surgery, chemotherapy, and radiotherapy if applicable. In locally advanced disease, a 3-weekly trastuzumab regimen has been used with neoadjuvant chemotherapy followed by adjuvant trastuzumab; however, the concurrent use of trastuzumab with anthracyclines should be limited to chemotherapy-naive patients and only using low-dose anthracycline regimens. Trastuzumab therapy is given for 1 year in total or until disease recurs, whichever occurs first.

In metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, trastuzumab is given in a 3-weekly infusion schedule with cisplatin and either capecitabine or 5-fluorouracil. Treatment is continued until disease progression.

If the patient misses an infusion dose of trastuzumab by 1 week or less, then the usual maintenance dose should be given as soon as possible, without waiting until the next planned cycle. Subsequent cycles are then given according to the previous schedule.

If the infusion dose is missed by more than 1 week, a re-loading dose of trastuzumab should be given, and subsequent maintenance doses given thereafter.

If a subcutaneous dose is missed, it should be given as soon as possible; the interval between doses should not be less than 3 weeks.

Trastuzumab emtansine (ado-trastuzumab emtansine) is given alone in the treatment of metastatic breast cancer. A dose of 3.6 mg/kg is given every 3 weeks until disease progression or there is unacceptable toxicity. The dose should be added to 250 mL of sodium chloride 0.9% for intravenous infusion. The first dose is infused over 90 minutes; subsequent doses may be given over 30 minutes if tolerated.

If a dose of trastuzumab emtansine is missed or delayed, it should be given as soon as possible and the schedule adjusted to keep an interval of 3 weeks between subsequent doses.

The dose of trastuzumab or trastuzumab emtansine may need to be delayed or reduced because of toxicity (see Administration in Subsequent Cycles, below).

References.

1. Smith I, *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007; 369: 29–36.
2. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. *N Engl J Med* 2007; 357: 39–51.
3. Orman JS, Perry CM. Trastuzumab: in HER2 and hormone receptor co-positive metastatic breast cancer. *Drugs* 2007; 67: 2781–9.
4. von Minckwitz G, *et al.* Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German Breast Group 26/Breast International Group 03-05 study. *J Clin Oncol* 2009; 27: 1999–2006.
5. Garnock-Jones KP, *et al.* Trastuzumab: a review of its use as adjuvant treatment in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. *Drugs* 2010; 70: 215–39. Correction. *ibid.* 2011; 71: 1578.
6. Bang Y-J, *et al.* ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; 376: 687–97. Correction. *ibid.*: 1302.
7. Croxtall JD, McKeage K. Trastuzumab: in HER2-positive metastatic gastric cancer. *Drugs* 2010; 70: 2259–67.
8. Slamon D, *et al.* Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365: 1273–83.
9. Verma S, *et al.* EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783–91.
10. Ballantyne A, Dhillon S. Trastuzumab emtansine: first global approval. *Drugs* 2013; 73: 755–65.
11. Hamizi S, *et al.* Subcutaneous trastuzumab: development of a new formulation for treatment of HER2-positive early breast cancer. *Onco Targets Ther* 2013; 6: 89–94.

Administration. Intrathecal trastuzumab has been tried in the treatment of leptomeningeal carcinomatosis in HER2-positive metastatic breast cancer. A review[1] of 17 case reports found that it had been given as monotherapy or in various regimens with other systemic or intrathecal treatments. Individual doses of trastuzumab ranged from 4 to 150 mg, and total doses ranging from 35 to 1110 mg (mean 399.8 mg) were reported. Slightly higher doses were recorded in 4 of the patients given intrathecal trastuzumab readministration beyond CNS progression (mean dose of 560 mg and cumulative dose of 1040 mg). Clinical and radiological improvement was reported in more than half of the patients and overall survival was prolonged to a median of 13.5 months compared with 5.9 months for published historical groups. Treatment was well tolerated.

1. Zagouri F, *et al.* Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis. *Breast Cancer Res Treat* 2013; 139: 13–22.

Administration in subsequent cycles. *Trastuzumab* infusion may need to be slowed or stopped in patients who develop infusion reactions. Parenteral treatment may need to be withheld or stopped if ventricular function deteriorates.

Similarly, *trastuzumab emtansine* infusion should be slowed or stopped for infusion reactions. The dose may need to be delayed or reduced for other adverse effects. The dose may be reduced step-wise from 3.6 mg/kg to 3 mg/kg, then to 2.4 mg/kg; if a further dose reduction is needed then trastuzumab emtansine should be stopped. The following modifications have been recommended in patients who develop increases in serum transaminases, hyperbilirubinaemia, or thrombocytopenia:

- serum transaminases > 2.5 to ≤ 5 X upper limit of normal (ULN): continue trastuzumab emtansine at the same dose
- serum transaminases > 5 to ≤ 20 X ULN: withhold until recovery to at least ≤ 5 X ULN and then reduce the dose by one step
- serum transaminases > 20 X ULN: permanently stop trastuzumab emtansine
- total bilirubin > 1.5 to ≤ 3 X ULN: withold until recovery to at least < 1.5 X ULN, then treat at the same dose
- total bilirubin > 3 to ≤ 10 X ULN: withold until recovery to at least < 1.5 X ULN, then reduce the dose by one step
- total bilirubin > 10 X ULN: permanently stop trastuzumab emtansine
- serum transaminases > 3 X ULN and total bilirubin > 2 X ULN: permanently stop trastuzumab emtansine
- patients diagnosed with nodular regenerative hyperplasia: permanently stop trastuzumab emtansine
- platelets 25 000 to < 50 000 cells/mm³: withhold until ≥ 75 000 cells/mm³ and then treat at the same dose
- platelets < 25 000 cells/mm³: withhold until ≥ 75 000 cells/mm³ and then reduce the dose by one step

In patients with left ventricular dysfunction, trastuzumab emtansine should be withheld if left ventricular ejection fraction is less than 40%, or between 40% and 45% and also 10% or more points below baseline. Treatment should be stopped if there is symptomatic congestive heart failure, or if function has not recovered in less than 3 weeks to within 10% points from baseline or to more than 40%.

Trastuzumab emtansine should be withheld in patients who develop grade 3 or 4 peripheral neuropathy, and permanently stopped in those who develop pulmonary toxicity.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 716.1, p. 730.2 and p. 732.2.

Trastuzumab has been associated with fatal hypersensitivity reactions, infusion reactions characteristic of a cytokine release syndrome, and pulmonary events including acute respiratory distress syndrome. These usually occur after the first dose of trastuzumab and are more common in patients with reduced lung function. Systemic and local reactions have occurred after subcutaneous injection. Use of trastuzumab is contra-indicated in patients with severe dyspnoea at rest. Cardiac dysfunction and congestive heart failure may also occur and left ventricular function should be monitored before and during therapy. The risk of cardiotoxicity is increased if trastuzumab is given with anthracyclines or cyclophosphamide (see below).

There is an increase in the incidence of leucopenia, thrombocytopenia, anaemia, and febrile neutropenia when trastuzumab is given with chemotherapy, but it infrequently causes myelosuppression when used alone. Diarrhoea occurs in about 25% of patients given trastuzumab as monotherapy; the incidence increases with combination therapy. Other gastrointestinal disturbances are common, as are chills, fever, headache, arthralgia, myalgia, and rashes. Asthenia, chest pain, and renal or liver disorders have also been reported.

The adverse effects of trastuzumab are also reported for *trastuzumab emtansine*. However, thrombocytopenia and hepatotoxicity are very common and may require dose adjustment. Peripheral neuropathy is also commonly reported with trastuzumab emtansine; it is generally a sensory neuropathy and may be severe in a small percentage of patients.

Effects on the heart. Cardiac events related to the use of trastuzumab include asymptomatic decreases in left ventricular ejection fraction, tachycardia, palpitations, dyspnoea, and chest pain. Congestive heart failure may develop.[1] Complete left bundle branch block, mimicking an acute coronary syndrome, has also been seen.[2]

In a pivotal comparative study,[3] an increased incidence of cardiac adverse events prompted a retrospective analysis. This independent review identified cardiac dysfunction in 27% of patients given trastuzumab, an anthracycline, and cyclophosphamide, compared with only 8% given an anthracycline and cyclophosphamide. In patients given trastuzumab and paclitaxel, 13% developed cardiac dysfunction compared with 1% of patients given paclitaxel alone, although all these patients had previously received an anthracycline. The incidence of severe dysfunction was highest in those patients given trastuzumab, an anthracycline, and cyclophosphamide.

Further analysis[4] of this and 6 other studies found that, in a total of 1219 patients, 10 heart-related deaths had been reported, and that 9 of these were patients who had taken trastuzumab. However, the risk of developing cardiotoxicity was less when trastuzumab was given alone than when given with anthracyclines. Advanced age was found to be a significant risk factor, whereas giving trastuzumab and the anthracycline at different times appeared to decrease the rate of cardiotoxicity.

Licensed product information for trastuzumab warns that patients who have previously had anthracyclines may also be at increased risk of cardiotoxicity with trastuzumab treatment. Furthermore, because the half-life of trastuzumab is about 4 to 5 weeks, trastuzumab may persist in the circulation for up to 20 to 25 weeks, and patients given anthracyclines after stopping trastuzumab may still be at increased risk of cardiotoxicity. If anthracyclines are used, the patient's cardiac function should be carefully monitored. Patients with pre-existing cardiovascular disease should also be treated with caution.

However, the majority of patients who develop congestive heart failure improve with standard treatment, including the use of ACE inhibitors, beta blockers, cardiac glycosides and diuretics.[1,5,6] Cardiotoxicity may improve even in those patients who continue with trastuzumab therapy.[5,6] A small retrospective study found that cardiotoxicity appeared to be largely reversible once trastuzumab was stopped, and that therapy might even be restarted. Findings from myocardial biopsy suggested that, while the mechanism of cardiotoxicity with trastuzumab remained uncertain, it differed from that with anthracyclines.[7] A retrospective review[8] of 173 patients with metastatic breast cancer who were treated with trastuzumab-based therapy for at least 1 year found that 28% of patients had a cardiac event; 10.9% had grade 3 cardiotoxicity, including 1 cardiac-related death. However, cardiotoxicity, whether symptomatic or not, was generally

reversible, with or without specific therapy, suggesting that maintenance or re-treatment with trastuzumab may be feasible in those patients for whom no alternative therapeutic options are available.

Analysis of symptomatic heart failure with trastuzumab suggests a lower incidence than that previously reported with retrospective data; however, this may be due to over-reported events in pivotal studies and the more recent exclusion of patients at risk of cardiotoxicity.[5] Analysis from a large study of patients given adjuvant chemotherapy with or without 1 year of trastuzumab found a cumulative incidence of cardiac events (defined as confirmed New York Heart Association class III or IV cardiac dysfunction, or cardiac death) with trastuzumab of 4.1% at 3 years. The difference in cumulative incidence was 3.3% when compared with the control group.[9] Additional follow-up to 7 years included some further reports of cardiac events in both groups, but the late development of heart failure in patients given trastuzumab was uncommon.[10] Cardiac function returned to the normal range in the majority of patients who had stopped trastuzumab because of dysfunction, although some decline from baseline persisted. In similar studies,[11,12] follow-up analyses at around 3 years also confirmed a higher incidence of cardiac events in patients given 1 year of trastuzumab therapy, but it remained low and cardiac dysfunction appeared to be reversible.

Reviews[13,14] have concluded that trastuzumab-induced cardiotoxicity is not dose-related and is generally reversible once the drug is stopped. However, others[15,16] have challenged the concept that cardiotoxicity is reversible, and the need for longer-term follow-up data, especially with respect to asymptomatic left ventricular dysfunction, has been emphasised.[13,15] As well as routine monitoring of cardiac function and for symptoms of heart failure, some suggest that increases in serum concentrations of troponin I during trastuzumab treatment are predictive of cardiotoxicity, and that further investigation of troponin I monitoring is warranted.[16]

1. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer* 2002; **95**: 1592–1600.
2. Tu C-M, *et al.* Trastuzumab (Herceptin)-associated cardiomyopathy presented as new onset of complete left bundle-branch block mimicking acute coronary syndrome: a case report and literature review. *Am J Emerg Med* 2009; **27**: 903.e1–903.e3.
3. Slamon DJ, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344**: 783–92.
4. Seidman A, *et al.* Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20**: 1215–21.
5. Suter TM, *et al.* Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast* 2004; **13**: 173–83.
6. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004; **22**: 322–9.
7. Ewer MS, *et al.* Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005; **23**: 7820–6.
8. Guarneri V, *et al.* Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol* 2006; **24**: 4107–15.
9. Tan-Chiu E, *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; **23**: 7811–19.
10. Romond EH, *et al.* Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2012; **30**: 3792–9.
11. Perez EA, *et al.* Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008; **26**: 1231–8.
12. Procter M, *et al.* Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. *J Clin Oncol* 2010; **28**: 3422–8.
13. Sengupta PP, *et al.* Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. *Mayo Clin Proc* 2008; **83**: 197–203.
14. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. *Drug Safety* 2008; **31**: 459–67.
15. Telli ML, *et al.* Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol* 2007; **25**: 3525–33.
16. Telli ML, Witteles RM. Trastuzumab-related cardiac dysfunction. *J Natl Compr Canc Netw* 2011; **9**: 243–9.

Effects on the liver. A 54-year-old African American woman was treated with 8 weeks of trastuzumab therapy. Her liver enzyme concentrations were normal before treatment was started but increased until trastuzumab had to be stopped, after which they returned to normal. Upon re-challenge, liver enzyme concentrations increased again. Liver function tests with close monitoring are advised during trastuzumab therapy.[1]

1. Srinivasan S, *et al.* Trastuzumab-induced hepatotoxicity. *Ann Pharmacother* 2008; **42**: 1497–1501.

Metastatic disease. There is some suggestion that patients treated with trastuzumab for metastatic breast cancer have a higher incidence of cerebral metastases. This may reflect increased survival of patients given trastuzumab, and the lack of CNS penetration by the drug,[1,2] or tumours overexpressing human epidermal growth receptor 2 (HER2) may be more likely to metastasise to the CNS.[2] A comparison[1] of trastuzumab-treated patients with a control group found that, although trastuzumab reduced the incidence of bone metastases, the development of brain metastases was similar in both groups. However, trastuzumab improved overall survival in all patients developing metastases, including those with brain metastases. A retrospective review[2] found an association between the development of cerebral metastases and both hormone-receptor negative status and the presence of visceral disease.

For the intrathecal use of trastuzumab in leptomeningeal carcinomatosis in metastatic breast cancer, see Administration under Uses and Administration, p. 876.2.

1. Lower EE, *et al.* Increased rate of brain metastasis with trastuzumab therapy not associated with impaired survival. *Clin Breast Cancer* 2003; **4**: 114–19.
2. Clayton AJ, *et al.* Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer* 2004; **91**: 639–43.

Peripheral vascular toxicity. A woman developed a painless prominence of the veins in her left arm and hand 3 days after receiving trastuzumab via a left hand vein. The veins were thickened and rope-like on palpation but there was no tenderness, oedema, or skin changes; there was no evidence of thrombus. She had previously received intravenous chemotherapy into left hand veins without sequelae. Biopsy suggested venous wall injury. Cardiac function was preserved, suggesting the mechanism of vascular injury was unrelated to cardiac dysfunction. Trastuzumab therapy was stopped permanently and her symptoms gradually resolved over the course of a year.[1]

1. Pansegrau GK, *et al.* Trastuzumab-associated peripheral vascular toxicity. *J Clin Oncol* 2007; **25**: 1438–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trastuzumab 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 29/09/11).

Pregnancy. Fetal exposure to *trastuzumab* in 18 pregnancies (19 newborns) has been reviewed.[1] The duration of maternal trastuzumab treatment ranged from 1 to 31 weeks, with a mean duration of 14.8 weeks, and it was given either alone or with other antineoplastics. Oligohydramnios and anhydramnios were the most commonly reported adverse events, affecting 11 of the 15 pregnancies exposed to trastuzumab in the second or third trimester. There was a trend towards an increase in risk with a longer duration of trastuzumab use. However, oligohydramnios seemed to be reversible after stopping the drug. There appeared to be no significant difference between weekly and 3-weekly exposure in relation to oligohydramnios and anhydramnios. Some cases showed intra-uterine growth restriction, dystrophy, and pulmonary hypoplasia. Conditions reported at birth in 9 neonates included respiratory distress, renal failure, and infection; 4 of these infants died within 6 months. The remaining 10 neonates were healthy at birth and at follow-up.

No adverse effects were found in the 3 cases exposed to trastuzumab during the first trimester only (up to 6 weeks of gestational age).[1] The authors suggested that this might be related to the poor trans-placental transfer of monoclonal antibodies during early pregnancy compared with later gestation. Also, the inhibitory effect of trastuzumab on epidermal growth factor receptors in the fetal kidney, which might inhibit amniotic fluid production, would only be significant after month 4 (before this the amniotic fluid is produced maternally). Nevertheless, the limited number of reports precludes any definite conclusion about the safety of trastuzumab in the first trimester.

Licensed product information advises the use of contraception during trastuzumab therapy and for at least 6 months after stopping treatment.

Information about fetal exposure to *trastuzumab emtansine* is lacking. However, in addition to the potential effects of trastuzumab, the cytotoxic component DM1 is expected to cause embryo-fetal toxicity.

1. Zagouri F, *et al.* Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013; **137**: 349–57.

Interactions

For reports of trastuzumab enhancing the effect of warfarin, see p. 1532.2.

Based on *in-vitro* studies, it is suggested that the concomitant use of strong inhibitors of the cytochrome P450 isoenzyme CYP3A4 and trastuzumab emtansine should be avoided if possible, because of the potential for an increased exposure to the DM1 component.

Pharmacokinetics

The pharmacokinetics of *trastuzumab* are non-linear, and clearance decreases with increasing dose. The half-life after short-duration intravenous infusions was found to be about 2 days after weekly 10-mg doses and 12 days after 500-mg doses. It has also been reported to be about 6 days with the recommended weekly infusion schedule (4 mg/kg initially, followed by 2 mg/kg weekly), and about 16 days with the 3-weekly infusion schedule (8 mg/kg initially, followed by 6 mg/kg every 3 weeks). However, limited sampling may underestimate terminal half-life. Population pharmacokinetic modelling, based on pooled data in a two-compartment model to take account of accumulation with long-term dosing, estimates a terminal elimination half-life of about 28.5 days. When given subcutaneously, trastuzumab peak plasma concentrations occur about 3 days after injection, but with high interindividual variability ranging from 1 to 14 days. It has an estimated bioavailability of about 82%.

Detectable concentrations of the cell surface protein of the HER2 receptor (shed antigen) have been found in patients' serum; those patients with higher baseline values for shed antigen had lower serum trough concentrations of trastuzumab, although target trastuzumab concentrations were still achieved after weekly dosing, and no relationship to clinical response was seen.

Trastuzumab emtansine has a shorter half-life than trastuzumab, of about 4 days. The small molecule component, DM1, is metabolised via the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 and is a substrate of P-glycoprotein.

References.

1. Baselga J, *et al.* Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Oncol* 2005; **23**: 2162–71.
2. Bruno R, *et al.* Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. *Cancer Chemother Pharmacol* 2005; **56**: 361–9.
3. Chudasama VL, *et al.* Semi-mechanistic population pharmacokinetic model of multivalent trastuzumab emtansine in patients with metastatic breast cancer. *Clin Pharmacol Ther* 2012; **92**: 520–7.
4. Lu D, *et al.* An integrated multiple-analyte pharmacokinetic model to characterize trastuzumab emtansine (T-DM1) clearance pathways and to evaluate reduced pharmacokinetic sampling in patients with HER2-positive metastatic breast cancer. *Clin Pharmacokinet* 2013; **52**: 657–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Herceptin; ***Austral.***: Herceptin; ***Austria***: Herceptin; ***Belg.***: Herceptin; ***Braz.***: Herceptin; ***Canad.***: Herceptin; ***Chile***: Herceptin; ***China***: Herceptin (赫赛汀); ***Cz.***: Herceptin; ***Denm.***: Herceptin; ***Fin.***: Herceptin; ***Fr.***: Herceptin; ***Ger.***: Herceptin; ***Gr.***: Herceptin; ***Hong Kong***: Herceptin; ***Hung.***: Herceptin; ***India***: Herceptin; ***Indon.***: Herceptin; ***Irl.***: Herceptin; ***Israel***: Herceptin; ***Ital.***: Herceptin; ***Jpn***: Herceptin; ***Malaysia***: Herceptin; ***Mex.***: Herceptin; ***Neth.***: Herceptin; ***Norw.***: Herceptin; ***NZ***: Herceptin; ***Philipp.***: Herceptin; ***Pol.***: Herceptin; ***Port.***: Herceptin; ***Rus.***: Herceptin (Герцептин); ***S.Afr.***: Herceptin; ***Singapore***: Herceptin; ***Spain***: Herceptin; ***Swed.***: Herceptin; ***Switz.***: Herceptin; ***Thai.***: Herceptin; ***Turk.***: Herceptin; ***UK***: Herceptin; ***Ukr.***: Herceptin (Герцептин); ***USA***: Herceptin; Kadcyla; ***Venez.***: Herceptin.

Treosulfan *(BAN, rINN)*

Dihydroxybusulphan; NSC-39069; Treosulfaani; Tréosulfan; Treosulfano; Treosulfanum; Треосульфан.

L-Threitol 1,4-dimethanesulphonate.

$C_6H_{14}O_8S_2$=278.3

CAS — 299-75-2.

ATC — L01AB02.

ATC Vet — QL01AB02.

UNII — CO61ER3EPI.

Profile

Treosulfan is an antineoplastic agent related to busulfan (p. 754.3), which is reported to act by alkylation after conversion *in vivo* to epoxide compounds. It is used palliatively or as an adjunct to surgery mainly in the treatment of ovarian cancer (p. 711.2).

Treosulfan may be given orally, intravenously, or intraperitoneally. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Treosulfan 1 g daily is licensed for *oral* use in 4 divided doses for 2 or 4 weeks followed by the same period without treatment. Alternatively 1.5 g daily in 3 divided doses may be given for 1 week, followed by 3 weeks without therapy. The cycle is then repeated, the dose being adjusted if necessary according to the effect on bone marrow. Doses of 3 to 8 g/m² may instead be given *intravenously* every 1 to 3 weeks. Doses larger than 3 g/m² should be given by infusion at a rate of 3 g/m² every 5 to 10 minutes. Doses up to 1.5 g/m² have been given *intraperitoneally*. Lower doses

should be used if treatment with other antineoplastic drugs or radiotherapy is being given.

Regular blood counts should be made and treatment should be interrupted if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p. 730.3). Because bone-marrow depression may be cumulative the interval between blood counts should be reduced after the second course of treatment with treosulfan.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Trofosfamide *(rINN)*

A-4828; NSC-109723; Trilophosphamide; Trofosfamid; Trofosfamida; Trofosfamidi; Trofosfamidum; Trophosphamide; Z-4828; Трофосфамид.

3-(2-Chloroethyl)-2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorine-2-oxide.

$C_9H_{18}Cl_3N_2O_2P$=323.6

CAS — 22089-22-1.

ATC — L01AA07.

ATC Vet — QL01AA07.

UNII — H64JRU6GJ0.

Profile

Trofosfamide is a derivative of cyclophosphamide (p. 771.1) and has the same general properties. It is used in the treatment of malignant disorders in usual initial oral doses of 300 to 400 mg daily. Doses of 50 to 150 mg daily have been given for maintenance therapy.

Uses. References[1-10] to the use of trofosfamide, including its investigational use with pioglitazone and rofecoxib as antiangiogenic therapy.[4,5,7]

1. Gunsilius E, *et al.* Palliative chemotherapy in pretreated patients with advanced cancer: oral trofosfamide is effective in ovarian carcinoma. *Cancer Invest* 2001; **19**: 808–11.
2. Reichardt P, *et al.* Oral trofosfamide: an active and well-tolerated maintenance therapy for adult patients with advanced bone and soft tissue sarcomas: results of a retrospective analysis. *Onkologie* 2002; **25**: 541–6.
3. Andersson PO, *et al.* Trofosfamide as salvage therapy for anaplastic large cell lymphoma relapsing after high-dose chemotherapy. *Leuk Lymphoma* 2002; **43**: 2351–3.
4. Vogt T, *et al.* Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors. *Cancer* 2003; **98**: 2251–6.
5. Reichle A, *et al.* Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. *Cancer* 2004; **101**: 2247–56.
6. Latz D, *et al.* Trofosfamide in the palliative treatment of cancer: a review of the literature. *Onkologie* 2004; **27**: 572–6.
7. Coras B, *et al.* Antiangiogenic therapy with pioglitazone, rofecoxib, and trofosfamide in a patient with endemic kaposi sarcoma. *Arch Dermatol* 2004; **140**: 1504–7.
8. Jahnke K, *et al.* Pharmacokinetics and efficacy of ifosfamide or trofosfamide in patients with intraocular lymphoma. *Ann Oncol* 2005; **16**: 1974–8.
9. Salminen EK, *et al.* Palliative chemotherapy with trofosfamide in advanced prostate cancer. *Anticancer Res* 2006; **26**: 539–42.
10. Görn M, *et al.* A pilot study of docetaxel and trofosfamide as second-line 'metronomic' chemotherapy in the treatment of metastatic non-small cell lung cancer (NSCLC). *Onkologie* 2008; **31**: 185–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trofosfamide 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 28/09/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Ixoten; *Gr.*: Ixoten.

Tumour Necrosis Factor

Factor de necrosis tumoral; TNF.

Tasonermin *(BAN, rINN)*

Tasonermini; Tasonermina; Tasonermine; Tasonerminum; TNFα-1a; Тазонермин.

$C_{774}H_{1225}N_{215}O_{231}S_5$=17350.8

CAS — 94948-59-1.

ATC — L03AX11.

ATC Vet — QL03AX11.

UNII — 23CA79S88F.

Profile

Tumour necrosis factor is a cytokine of which 2 forms have been identified with similar biological properties: TNFα or cachectin, which is produced mainly by macrophages, and TNFβ or lymphotoxin, which is produced by lymphocytes. Various recombinant forms of TNFα, both human and mouse, are available: the names sonermin and sertenef have been used for such products.

The antitumour effects of tumour necrosis factor *in vitro* and in *animals* have prompted investigation of recombinant TNFα in the treatment of cancer either alone or with other cytokines such as interleukin-2 or the interferons. Tasonermin is a recombinant TNFα used with melphalan (p. 819.1) for soft tissue sarcomas. It is given by mildly hyperthermic isolated limb perfusion at a total dose of 3 mg for an upper limb and 4 mg for a lower limb.

Leakage of tasonermin into the systemic circulation should not exceed 10%, as severe toxicity may occur. Local adverse effects include skin reactions, oedema, and pain; less commonly, vascular thrombosis, onycholysis, or severe tissue damage have occurred. Systemic effects include fever, chills, nausea and vomiting, arrhythmias, hepatotoxicity, and infections. Shock or hypotension, neurological disorders, thrombocytopenia, leucopenia, acute renal failure, and hypersensitivity reactions have all been reported.

References.

1. van Der Veen AH, *et al.* An overview on the use of TNF-alpha: our experience with regional administration and developments towards new opportunities for systemic application. *Anticancer Res* 2000; **20**: 3467–74.
2. Eggermont AM, ten Hagen TL. Tumor necrosis factor-based isolated limb perfusion for soft tissue sarcoma and melanoma: ten years of successful antivascular therapy. *Curr Oncol Rep* 2003; **5**: 79–80.
3. ten Hagen TL, Eggermont AM. Solid tumor therapy: manipulation of the vasculature with TNF. *Technol Cancer Res Treat* 2003; **2**: 195–203.
4. Corti A. Strategies for improving the anti-neoplastic activity of TNF by tumor targeting. *Methods Mol Med* 2004; **98**: 247–64.
5. Lejeune FJ, *et al.* Efficiency of recombinant human TNF in human cancer therapy. *Cancer Immun* 2006; **6**: 6.
6. van Horssen R, *et al.* TNF-α in cancer treatment: molecular insights, antitumor effects, and clinical utility. *Oncologist* 2006; **11**: 397–408.
7. Lejeune FJ, Rüegg C. Recombinant human tumor necrosis factor: an efficient agent for cancer treatment. *Bull Cancer* 2006; **93**: E90–E100.
8. Pilati P, *et al.* Strategies to enhance the anticancer potential of TNF. *Front Biosci* 2008; **13**: 3181–93.
9. Grünhagen DJ, *et al.* Isolated limb perfusion with TNF-alpha and melphalan in locally advanced soft tissue sarcomas of the extremities. *Recent Results Cancer Res* 2009; **179**: 257–70.
10. Bellavance EC, Alexander HR. TNF-based isolated hepatic perfusion. *Front Biosci* 2009; **14**: 1771–84.

Units. The first International Standard for human tumour necrosis factor α, which contained 40 000 international units/ampoule, was considered unsuitable for the assay of recombinant *mouse* tumour necrosis factor α, for human tumour necrosis factor β, or for preparations of tumour necrosis factor α of modified structure.[1] The second International Standard for human tumour necrosis factor α has been established as having a potency of 46 500 international units/ampoule.[2]

The first Reference Reagent for tumour necrosis factor β had an assigned potency of 150 000 units/ampoule.[3]

1. WHO. WHO expert committee on biological standardization: forty-second report. *WHO Tech Rep Ser 822* 1992. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf (accessed 01/08/08)
2. WHO. WHO expert committee on biological standardization: fifty-fourth report. *WHO Tech Rep Ser 927* 2005. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_927_eng.pdf (accessed 01/08/08)
3. WHO. WHO expert committee on biological standardization: forty-seventh report. *WHO Tech Rep Ser 878* 1998. Available at: http://libdoc.who.int/trs/WHO_TRS_878.pdf (accessed 01/08/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tasonermin 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 28/09/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Beromun; *China*: Na Ke Si (纳科思); Tian En Fu (天恩福); *Cz.*: Beromun; *Gr.*: Beromun; *Irl.*: Beromun; *Ital.*: Beromun; *Neth.*: Beromun; *Pol.*: Beromun; *Port.*: Beromun; *Rus.*: Refnot (Рефнот); *Spain*: Beromun; *Swed.*: Beromun; *UK*: Beromun.

Ubenimex *(rINN)*

NK-421; NSC-265489; Ubénimex; Ubenimexum; Убенимекс.

(-)-*N*-[(2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutyryl]-L-leucine.

$C_{16}H_{24}N_2O_4$=308.4

CAS — 58970-76-6.

UNII — 10I33N5627.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Ubenimex is a peptide derived from *Streptomyces olivoreticuli*. It is reported to have antineoplastic and immunostimulant properties. It has been used in the adjuvant treatment of acute myeloid leukaemia and is under investigation for the treatment of lung cancer. Adverse effects include gastrointestinal and hepatic function disturbances, skin rashes, headache, and paraesthesias.

References.

1. Ichinose Y, *et al.* Randomized double-blind placebo-controlled trial of bestatin in patients with resected stage I squamous-cell lung carcinoma. *J Natl Cancer Inst* 2003; **95**: 605–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bai Shi Xin (百士欣); *Jpn*: Bestatin.

Valrubicin *(USAN, rINN)*

AD-32; NSC-246131; *N*-Trifluoroacetyladriamycin-14-valerate; *N*-Trifluoroacetyldoxorubicin-14-valerate; Valrubicina; Valrubicine; Valrubicinum; Вальрубицин.

(8*S*,10*S*)-8-Glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-{[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl]oxy}-5,12-naphthacenedione 8^2-valerate.

$C_{34}H_{36}F_3NO_{13}$=723.7

CAS — 56124-62-0.

ATC — L01DB09.

ATC Vet — QL01DB09.

UNII — 2C6NUM6878.

Pharmacopoeias. In *US.*

USP 36: (Valrubicin). An orange to orange-red crystalline powder. Very slightly soluble in water, in hexane, and in petroleum spirit; soluble in dehydrated alcohol, in acetone, in dichloromethane, and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Valrubicin is a semisynthetic analogue of the anthracycline doxorubicin (p. 782.3). It is used for carcinoma *in situ* (CIS) of the bladder (p. 700.2) refractory to BCG vaccine, when surgery is contra-indicated, although only about 20% of such patients exhibit a complete response. A dose of 800 mg is given intravesically once a week for 6 weeks. Valrubicin is diluted with sodium chloride 0.9% to a total volume of 75 mL. The solution should be retained for 2 hours if possible before voiding.

Because of the risk of metastasis, cystectomy should be reconsidered for patients with CIS who do not respond completely to valrubicin treatment after 3 months.

References.

1. Steinberg G, *et al.* Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. *J Urol (Baltimore)* 2000; **163**: 761–7.
2. Kuznetsov DD, *et al.* Intravesical valrubicin in the treatment of carcinoma in situ of the bladder. *Expert Opin Pharmacother* 2001; **2**: 1039–13.

Adverse Effects, Treatment, and Precautions

Increased urinary frequency and urgency, dysuria, bladder spasm and pain may follow intravesical use of valrubicin due to local irritation of the bladder, and usually resolve within 1 to 7 days of treatment. Gross haematuria has occurred rarely but should be distinguished from drug-induced red coloration of the urine. Abdominal pain and nausea may occur.

Myelosuppression similar to that seen with other anthracyclines (see Adverse Effects of Doxorubicin, p. 784.1) is possible if significant systemic exposure occurs. Therefore valrubicin should not be given to patients with a perforated bladder or compromised bladder mucosa.

Because of the risk of metastasis, cystectomy should be reconsidered for patients with carcinoma *in situ* who do not respond completely to valrubicin treatment after 3 months.

Pharmacokinetics

On intravesical use valrubicin penetrates the bladder wall but systemic absorption is low in patients who have an intact bladder mucosa. The drug is almost entirely excreted by voiding after the installation period.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Valtaxin; *Israel*: Valstar†; *USA*: Valstar.

Pharmacopoeial Preparations

USP 36: Valrubicin Intravesical Solution.

Vandetanib (BAN, USAN, rINN)

AZD-6474; Vandétanib; Vandetanibum; ZD-6474; Вандетаниб.

N-(4-Bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine.

$C_{22}H_{24}BrFN_4O_2$=475.4

CAS — 338992-00-0; 443913-73-3.

ATC — L01XE12.

ATC Vet — QL01XE12.

UNII — YO460OQ37K.

NOTE. The name Zactima has been used as a trade mark for vandetanib.

Uses and Administration

Vandetanib is a tyrosine kinase inhibitor targeted at receptors for vascular endothelial growth factor and epidermal growth factor. It is used for the treatment of symptomatic or progressive medullary thyroid cancer (p. 716.1) in patients with unresectable locally advanced or metastatic disease. The recommended dose is 300 mg orally once daily. Treatment is continued until patients no longer benefit, or unacceptable toxicity occurs. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* If a daily dose of vandetanib is missed, no catch-up dose is recommended if it is less than 12 hours before the next dose. In the event of severe toxicity, treatment is interrupted until toxicity resolves or improves; dosage may be resumed at 200 mg once daily; doses may be reduced further to 100 mg once daily if needed. For use in hepatic and renal impairment, see below. In the event of a corrected QT interval (QTcF) greater than 500 milliseconds, treatment should be interrupted until the QTcF returns to less than 450 milliseconds; treatment is resumed at a reduced dose.

Vandetanib is also under investigation in the treatment of other solid malignancies.

Reviews.

1. Herbst RS, *et al.* Vandetanib (ZD6474): an orally available receptor tyrosine kinase inhibitor that selectively targets pathways critical for tumor growth and angiogenesis. *Expert Opin Invest Drugs* 2007; 16: 239–49.
2. Hanrahan EO, Heymach JV. Vascular endothelial growth factor receptor tyrosine kinase inhibitors vandetanib (ZD6474) and AZD2171 in lung cancer. *Clin Cancer Res* 2007; 13 (15 suppl): s4617–s4622.
3. Natale RB. Dual targeting of the vascular endothelial growth factor receptor and epidermal growth factor receptor pathways with vandetinib [sic] (ZD6474) in patients with advanced or metastatic non-small cell lung cancer. *J Thorac Oncol* 2008; 3 (suppl 2): S128–S130.
4. Morabito A, *et al.* Vandetanib (ZD6474), a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) tyrosine kinases: current status and future directions. *Oncologist* 2009; 14: 378–90.
5. Morabito A, *et al.* Vandetanib: an overview of its clinical development in NSCLC and other tumors. *Drugs Today* 2010; 46: 683–98.
6. Commander H, *et al.* Vandetanib: first global approval. *Drugs* 2011; 71: 1355–65.

Administration. As for Gefitinib, p. 800.3.

Administration in hepatic impairment. A pharmacokinetic study[1] in subjects given a single oral dose of vandetanib 800 mg found that hepatic impairment was associated with reduced peak plasma concentrations, especially in those with severe disease, but that the area under the concentration-time curve was unaltered. Exposure to *N*-desmethylvandetanib (see Pharmacokinetics, below) was reduced in subjects with hepatic impairment, consistent with impaired oxidative drug metabolism. It was concluded that, while hepatic impairment would not affect the magnitude of steady-state exposure, the time taken to achieve it would be increased, especially in those with severe disease. The authors concluded that no dose adjustment would be needed in patients with hepatic impairment.

US licensed product information states that data are limited in patients with hepatic impairment (serum bilirubin > 1.5 times the upper limit of normal) and that vandetanib is not recommended for use in patients with moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment, as safety and efficacy have not been established.

1. Weil A, *et al.* Pharmacokinetics of vandetanib in subjects with renal or hepatic impairment. *Clin Pharmacokinet* 2010; 49: 607–18.

Administration in renal impairment. A pharmacokinetic study[1] in subjects given a single oral dose of vandetanib 800 mg found that renal impairment resulted in statistically significant increased exposure and reduced plasma clearance. Mean area under the concentration-time curve values were 46%, 62%, and 79% higher in subjects with mild, moderate, and severe renal impairment, respectively.

US licensed product information states that the initial dose of vandetanib (see Uses and Administration, above) should be reduced to 200 mg orally once daily in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

1. Weil A, *et al.* Pharmacokinetics of vandetanib in subjects with renal or hepatic impairment. *Clin Pharmacokinet* 2010; 49: 607–18.

Adverse Effects, Treatment, and Precautions

The most common adverse effects with vandetanib are gastrointestinal disturbances, abdominal pain, rash, acne, headache, fatigue, and decreased appetite. Diarrhoea can be severe, and routine anti-diarrhoeals are recommended; vandetanib may need to be interrupted, and treatment resumed at a reduced dose upon improvement. Hypertension is also common, and hypertensive crisis has been reported; dose reduction or interruption of therapy may be needed, and if blood pressure cannot be controlled, vandetanib should not be restarted. Other adverse effects include hypocalcaemia, proteinuria, pancreatitis, blurred vision, and depression. Electrolyte abnormalities, decreased glucose, increased alanine aminotransferase (ALT) concentrations, increased bilirubin, and increased creatinine can occur.

Vandetanib can prolong the QT interval; because of the drug's long half-life (see Pharmacokinetics, below), this and other adverse effects may not resolve quickly. ECG monitoring is recommended at baseline, after 2 to 4 weeks, again at 8 to 12 weeks after starting treatment, and every 3 months thereafter. Torsade de pointes, ventricular tachycardia, and sudden death have been reported. Vandetanib therapy should not be started in patients whose corrected QT interval (QTcF) is greater than 450 milliseconds (see also Uses and Administration, above), and the drug should not be given to those with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated cardiac failure. It should also not be given if the patient has hypocalcaemia, hypokalaemia, or hypomagnesaemia, which should be corrected before starting therapy with vandetanib, and periodically monitored.

Severe skin reactions, including Stevens-Johnson syndrome, have occurred with vandetanib; fatalities have been reported. Treatment involves stopping therapy and the use of systemic corticosteroids. If vandetanib is restarted, a reduced dose should be used. Mild to moderate reactions can include rash, dry skin, dermatitis, pruritus, photosensitivity reactions, and palmar-plantar erythrodysesthesia syndrome; these may be treated with topical and systemic corticosteroids, oral antihistamines, and topical and systemic antibacterial therapy. Sunscreens and protective clothing are advised if the patient is exposed to sunlight; this should continue for 4 months after vandetanib therapy is stopped.

Fatalities due to cardiac failure, ischaemic cerebrovascular events, or serious haemorrhage have been reported in patients taking vandetanib; therapy should be stopped. Interstitial lung disease has also occurred, in some cases fatal, and patients should be advised to report any new or worsening respiratory symptoms. Therapy may need to be interrupted or stopped permanently in severe cases; corticosteroids and antibacterials may be indicated for management.

Reversible posterior leukoencephalopathy syndrome (RPLS) has also been seen, and this diagnosis should be considered if patients present with seizures, headache, visual disturbances, or confusion. Therapy may need to be stopped if RPLS occurs.

Patients who are treated with vandetanib and who have had a thyroidectomy have required higher doses of thyroid hormone replacement therapy; thyroid stimulating hormone concentrations should be measured at baseline, at 2 to 4 weeks, at 8 to 12 weeks, and every 3 months thereafter.

Vandetanib may be fetotoxic; women should be advised to avoid pregnancy during treatment and for at least 4 months after the last dose.

Interactions

Vandetanib is metabolised by the cytochrome P450 isoenzyme CYP3A4. Inducers of this isoenzyme can reduce plasma vandetanib concentrations and use with potent CYP3A4 inducers (such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifabutin, rifampicin, and rifapentine) should be avoided. St John's wort can decrease vandetanib exposure unpredictably and use together is not recommended. No significant interaction was seen between vandetanib and the potent CYP3A4 inhibitor itraconazole in healthy subjects. Vandetanib can prolong the QT interval and use with antiarrhythmic drugs (such as amiodarone, disopyramide, dofetilide, procainamide, and sotalol) and other drugs that prolong the QT interval (such as chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide) should be avoided.

Pharmacokinetics

Absorption of vandetanib after oral ingestion is slow, with peak plasma concentrations occurring at about 6 hours (range 4 to 10 hours) after dosing. Steady-state concentrations occur at about 3 months. Plasma protein binding is about 90%. Vandetanib is metabolised by cytochrome P450 isoenzyme CYP3A4, mainly to *N*-desmethylvandetanib, and by flavin-containing mono-oxygenase enzymes FM01 and FM03 to vandetanib-*N*-oxide. The plasma half-life is about 19 days. Vandetanib and its metabolites are slowly excreted in the urine and faeces. Exposure to vandetanib is increased by renal impairment. Japanese and Chinese patients have been reported to have higher exposure to vandetanib compared with Caucasian patients.

References.

1. Weil A, *et al.* Pharmacokinetics of vandetanib in subjects with renal or hepatic impairment. *Clin Pharmacokinet* 2010; 49: 607–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Caprelsa; *Canad.*: Caprelsa; *Denm.*: Caprelsa; *Fr.*: Caprelsa; *Israel*: Caprelsa; *Neth.*: Caprelsa; *Norw.*: Caprelsa; *Swed.*: Caprelsa; *Switz.*: Caprelsa; *UK*: Caprelsa; *USA*: Caprelsa.

Veltuzumab (USAN, rINN)

Immu-106; Veltuzumabum; Вептузумаб.

Immunoglobulin G1, anti-(human CD20 (antigen)) (human-mouse monoclonal hA20 heavy chain), disulfide with human-mouse monoclonal hA20 κ-chain, dimer.

CAS — 728917-18-8.

UNII — BPD4DGQ314.

Profile

Veltuzumab is a humanised monoclonal antibody that targets CD20 receptors on B-lymphocytes. It is under investigation for the treatment of chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, idiopathic thrombocytopenia purpura, and rheumatoid arthritis.

References.

1. Goldenberg DM, *et al.* Properties and structure-function relationships of veltuzumab (hA20), a humanized anti-CD20 monoclonal antibody. *Blood* 2009; 113: 1062–70. Correction. *ibid.*; 5368.
2. Milani C, Castillo J. Veltuzumab, an anti-CD20 mAb for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia and immune thrombocytopenic purpura. *Curr Opin Mol Ther* 2009; 11: 200–7.
3. Goldenberg DM, *et al.* Veltuzumab (humanized anti-CD20 monoclonal antibody): characterization, current clinical results, and future prospects. *Leuk Lymphoma* 2010; 51: 747–55.

Vemurafenib (USAN, rINN)

PLX-4032; RG-7204; RO-5185426; Vémurafénib; Vemurafenibum; Вемурафениб.

N-[3-[5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-carbonyl]-2,4-difluorophenyl]propane-1-sulfonamide.

$C_{23}H_{18}ClF_2N_3O_3S$=489.9

CAS — 918504-65-1.

UNII — 207SMY3FQT.

Uses and Administration

Vemurafenib is a BRAF kinase inhibitor that is used for the treatment of unresectable or metastatic melanoma (p. 714.3) with $BRAF^{V600}$ mutation. The recommended oral dose is 960 mg twice daily. A missed dose may be taken up to 4 hours before the next dose. Tablets should be swallowed whole and not crushed or chewed. Vemurafenib may be taken with or without food, but regularly taking both daily doses on an empty stomach should be avoided as this may reduce its exposure (see Pharmacokinetics, p. 880.2). *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.* Treatment is continued until disease progression or unacceptable toxicity occurs. The dose may need to be modified or withheld if toxicity occurs, see Administration in Subsequent Cycles, p. 880.1.

Vemurafenib is also under investigation for the treatment of thyroid cancer.

References.

1. Smalley KS, PLX-4032, a small-molecule B-raf inhibitor for the potential treatment of malignant melanoma. *Curr Opin Investig Drugs* 2010; 11: 699–706.
2. Chapman PB, *et al.* BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364: 2507–16.
3. Heakal Y, *et al.* Vemurafenib (PLX4032): an orally available inhibitor of mutated BRAF for the treatment of metastatic melanoma. *Ann Pharmacother* 2011; 45: 1399–1405.
4. NICE. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma: Technology Appraisal Guidance 269 (issued December 2012). Available at: http://www.nice.org.uk/nicemedia/live/14005/61877/61877.pdf (accessed 19/08/13)

Administration in subsequent cycles. Oral doses of vemurafenib may need to be withheld, reduced, or treatment stopped if toxicity occurs.

- For grade 3 or intolerable grade 2 adverse effects: withhold treatment until effects have resolved to ≤grade 1. Treatment may be resumed at a dose of 720 mg twice daily after the first occurrence; after the second occurrence treatment should be resumed at 480 mg twice daily. If the same adverse effect recurs for a third time, vemurafenib should be permanently stopped.
- For grade 4 adverse effects: either permanently stop vemurafenib, or withhold until effects have resolved to ≤ grade 1 and then resume treatment at a dose of 480 mg twice daily. If the same adverse effect recurs for a second time, vemurafenib should be permanently stopped.
- For those with a QTc > 500 milliseconds during treatment: vemurafenib should be withheld and risk factors for QT interval prolongation controlled. Once the QTc has recovered to < 500 milliseconds, treatment may be resumed at a dose of 720 mg twice daily after the first occurrence; after the second occurrence treatment should be resumed at 480 mg twice daily. If QT interval prolongation recurs for a third time, vemurafenib should be permanently stopped. If, after risk factors for QT interval prolongation have been controlled, the QTc is still > 500 milliseconds and there is > 60 milliseconds increase from pretreatment values, vemurafenib should be permanently stopped.

Adverse Effects, Treatment, and Precautions

The most common adverse effects with vemurafenib are arthralgia, alopecia, fatigue, nausea, rash, photosensitivity, pruritus, and skin papilloma. Patients should avoid sun exposure, wear protective clothing, and apply sunscreen when outdoors to avoid photosensitivity. For intolerable grade 2 erythema, dose modifications are recommended, see Administration in Subsequent Cycles, above. Other effects on the skin include dry skin, actinic keratosis, palmar-plantar erythrodysesthesia syndrome, keratosis pilaris, seborrhoeic keratosis, and erythema nodosum. Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely; treatment should be permanently stopped in those who have a severe skin reaction.

Cutaneous squamous cell carcinomas have been reported in patients treated with vemurafenib, usually early in the course of treatment with a median time to first appearance of 7 to 8 weeks. Non-cutaneous squamous cell carcinoma, basal cell carcinoma, and new primary cases of malignant melanoma have also occurred. Monitoring for malignancies should be undertaken before, during, and for up to 6 months after treatment.

Hypersensitivity reactions include anaphylaxis, rash, erythema, and hypotension; treatment should be permanently stopped in those who have a severe reaction.

QT prolongation has been seen with vemurafenib, and treatment is not recommended in those with long QT syndrome, uncorrected electrolyte abnormalities, or those taking other medicines known to prolong the QT interval. ECG and electrolytes should be monitored before starting vemurafenib and after changing the dose. ECGs should also be checked 15 days after the start of treatment, monthly during the first 3 months of treatment, and then every 3 months thereafter (or more often if needed). Treatment should not be started in those with a QTc > 500 milliseconds; the dose may need to be withheld or reduced, or vemurafenib stopped, in those with a prolonged QT interval during treatment, see Administration in Subsequent Cycles, above.

Abnormalities in liver function tests have occurred during vemurafenib treatment, and liver function should be measured before starting treatment, and monthly during treatment or as needed. Vemurafenib may need to be withheld, the dose reduced, or treatment stopped if abnormalities occur, see Administration in Subsequent Cycles, above.

Effects on the eyes include blurred vision, iritis, photophobia, retinal vein occlusion, and uveitis. Patients should be monitored for signs of uveitis; treatment with corticosteroid and mydriatic eye drops may be required if uveitis occurs.

Other adverse effects that have occurred with vemurafenib include myalgia, musculoskeletal pain, oedema, fever, headache, dysgeusia, gastrointestinal disorders, cough, dizziness, peripheral neuropathy, Bell's palsy, folliculitis, vasculitis, and atrial fibrillation.

References.

1. Sinha R, *et al.* Cutaneous adverse events associated with vemurafenib in patients with metastatic melanoma: practical advice on diagnosis, prevention and management of the main treatment-related skin toxicities. *Br J Dermatol* 2012; 167: 987–94.

Interactions

In-vitro studies indicate that vemurafenib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and therefore inhibitors or inducers of this enzyme may alter vemurafenib concentrations. Caution is required when vemurafenib is used with strong CYP3A4 inhibitors or inducers.

Vemurafenib is also a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor, and a CYP3A4 inducer; use is not recommended with drugs that are metabolised via these routes and have a narrow therapeutic window. Exposure to caffeine (a CYP1A2 substrate) and dextromethorphan (a CYP2D6 substrate) was increased when given with vemurafenib, and a reduced dose of CYP1A2 and CYP2D6 substrates may be required if they must be given with vemurafenib. Exposure to midazolam (a CYP3A4 substrate) was decreased with vemurafenib.

Pharmacokinetics

When vemurafenib is taken orally at usual doses, peak plasma concentrations occur after about 3 to 4 hours and steady state is achieved in 15 to 22 days. Regularly taking vemurafenib on an empty stomach may lead to significantly lower steady state exposure than when taken with or just after food. Vemurafenib is highly protein bound (> 99%) to albumin and α-1 acid glycoprotein. *In-vitro* studies have shown that vemurafenib is a substrate and an inhibitor of P-glycoprotein. Only 5% of a dose of vemurafenib is metabolised; 94% of the dose is excreted in the faeces and 1% in the urine. The median elimination half-life is about 57 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Zelboraf; *Belg.*: Zelboraf; *Canad.*: Zelboraf; *Denm.*: Zelboraf; *Fr.*: Zelboraf; *Israel*: Zelboraf; *Neth.*: Zelboraf; *Norw.*: Zelboraf; *Swed.*: Zelboraf; *Switz.*: Zelboraf; *UK*: Zelboraf; *USA*: Zelboraf.

Verteporfin *(BAN, USAN, rINN)*

Benzoporphyrin Derivative; BPD; CL-318952; Verteporfiini; Verteporfina; Vertéporfine; Verteporfinum; Верпорфин.

trans-18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropanoic acid monomethyl ester.

$C_{41}H_{42}N_4O_8$=718.8

CAS — 129497-78-5.

ATC — S01LA01.

ATC Vet — QS01LA01.

UNII — 0X9PA28K43.

Pharmacopoeias. In *US.*

USP 36: (Verteporfin). Store at a temperature between -25 degrees and -10 degrees in airtight containers.

Uses and Administration

Verteporfin is a photosensitiser used in photodynamic therapy (see under Porfimer Sodium, p. 849.1). It is used to treat neovascular (wet) age-related macular degeneration (see below). After intravenous dosage verteporfin accumulates preferentially in the endothelial cells of actively growing blood vessels, including those in the choroid. When activated by laser light it produces local vascular occlusion and this inhibits neovascularisation and reduces the decline in visual acuity. It is given by intravenous infusion over 10 minutes at a dose of 6 mg/m^2. This is followed 15 minutes after the start of the infusion by activation using a laser tuned to a wavelength of 689 nanometres and delivered to the eye via a fibre optic device and a slit lamp, together with a suitable contact lens. The recommended light dose is 50 J/cm^2, given over 83 seconds. Therapy may be repeated every 3 months for recurrent choroidal neovascular leakage. Verteporfin has also been investigated in the photodynamic therapy of a variety of other disorders including malignant neoplasms.

Age-related macular degeneration. Age-related macular degeneration (AMD) is a degenerative disease usually occurring in people over the age of 50 years.[1-3] The central portion of the retina (the macula) deteriorates[2,4,5] and it is a major cause of severe visual loss in people over 60 years old in North America and Europe.[4,6] There are two main types of AMD.[2,4,6-9]

- In geographic atrophy or *non-neovascular* or *non-exudative (dry) AMD*, which occurs at an early stage of AMD, the retinal pigment epithelium is lost completely in localised areas, causing a gradual loss of central vision in the affected eye(s). It is characterised by retinal hypo- or hyperpigmentation, and yellow deposits of acellular amorphous debris beneath the retina, called drusen. These are usually large, or soft (with indistinct margins); small hard drusen occur naturally with ageing but, unlike drusen in AMD, do not progress.
- In *neovascular* or *exudative (wet) AMD*, new blood vessels develop in the choroidal layer beneath the retina; leaks or haemorrhage from these lead to macular oedema, retinal scarring, and often acute, significant loss of vision. This process of *choroidal neovascularisation* (CNV) is defined as classic or occult according to its appearance on fluorescein angiography;[2,5,8,10] the classic form is associated with more rapid progression than the occult form.[2,8] CNV lesions are also classified according to their location relative to the fovea.[1,2,11] Although the neovascular form accounts for only about 20% of all cases of AMD, the risk of severe visual loss with this form is much higher than with dry AMD.[1,8,12] However, about 10 to 20% of patients with dry AMD can progress to the neovascular form,[1,9] and both forms can occasionally co-exist in the same patient.[10]

Risk factors, besides older age, include a family history of the disorder, polymorphisms in either the complement factor H (CFH) or age-related maculopathy susceptibility 2 (ARMS2 or LOC387715) genes, smoking, white race, and increased body-mass index;[3,12,13] female sex, atherosclerosis, dietary fat or fish intake, alcohol or caffeine consumption, refractive error, iris colour, and increased exposure to sunlight have also been proposed as risk factors but have not consistently been related to development of AMD.[13]

There is currently no **treatment** that effectively prevents visual loss or improves vision in all patients with AMD.[14]

- Laser photocoagulation treatment is of proven efficacy for neovascular AMD, especially for extrafoveal CNV;[15] however, rates of recurrence are high.[1,6,13,14]
- Photodynamic therapy (see under Porfimer Sodium, p. 849.1) with verteporfin has been shown to decrease the risk of visual loss in patients with neovascular AMD, including subfoveal CNV.[1,4,8,10,11,14,16-20] Systematic reviews have noted that although photodynamic therapy with verteporfin is probably effective in preventing visual loss in those with classic and occult CNV due to AMD, the size of the effect remains in doubt.[5,21] Furthermore, the therapy can only be effective during the proliferative stage of the disease while the neovascular process is active.[5]

  In the UK, NICE guidelines considered the evidence to show a larger treatment effect in patients with classic CNV, and recommend photodynamic therapy in those patients with neovascular AMD with a confirmed diagnosis of classic, with no occult, subfoveal CNV.[2] However, other guidelines[22] on the use of verteporfin recommend that verteporfin treatment be considered for patients with minimally classic subfoveal CNV who have relatively small lesions, or where the proportion of classic CNV is increasing. For those patients with occult CNV and who are presumed to have recent disease progression, verteporfin may be considered in those with smaller lesions or lower levels of visual acuity; for those with large occult lesions, treatment may be considered if levels of visual acuity are rapidly decreasing. Patients should be followed up at least as often as every 3 months after initial therapy, and re-treated if necessary.[22] Subsequent results suggest that verteporfin is ineffective in occult lesions.[20]

  While photodynamic therapy is considered to have minimal adverse effects and a low complication rate, some have cautioned that patients should be counselled that verteporfin therapy rarely leads to an improvement in vision.[23]
- Vascular endothelial growth factor (VEGF) plays a role in the development of CNV secondary to AMD; pegaptanib and ranibizumab are VEGF inhibitors used in the treatment of neovascular (wet) AMD.[24-26] Systematic reviews[27,28] of randomised controlled studies of these drugs concluded that both show benefit in slowing or stopping the progression of disease. Greater effect was seen with ranibizumab than with pegaptanib, although head-to-head comparative studies are needed to confirm this. Use of pegaptanib is not recommended by NICE in the UK.[29] Early studies have reported benefit from the use of aflibercept.[30,31] Bevacizumab is also used, although its use is unlicensed and controversial.[6,15,32] (For further discussion, see Age-related Macular Degeneration, under Bevacizumab, p. 747.2.) Triamcinolone acetonide, a corticosteroid that may also downregulate VEGF, has been given intravitreally with variable results; combination treatment with photodynamic therapy is under investigation,[9,13,33] and initial results have been promising.[15]
- Angiogenesis inhibitors such as anecortave[3,9,13,14,33] and squalamine[15] are under investigation for neovascular AMD. Interferon alfa gave encouraging preliminary results, but controlled data showed no benefit.[9,13] Thalidomide has been tried, but studies were stopped due to adverse effects.[9,13]
- Vitamin and mineral supplements may be of use in selected patients; the AREDS study found that antoxidants (vitamin C, vitamin E, and betacarotene) plus zinc modestly benefited those with moderate to severe signs of the disease.[10,12,14] However, betacarotene

should be avoided in smokers,[3,6,9] and high doses of vitamins may have adverse effects.[12] The carotenoids, lutein and zeaxanthin, have been promoted as retinal protectants, but controlled data are lacking.[9,10,14,34,35] Some recommend that those at risk of AMD should be encouraged to stop smoking and to consume a diet including vegetables, fish, whole grains, and nuts, and to reduce consumption of fats especially vegetable oil.[7,12,34] A prospective cohort study found that a high dietary intake of vitamin E and zinc, or an above-median intake of the combination of vitamins C and E, betacarotene, and zinc were associated with a lower risk of incident AMD.[36] Daily supplementation with folic acid, pyridoxine, and cyanocobalamin during an average of 7.3 years of follow-up reduced the risk of AMD in a large cohort of women at increased risk for vascular disease; benefit emerged at about 2 years of follow-up and persisted throughout the study.[37] However, systematic reviews[38,39] have found no evidence to support the role of antoxidant vitamin and mineral supplements in the primary prevention of AMD.

- Retinal or macular surgery, and transpupillary thermotherapy have been investigated;[1,10,13,14,33] however, long-term data are lacking for surgery,[12] and use of transpupillary thermotherapy is not recommended.[15] Radiotherapy has also been tried with mixed results.[9,13] Retinal transplantation is under investigation.[6,10,14] Gene silencing with bevasiranib, a short interfering RNA (siRNA) therapeutic designed to turn off or silence the gene that produces VEGF, is also under investigation for wet AMD.[12,40,41]

1. Soubrane G, Bressler NM. Treatment of subfoveal choroidal neovascularisation in age related macular degeneration: focus on clinical application of verteporfin photodynamic therapy. *Br J Ophthalmol* 2001; **85**: 483–95.
2. NICE. Guidance on the use of photodynamic therapy for age-related macular degeneration: Technology Appraisal 68 (issued September 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/68_PDTGuidance.pdf (accessed 01/10/09)
3. El-Amir AN, *et al.* Age-related macular degeneration. *Br J Hosp Med* 2005; **66**: 677–81.
4. Messmer KJ, Abel SR. Verteporfin for age-related macular degeneration. *Ann Pharmacother* 2001; **35**: 1593–8.
5. Wormald R, *et al.* Photodynamic therapy for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 01/08/08).
6. Cook HL, *et al.* Age-related macular degeneration: diagnosis and management. *Br Med Bull* 2008; **85**: 127–49.
7. Constable IJ. Age-related macular degeneration and its possible prevention. *Med J Aust* 2004; **181**: 471–2.
8. Yang YC. Preserving vision with verteporfin photodynamic therapy. *Hosp Med* 2004; **65**: 39–43.
9. Comer GM, *et al.* Current and future treatment options for nonexudative and exudative age-related macular degeneration. *Drugs Aging* 2004; **21**: 967–92.
10. Bylsma GW, Guymer RH. Treatment of age-related macular degeneration. *Clin Exp Optom* 2005; **88**: 322–34.
11. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report 1. *Arch Ophthalmol* 1999; **117**: 1329–45.
12. Jager RD, *et al.* Age-related macular degeneration. *N Engl J Med* 2008; **358**: 2606–17.
13. Sun JK, Miller JW. Medical treatment of choroidal neovascularization secondary to age-related macular degeneration. *Int Ophthalmol Clin* 2005; **45**: 115–32.
14. Lois N. Neovascular age-related macular degeneration. *Compr Ophthalmol Update* 2004; **5**: 143–61.
15. Chakravarthy U, *et al.* Evolving European guidance on the medical management of neovascular age related macular degeneration. *Br J Ophthalmol* 2006; **90**: 1188–96.
16. Blumenkranz MS, *et al.* Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials—TAP report no. 5. *Arch Ophthalmol* 2002; **120**: 1307–14.
17. Blinder KJ, *et al.* Verteporfin therapy of subfoveal choroidal neovascularization in pathologic myopia: 2-year results of a randomized clinical trial—VIP report no. 3. *Ophthalmology* 2003; **110**: 667–73.
18. Keam SJ, *et al.* Verteporfin: a review of its use in the management of subfoveal choroidal neovascularisation. *Drugs* 2003; **63**: 2521–54.
19. Wickens J, Blinder KJ. A preliminary benefit-risk assessment of verteporfin in age-related macular degeneration. *Drug Safety* 2006; **29**: 189–99.
20. Cruess AF, *et al.* Photodynamic therapy with verteporfin in age-related macular degeneration: a systematic review of efficacy, safety, treatment modifications and pharmacoeconomic properties. *Acta Ophthalmol* 2009; **87**: 118–32.
21. Meads C, Hyde C. Photodynamic therapy with verteporfin is effective, but how big is its effect? Results of a systematic review. *Br J Ophthalmol* 2004; **88**: 212–17.
22. Verteporfin Roundtable Participants. Guidelines for using verteporfin (Visudyne) in photodynamic therapy for choroidal neovascularization due to age-related macular degeneration and other causes: update. *Retina* 2005; **25**: 119–34.
23. Sternberg P, Lewis H. Photodynamic therapy for age-related macular degeneration: a candid appraisal. *Am J Ophthalmol* 2004; **137**: 483–5.
24. Anonymous. A view on new drugs for macular degeneration. *Drug Ther Bull* 2007; **45**: 49–52.
25. Rosenfeld PJ, *et al.* MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1419–31.
26. Brown DM, *et al.* ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1432–44.
27. Takeda AL, *et al.* Pegaptanib and ranibizumab for neovascular age-related macular degeneration: a systematic review. *Br J Ophthalmol* 2007; **91**: 1177–82.
28. Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/05/08).
29. NICE. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: Technology Appraisal Guidance 155 (issued August 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA155guidance.pdf (accessed 01/10/09)
30. Brown DM, *et al.* CLEAR-IT 2 Investigators. Primary endpoint results of a phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration. *Ophthalmology* 2011; **118**: 1089–97.
31. Heier JS, *et al.* CLEAR-IT 2 Investigators. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. *Ophthalmology* 2011; **118**: 1098–1106. Correction. *Ibid.*: 1700.
32. Wong TY, *et al.* Clinical update: new treatments for age-related macular degeneration. *Lancet* 2007; **370**: 204–6.
33. Liu M, Regillo CD. A review of treatments for macular degeneration: a synopsis of currently approved treatments and ongoing clinical trials. *Curr Opin Ophthalmol* 2004; **15**: 221–6.
34. Anonymous. Nutritional supplements for macular degeneration. *Drug Ther Bull* 2006; **44**: 9–11.
35. Zhao L, Sweet BV. Lutein and zeaxanthin for macular degeneration. *Am J Health-Syst Pharm* 2008; **65**: 1232–8.
36. van Leeuwen R, *et al.* Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA* 2005; **294**: 3101–7.
37. Christen WG, *et al.* Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. *Arch Intern Med* 2009; **169**: 335–41.
38. Chong EW-T, *et al.* Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *BMJ* 2007; **335**: 755–9.
39. Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 09/05/08).
40. Arjamaa O. Gene silencing in wet age-related macular degeneration. *Lancet* 2006; **368**: 630–1.
41. Chappelow AV, Kaiser PK. Neovascular age-related macular degeneration: potential therapies. *Drugs* 2008; **68**: 1029–36.

Adverse Effects and Precautions

Photosensitivity will occur in all patients treated with verteporfin and patients should not be exposed to direct sunlight for 2 to 5 days after treatment. However, exposure to ambient indoor light is encouraged, as it allows gradual inactivation of any remaining drug. Headaches, injection site reactions, and visual disturbances occur frequently. Extravasation at the injection site may produce severe pain and inflammation and requires interruption of therapy. Patients who have a severe decrease in vision should not be re-treated until their vision recovers. Other reported adverse effects include hypersensitivity, infusion-related pain (mainly presenting as back pain), chest pain, gastrointestinal disturbances, atrial fibrillation, hypertension, decreased hearing, and anaemia. Verteporfin should be used with care in patients with hepatic impairment and may be contra-indicated if impairment is severe.

Porphyria. Licensed product information states that the use of verteporfin is contra-indicated in patients with porphyria. However, the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies verteporfin 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 11/11/11)

Interactions

Use of verteporfin with other drugs causing photosensitivity should be avoided as the reaction may be increased.

Pharmacokinetics

After intravenous doses, elimination of verteporfin is bi-exponential, with a terminal plasma elimination half-life of about 5 to 6 hours. Protein binding is about 90%. It is metabolised in the liver. It is excreted in faeces via the bile, mostly as unchanged drug, with less than 1% of a dose recovered in the urine.

References.

1. Houle J-M, Strong A. Clinical pharmacokinetics of verteporfin. *J Clin Pharmacol* 2002; **42**: 547–57.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Visudyne; *Austral.*: Visudyne; *Austria*: Visudyne; *Belg.*: Visudyne; *Braz.*: Visudyne; *Canad.*: Visudyne; *Chile*: Visudyne†; *China*: Visudyne (维速达尔); *Cz.*: Visudyne; *Denm.*: Visudyne; *Fin.*: Visudyne; *Fr.*: Visudyne; *Ger.*: Visudyne; *Gr.*: Visudine; *Hong Kong*: Visudyne; *Hung.*: Visudyne; *Indon.*: Visudyne; *Irl.*: Visudyne; *Israel*: Visudyne; *Ital.*: Visudyne; *Jpn*: Visudyne; *Malaysia*: Visudyne; *Neth.*: Visudyne; *Norw.*: Visudyne; *NZ*: Visudyne; *Philipp.*: Visudyne; *Pol.*: Visudyne; *Port.*: Visudyne; *Rus.*: Visudyne (Визудин); *S.Afr.*: Visudyne; *Singapore*: Visudyne; *Spain*: Visudyne; *Swed.*: Visudyne; *Switz.*: Visudyne; *Thai.*: Visudyne; *Turk.*: Visudyne; *UK*: Visudyne; *USA*: Visudyne; *Venez.*: Visudyne.

Pharmacopoeial Preparations
USP 36: Verteporfin for Injection.

Vinblastine Sulfate *(BANM, USAN, rINNM)*

29060-LE; NSC-49842; Sulfato de Vinblastina; Sulfato de vinblastina; Vinblastiinisulfaatti; Vinblastin Sulfat; Vinblastina, sulfato de; Vinblastine, Sulfate de; Vinblastine Sulphate; Vinblastini Sulfas; Vinblastino sulfatas; Vinblastinsulfat; Vinblastin-sulfát; Vinblasztin-szulfát; Vincaleukoblastine Sulphate; VLB (vinblastine); Winblastyny siarczan; Винбластина Сульфат.

$C_{46}H_{58}N_4O_9.H_2SO_4$=909.1

CAS — 865-21-4 (vinblastine); 143-67-9 (vinblastine sulfate).

ATC — L01CA01.

ATC Vet — QL01CA01.

UNII — N00W22YO2B.

Description. Vinblastine sulfate is the sulfate of an alkaloid, vincaleukoblastine, extracted from *Catharanthus roseus* (*Vinca rosea*) (Apocynaceae).

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

Ph. Eur. 8: (Vinblastine Sulfate). A white or slightly yellowish, very hygroscopic, crystalline powder. It loses not more than 15% of its weight on drying. Freely soluble in water; practically insoluble in alcohol. A 0.15% solution in water has a pH of 3.5 to 5.0. Store at a temperature not exceeding -20 degrees in airtight glass containers. Protect from light.

USP 36: (Vinblastine Sulfate). A white or slightly yellow, odourless, hygroscopic, amorphous or crystalline powder. It loses not more than 15% of its weight on drying. Freely soluble in water. A 0.15% solution in water has a pH of 3.5 to 5.0. Store at a temperature between -25 degrees and -10 degrees in airtight containers. Protect from light.

Stability. Between about 5 and 20% of active drug was lost from solution when a solution of vinblastine sulfate 3 micrograms/mL in glucose 5% injection was stored for 48 hours in a range of intravenous burette giving sets, the highest loss being from cellulose propionate sets and the lowest from one made from methacrylate butadiene styrene.[1] Similarly, storage in PVC tubing led to a 42 to 44% loss from solution whereas only about 6% was lost over the 48 hours in polybutadiene tubing. The losses appeared to be due to drug sorption, and were therefore greater from the tubing which had a greater surface-area-to-volume ratio than the burettes.

1. McElnay JC, *et al.* Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; **47**: 239–47.

Uses and Administration

Vinblastine sulfate is an antineoplastic vinca alkaloid that apparently acts by binding to the microtubular proteins of the spindle and arresting mitosis at the metaphase; it is thus specific for the M phase of the cell cycle. It also interferes with amino acid metabolism and possibly nucleic acid synthesis, and has some immunosuppressant activity. Multidrug resistance may occur.

Vinblastine sulfate is used, usually with other antineoplastics, in the treatment of Hodgkin's disease and other lymphomas, for some inoperable malignant neoplasms including those of the breast, bladder, and kidney, and in non-small cell lung cancer, choriocarcinoma, and Kaposi's sarcoma; vinblastine has also been used in the management of Langerhans-cell histiocytosis and advanced mycosis fungoides. It was formerly used with bleomycin and cisplatin (PVB) for testicular cancer, but other regimens are now preferred. See the cross-references given below.

Vinblastine sulfate is given by **intravenous** injection. Care should be taken to avoid extravasation and the intravenous injection may be given over 1 minute into a freely-running infusion of sodium chloride 0.9% if preferred. However, UK guidelines recommend that for adults and adolescents, the required dose should be supplied in a 50 mL infusion bag of sodium chloride 0.9% and infused intravenously over 5 to 10 minutes. (For adolescents treated in specialised paediatric units, see Administration in Children, p. 882.1.)

The usual dose of vinblastine sulfate is about 6 mg/m², not more often than once every 7 days. Single doses starting at 3.7 mg/m² and increasing at weekly intervals, over 4 weeks, to a usual maximum dose of 11.1 mg/m² have been given; doses have been increased above this, but should not exceed 18.5 mg/m². If a maintenance dose is required, it may be given every 7 days provided white cell counts permit (see below), and should be the maximum dose that the patient is able to tolerate without serious leucopenia occurring.

For doses in children, see p. 882.1.

White cell counts should be made before each injection and some sources suggest a repeat dose should not be given

unless the count has risen to at least 4000 cells/mm³ (but see also Bone-marrow Depression, p. 730.3). Dosage reduction is recommended in patients with hepatic impairment (see below).

Administration. Administration errors have occurred with the vinca alkaloids (see Administration Error, below). For UK guidelines on dilution of vinca alkaloids to avoid inadvertent intrathecal use, see p. 883.2.

Administration in children. Doses of vinblastine sulfate in children vary according to the disease treated, the schedule used, and whether it is used as a single agent or as part of a combination chemotherapy regimen. The usual dose is about 6 mg/m² given intravenously, not more often than once every 7 days. Single doses starting at 2.5 mg/m² and increasing at weekly intervals, over 4 weeks, to a usual maximum dose of 7.5 mg/m² have been given; doses have been increased above this, but should not exceed 12.5 mg/m².

UK guidelines state that doses of vinca alkaloids may be given via a syringe to children and adolescents treated in paediatric units.[1] For adolescents treated in adolescent or adult units, recommendations for administration are as for adults (see Uses and Administration, p. 881.3).

1. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR004 (issued 11th August, 2008): using vinca alkaloid minibags (adult/adolescent units). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60290&type=full&servicetype=Attachment (accessed 29/09/09)

Administration in hepatic impairment. Licensed product information states that the dose of vinblastine should be reduced by 50% in patients having a direct serum bilirubin value above 3 mg per 100 mL.

Blood disorders, non-malignant. The vinca alkaloids vinblastine and vincristine have been used in the treatment of auto-immune blood disorders such as immune thrombocytopenia (p. 1606.1). There are also reports of the haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura responding to treatment with intravenous injection of vincristine.[1-3] For further details on the treatment of thrombotic microangiopathies, see under Plasma, p. 1159.1. Vincristine has been given with normal immunoglobulin in the management of a patient with life-threatening thrombocytopenia due to sarcoidosis.[4] Vincristine has also been used for life-threatening haemangioma (p. 1605.3).

1. Gutterman LA, *et al.* The hemolytic-uremic syndrome: recovery after treatment with vincristine. *Ann Intern Med* 1983; 98: 612–13.
2. Ferrara F, *et al.* Vincristine as salvage treatment for refractory thrombotic thrombocytopenic purpura. *Ann Hematol* 1999; 78: 521–3.
3. Ferrara F, *et al.* Vincristine as treatment for recurrent episodes of thrombotic thrombocytopenic purpura. *Ann Hematol* 2002; 81: 7–10.
4. Larner AJ. Life threatening thrombocytopenia in sarcoidosis. *BMJ* 1990; 300: 317–19.

Histiocytic syndromes. The value of systemic chemotherapy in patients with Langerhans-cell histiocytosis (p. 692.1) is uncertain; however, it is certainly widely used in extensive disease, vinblastine being one of the drugs often employed.[1,2]

1. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. *Arch Dis Child* 1996; 75: 17–24.
2. Gadner H, *et al.* A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *J Pediatr* 2001; 138: 728–34. Correction. *ibid.*; 139: 170.

Malignant neoplasms. Vinblastine plays an important role in the ABVD regimen in patients with Hodgkin's disease (p. 696.1). It also formed part of the effective, if toxic, PVB regimen used to treat germ cell (ovarian or testicular) cancer, p. 711.2 and p. 715.1 respectively, although other regimens tend now to be preferred. The vinca alkaloids are also active in gestational trophoblastic tumours (p. 691.2), and vinblastine is also used in the therapy of invasive bladder cancer (p. 700.2); it may be used in the adjuvant or palliative treatment of non-small-cell lung cancer (p. 710.2) and in the palliative care of advanced breast cancer (p. 702.1). It has been used in malignancies of the kidney (p. 708.3). Vinca alkaloids are also used to treat Kaposi's sarcoma (p. 718.1).

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Bone-marrow depression, especially leucopenia, is the most common adverse effect with vinblastine and tends to be dose-limiting. Maximum depression occurs 5 to 10 days after a dose with recovery in a further 7 to 14 days. Leucopenia may be more severe in patients with cachexia or extensive skin ulceration: vinblastine should not be used in elderly patients with these conditions. Stomatitis, gastrointestinal bleeding, and abdominal pain may occur; nausea and vomiting respond to treatment with antiemetics.

The vinca alkaloids can produce central and peripheral (including autonomic) neurotoxicity, although these effects are less frequent with vinblastine. Symptoms include malaise, weakness, headache, depression, paraesthesia and numbness, loss of deep tendon reflexes, peripheral neuropathies, constipation and adynamic ileus, jaw pain, and convulsions. Damage to the eighth cranial nerve may result in vestibular and auditory toxicity leading to dizziness, nystagmus, vertigo, and partial or total deafness. A routine prophylactic regimen against constipation is recommended in patients receiving high doses of vinblastine. Overdosage has caused permanent damage to the CNS. Intrathecal use of the vinca alkaloids is contra-indicated because of the likelihood of fatal neurotoxicity (see Administration Error, below).

Other reported effects include skin reactions, alopecia, ischaemic cardiotoxicity, hypertension, dyspnoea and bronchospasm, and bone and tumour pain. A syndrome of inappropriate secretion of antidiuretic hormone has occurred at high doses, and may be relieved by fluid restriction and, if necessary, a suitable diuretic. Rare cases of anaphylaxis and anaphylactoid-type reactions have been reported with the vinca alkaloids.

Vinblastine is irritant to the skin and mucous membranes and extravasation may cause necrosis, cellulitis, and sloughing. The application of warmth and local injection of hyaluronidase may be of benefit in relieving the effects of extravasation. By analogy with its use in the management of vincristine overdosage (see p. 883.2), folinic acid has been suggested for use in overdosage with vinblastine.

Vinblastine should not be injected into an extremity with impaired circulation because of an increased risk of thrombosis. It should be given with caution and at reduced dosage to patients with hepatic impairment (see under Uses, above).

Administration error. *Intrathecal doses of vinca alkaloids, including vinblastine, result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK guidelines on dilution of vinca alkaloids to avoid intrathecal use, see p. 883.2.

Handling and disposal. A method for the destruction of vincristine or vinblastine *wastes* using sulfuric acid and potassium permanganate.[1] Residues produced by degradation of either drug by this method showed no mutagenicity *in vitro*.

Urine and faeces produced for up to 4 and 7 days respectively after a dose of vinblastine should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73* Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; 235: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vinblastine 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 26/09/11)

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Use with drugs that inhibit cytochrome P450 isoenzymes of the CYP3A subfamily may result in decreased metabolism of vinblastine and increased toxicity. Use with cisplatin has been reported to increase vinblastine plasma concentrations. For a report of the possible contribution of vinblastine to reduced plasma concentrations of phenytoin, see p. 544.1.

Analgesics. A report of enhanced hepatotoxicity in patients treated with interferon alfa and vinblastine who were given *paracetamol*.[1]

1. Kellokumpu-Lehtinen P, *et al.* Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* 1989; i: 1143.

Antibacterials. There is a report of severe vinblastine toxicity in 3 patients who received vinblastine and ciclosporin with *erythromycin*.[1] Adverse effects resolved on stopping erythromycin and recurred in 1 patient who was rechallenged with erythromycin.

1. Tobe SW, *et al.* Vinblastine and erythromycin: an unrecognised serious drug interaction. *Cancer Chemother Pharmacol* 1995; 35: 188–90.

Antineoplastics. Acute bronchospastic reactions after injection of a vinca alkaloid have been reported, usually in patients also given *mitomycin*,[1] and presenting as acute respiratory distress, cyanosis, and dyspnoea, often with the development of pulmonary infiltrates and pneumonitis.[2,3] Several fatalities due to respiratory complications have occurred. For reports of vascular toxicity and Raynaud's syndrome associated with the use of vinca alkaloids with *bleomycin* and other drugs, see Effects on the Cardiovascular System, p. 727.2.

1. Dyke RW. Acute bronchospasm after a vinca alkaloid in patients previously treated with mitomycin. *N Engl J Med* 1984; 310: 389.
2. Konits PM, *et al.* Possible pulmonary toxicity secondary to vinblastine. *Cancer* 1982; 50: 2771–4.
3. Ozols RF, *et al.* MVP (mitomycin, vinblastine, and progesterone): a second-line regimen in ovarian cancer with a high incidence of pulmonary toxicity. *Cancer Treat Rep* 1983; 67: 721–2.

Antivirals. Severe myelosuppression has occurred in patients given relatively high doses of vinblastine with *interferon alfa-n1*.

A patient who had been given vinblastine 6 mg/m² every 3 weeks had severe gastrointestinal and haematological toxicity and moderate renal failure when *HAART* with zidovudine, lamivudine, abacavir, nevirapine, and lopinavir with ritonavir was reintroduced.[1] The vinblastine dosage was eventually stabilised at 2 mg/m² during HAART without toxicity.

1. Korb R, *et al.* Life-threatening interaction between antiretroviral therapy and vinblastine in HIV-associated multicentric Castleman's disease. *Eur J Haematol* 2006; 76: 269–71.

Pharmacokinetics

Vinblastine is not reliably absorbed from the gastrointestinal tract. After intravenous use it is rapidly cleared from the blood and distributed to tissues; it is reported to be concentrated in blood platelets. It is extensively protein bound. Vinblastine is metabolised in the liver, by cytochrome P450 isoenzymes of the CYP3A subfamily, to an active metabolite desacetylvinblastine, and is excreted in faeces via the bile, and in urine; some is excreted as unchanged drug. The terminal half-life is reported to be about 25 hours. It does not cross the blood-brain barrier in significant amounts.

References.

1. Levêque D, Jehl F. Molecular pharmacokinetics of Catharanthus (vinca) alkaloids. *J Clin Pharmacol* 2007; 47: 579–88.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Blastovin; *Austral.*: Velbe†; *Austria*: Velbe; *Belg.*: Vinblasin†; *Braz.*: Faulblastina; Velban; Vinatin; *Chile*: Lemblastine; *China*: Weibaoding (威保定); *Denm.*: Velbe; *Fin.*: Velbe; *Fr.*: Velbe; *Gr.*: Velbe; *Hong Kong*: Velbastine; *India*: Cytoblastin; *Israel*: Blastovin; *Ital.*: Velbe; *Mex.*: Lemblastine; *Neth.*: Blastivin†; *Norw.*: Velbe; *Philipp.*: Oncostin; Velbastine; *Port.*: Solblastin; *S.Afr.*: Cytoblastin; *Singapore*: Velbastine; *Swed.*: Velbe; *Switz.*: Velbe; *Turk.*: Velbe; *UK*: Velbe; *USA*: Velban.

Pharmacopoeial Preparations
BP 2014: Vinblastine Injection;
USP 36: Vinblastine Sulfate for Injection.

Vincristine Sulfate *(BANM, USAN, rINNM)*

Compound 37231; Leurocristine Sulphate; NSC-67574; 22-Oxovincaleukoblastine Sulphate; Sulfato de leurocristina; Sulfato de vincristina; Vincristina, sulfato de; Vincristine, Sulfate de; Vincristine Sulphate; Vincristini sulfas; Vincristinsulfat; Vinkristiinisulfaatti; Vinkristin Sülfat; Vinkristino sulfatas; Vinkristinsulfat; Vinkristin-sulfát; Vinkristin-szulfát; Winkrystyny siarczan; Винкристина Сульфат.

$C_{46}H_{56}N_4O_{10}H_2SO_4$=923.0

CAS — 57-22-7 (vincristine); 2068-78-2 (vincristine sulfate).
ATC — L01CA02.
ATC Vet — QL01CA02.
UNII — T5IRO3534A.

Description. Vincristine sulfate is the sulfate of an alkaloid, 22-oxovincaleukoblastine, obtained from *Catharanthus roseus* (*Vinca rosea*) (Apocynaceae).

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

Ph. Eur. 8: (Vincristine Sulfate). A white or slightly yellowish, very hygroscopic, crystalline powder. It loses not more than 12% of its weight on drying. Freely soluble in water; slightly soluble in alcohol. A 0.1% solution in water has a pH of 3.5 to 4.5. Store at a temperature not exceeding -20 degrees in airtight glass containers. Protect from light.

USP 36: (Vincristine Sulfate). A white to slightly yellow, odourless, hygroscopic, amorphous or crystalline powder. It loses not more than 12% of its weight on drying. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. A 0.1% solution in water has a pH of 3.5 to 4.5. Store at a temperature between -25 degrees and -20 degrees in airtight containers. Protect from light.

Uses and Administration

Vincristine is an antineoplastic vinca alkaloid that may act similarly to vinblastine (p. 881.3) by arresting mitosis at the metaphase.

Vincristine sulfate is used mainly in combination chemotherapy regimens for acute and chronic leukaemias, lymphomas, including Hodgkin's disease and non-Hodgkin's lymphomas, and multiple myeloma. It is also used for tumours of the breast, lung, head and neck, and soft-tissue sarcomas, as well as for paediatric solid tumours including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumour, retinoblastoma, and medulloblastoma. Vincristine has also been used in immune thrombocytopenia refractory to other agents. See also the cross-references given below.

Vincristine sulfate is given by **intravenous** injection. Care should be taken to avoid extravasation and the injection may be given over 1 minute into a freely-running intravenous infusion (usually sodium chloride 0.9%) if preferred. However, UK guidelines recommend that for adults and adolescents, the required dose should be supplied in a 50 mL infusion bag of sodium chloride 0.9% and infused intravenously over 5 to 10 minutes. (For adolescents treated in specialised paediatric units, see Administration in Children, below.)

The usual dose of vincristine sulfate is 1.4 to 1.5 mg/m^2 once weekly, up to a maximum weekly dose of 2 mg (see also Administration, below).

For doses in children, see below.

Blood counts should be carried out before giving each dose. Dosage reduction is recommended in patients with hepatic impairment (see below).

A *liposomal* formulation of vincristine is used in the treatment of patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia who have had at least 2 relapses or whose disease has progressed following 2 or more anti-leukaemia therapies. Vincristine sulfate liposome injection is given by intravenous infusion (in sodium chloride 0.9% or glucose 5%) over 1 hour in a dose of 2.25 mg/m^2 once every 7 days. Doses may need to be modified if toxicity occurs. A liposomal formulation is also under investigation for metastatic uveal melanoma.

Action. Results *in vitro* suggested[1] a selective action of vincristine against lymphocytes of patients with chronic lymphocytic leukaemia; lymphocytes of healthy subjects were not so affected. A further study[2] confirmed these findings, and also found marked variation in vincristine susceptibility among individual chronic lymphocytic leukaemic cells. This suggests that vincristine may have effects other than arrest of mitosis.

1. Vilpo J, Vilpo L. Selective toxicity of vincristine against chronic lymphocytic leukaemia in vitro. *Lancet* 1996; 347: 1491–2.
2. Vilpo JA, *et al.* Selective toxicity of vincristine against chronic lymphocytic leukemia cells in vitro. *Eur J Haematol* 2000; 65: 370–8.

Administration. Although a maximum single dose of 2 mg is recommended for vincristine sulfate to reduce neurotoxicity, a review[1] has suggested that this guideline is overly rigid, since it does not take into account interindividual variations in pharmacokinetics and susceptibility to toxicity, which may be considerable. Furthermore the authors considered the evidence for effectiveness of this dosage limitation to be equivocal. They suggested beginning therapy at 1.4 mg/m^2 and adjusting subsequent doses according to toxicity.

Administration errors have occurred with the vinca alkaloids. For UK guidelines on dilution of intravenous vinca alkaloids to avoid inadvertent intrathecal use, see Administration Error, under Adverse Effects, below.

1. McCune JS, Lindley C. Appropriateness of maximum-dose guidelines for vincristine. *Am J Health-Syst Pharm* 1997; 54: 1755–8.

Administration in children. The suggested dose of vincristine sulfate for the treatment of paediatric tumours in children weighing over 10 kg is 1.4 to 2 mg/m^2, given **intravenously** once weekly, up to a maximum weekly dose of 2 mg. For those weighing 10 kg or less, the suggested initial dose is 50 micrograms/kg, given once weekly.

UK guidelines state that doses of vinca alkaloids may be given via a syringe to children and adolescents treated in paediatric units.[1] For adolescents treated in adolescent or adult units, recommendations for administration are as for adults (see Uses and Administration, above).

1. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR004 (issued 11th August, 2008): using vinca alkaloid minibags (adult/adolescent units). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60290&type=full&servicetype=Attachment (accessed 29/09/09)

Administration in hepatic impairment. Licensed product information states that the dose of vincristine should be reduced by 50% in patients having a serum bilirubin value above 3 mg per 100 mL (51 micromoles/litre).

Amyloidosis. For mention of regimens including vincristine used in the management of amyloidosis, see p. 819.3.

Blood disorders, non-malignant. Vincristine may be employed in the treatment of various auto-immune blood disorders, see under Vinblastine, p. 882.1.

Malignant neoplasms. Vincristine is widely used in the treatment of malignant neoplasms. It is a fundamental part of potentially curative regimens for acute lymphoblastic leukaemia, Hodgkin's disease and aggressive non-Hodgkins lymphomas (see p. 692.3, p. 696.1 and p. 696.3). It has also been used in chronic lymphocytic leukaemia (p. 693.3) and in other non-Hodgkin's lymphomas including AIDS-related lymphoma (p. 697.2), Burkitt's lymphoma (p. 697.3) and mycosis fungoides (p. 698.3). Other haematological malignancies in which it may be tried include multiple myeloma (p. 699.2). Among the solid neoplasms, vincristine is used in regimens to treat gestational trophoblastic tumours (p. 691.2), tumours of the brain (p. 701.2), head and neck (p. 708.1), Wilms' tumour (p. 709.1), small-cell lung cancer (p. 710.2), and thymoma (p. 715.3). It is also employed in regimens for neuroblastoma (p. 716.2), retinoblastoma (p. 717.2), and some sarcomas including sarcomas of bone, Kaposi's sarcoma, and rhabdomyosarcoma (see p. 717.3, p. 718.1, and p. 718.2).

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p. 882.1.

Bone-marrow depression occurs less commonly than with vinblastine but neurological and neuromuscular effects are more severe with vincristine and are dose-limiting. Walking may be impaired and the neurological effects may not be reversed for several months after the drug is stopped. Convulsions, often with hypertension, have occurred. Constipation is common and there may be abdominal pain. Urinary disturbances have occurred and alopecia is frequent.

Folinic acid has been given for the treatment of overdosage: suggested doses are as much as 100 mg of folinic acid intravenously every 3 hours for 24 hours, then every 6 hours for at least 48 hours. However, this is unlikely to be of benefit in reversing neuromuscular toxicity. For mention of the use of glutamic acid in managing the usually fatal consequences of inadvertent intrathecal dosage, see below.

Because severe constipation and impaction of faeces often occur with vincristine, laxatives or enemas may be necessary to ensure regular bowel function. Vincristine should be given with caution to patients with pre-existing neuromuscular disease and is contra-indicated in patients with the demyelinating form of Charcot-Marie-Tooth syndrome (see under Effects on the Nervous System, below). Doses may need to be adjusted in patients with hepatic impairment. Care should also be taken in elderly patients, who may be more susceptible to neurotoxicity.

A liposomal formulation of vincristine has been associated with hepatotoxicity and increased liver enzyme tests; hepatic function should be monitored.

Administration error. *Inadvertent intrathecal doses of vincristine result in ascending paralysis and death.*[1-3] However, in one case[1] treatment immediately after the error, and consisting of removal of contaminated spinal fluid and flushing with lactated Ringer's solution and fresh frozen plasma diluted in lactated Ringer's solution, plus intravenous and oral glutamic acid, was reported successful in stabilising neurological dysfunction and preventing death. A similar case of successful treatment has subsequently been reported,[4] in which immediate CSF aspiration and irrigation (with lactated Ringer's solution containing fresh frozen plasma to bind vincristine) for 6 days was combined with intravenous folate, glutamic acid, and pyridoxine.

Licensed product information therefore recommends the following treatment as soon as possible after inadvertent intrathecal injection:

- removal of as much CSF as is safely possible through the lumbar access
- CSF irrigation with lactated Ringer's solution, by continuous infusion at a rate of 150 mL/hour
- as soon as it is available, 25 mL of fresh frozen plasma should be added to every 1 litre of lactated Ringer's solution and infused at a rate of 75 mL/hour; the rate of infusion should then be adjusted to maintain a spinal fluid protein concentration of 150 mg per 100 mL

While stating that the roles of the following drugs in the reduction of neurotoxicity are uncertain, licensed product information also allows the use of:

- glutamic acid 10 g intravenously over 24 hours, followed by 500 mg orally, three times daily, for one month or until the neurological dysfunction has stabilised
- folinic acid 100 mg as an intravenous bolus, and then infused at a rate of 25 mg/hour for 24 hours, then 25 mg intravenously every six hours for 1 week
- pyridoxine 50 mg intravenously over 30 minutes, every 8 hours

While early recognition and immediate treatment with cerebrospinal fluid drainage and exchange may improve survival,[5] fatalities still occur despite these measures.[5,6] Recommendations[2,6] have been made in order to prevent further errors occurring, including restrictions on the prescription, administration, and storage of intrathecal drugs. In the UK, recommendations state that when vinca alkaloids are prescribed for adults and adolescents, syringes should not be used to administer the dose; instead, the required dose of vinca alkaloid should be supplied in a 50 mL infusion bag of sodium chloride 0.9%, and infused over 5 to 10 minutes. All vinca alkaloids should be labelled as being for intravenous use only, with a clear warning of the consequences of use by other routes. However, for children and adolescents being treated in specialised paediatric units, the use of syringes to administer vinca alkaloids is permitted.[7]

1. Dyke RW. Treatment of inadvertent intrathecal injection of vincristine. *N Engl J Med* 1989; 321: 1270–1.
2. DoH. Updated national guidance on the safe administration of intrathecal chemotherapy (HSC 2008/001, issued 11th August, 2008). Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_086844.pdf (accessed 16/09/09)
3. Hennipman B, *et al.* Intrathecal vincristine: 3 fatal cases and a review of the literature. *J Pediatr Hematol Oncol* 2009; 31: 816–19.
4. Qweider M, *et al.* Inadvertent intrathecal vincristine administration: a neurosurgical emergency. Case report. *J Neurosurg Spine* 2007; 6: 280–3.
5. Alcaraz A, *et al.* Intrathecal vincristine: fatal myeloencephalopathy despite cerebrospinal fluid perfusion. *J Toxicol Clin Toxicol* 2002; 40: 557–61.
6. Fernandez CV, *et al.* Intrathecal vincristine: an analysis of reasons for recurrent fatal chemotherapeutic error with recommendations for prevention. *J Pediatr Hematol Oncol* 1998; 20: 587–90.
7. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR004 (issued 11th August, 2008): using vinca alkaloid minibags (adult/adolescent units). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60290&type=full&servicetype=Attachment (accessed 29/09/09)

Effects on the nervous system. In its most typical form, vincristine neurotoxicity[8] manifests as a mixed sensorimotor neuropathy of the distal type. The earliest symptoms are sensory changes in the form of paraesthesias, accompanied by impairment and ultimately loss of deep tendon reflexes. In more severe forms, impairment of motor function occurs with wrist drop and foot drop, ataxia and gait abnormalities, and occasionally progressive quadriparesis.

In contrast to these peripheral neuropathies, which are usually associated with long-term usage, there may be short-term autonomic neuropathy resulting in constipation and occasionally ileus, abdominal pain, atony of the urinary bladder (which may lead to urinary retention), orthostatic hypotension, and rarely, impotence. Effects on the cranial nerves may result in ptosis, hoarseness (due to laryngeal nerve paralysis), or optic neuropathies. Effects on the CNS are rare, probably in part because of poor penetration into CSF, but include excessive release of antidiuretic hormone and consequent hyponatraemia.

Hallucinations have occurred[2] and effects on the special senses have been reported: both bilateral optic atrophy and blindness,[3] and profound neurological deafness (which was largely reversible on drug withdrawal)[4] have occurred. Convulsions associated with hypertension are another feature of vincristine toxicity.[5]

Toxicity is related to both the cumulative and the individual dose.[1] It usually begins in adults after receiving a total of 5 to 6 mg, and is significant by the time a cumulative dose of 15 to 20 mg is reached. If individual doses are low (less than 2 mg) or intervals between doses are longer than the usual week, patients can tolerate higher cumulative doses. Children tolerate vincristine better than adults, but the elderly are particularly prone to neurotoxicity. Patients with existing neurological disorders such as poliomyelitis or the Charcot-Marie-Tooth syndrome may be at increased risk of neurotoxicity.[8,9] It has been suggested that increased neurotoxicity may be associated with the use of ready-to-use solutions rather than reconstituted lyophilised preparations but this is unproven.[10-14]

There is no good treatment for the effects of vincristine on the nervous system: symptoms are largely reversible once dosage is interrupted, and should be managed with appropriate symptomatic care.[1] However, there is some suggestion that glutamic acid may be of benefit in treating neurotoxicity[15]—see also Administration Error, above. For the use of dinoprost to alleviate ileus induced by vinca alkaloids, see p. 2134.1.

1. Legha SS. Vincristine neurotoxicity: pathophysiology and management. *Med Toxicol* 1986; 1: 421–7.
2. Holland JF, *et al.* Vincristine treatment of advanced cancer: a cooperative study of 392 cases. *Cancer Res* 1973; 33: 1258–64.
3. Awidi AS. Blindness and vincristine. *Ann Intern Med* 1980; 93: 781.
4. Yousif R, *et al.* Partially reversible nerve deafness due to vincristine. *Postgrad Med J* 1990; 66: 688–9.
5. Ito S, *et al.* Seizures and hypertension complicating vincristine therapy in children. *Clin Pharmacol Ther* 1995; 57: 208.
6. Kogan-Dann CM, *et al.* Polyneuropathy following vincristine therapy in two patients with Charcot-Marie-Tooth syndrome. *JAMA* 1984; 252: 2862–3.

7. Miller BR. Neurotoxicity and vincristine. *JAMA* 1985; **253**: 2045.
8. Chauncey TR, *et al.* Vincristine neurotoxicity. *JAMA* 1985; **254**: 507.
9. Griffiths JD, *et al.* Vincristine neurotoxicity in Charcot-Marie-Tooth syndrome. *Med J Aust* 1985; **143**: 305–6.
10. Arnold AM, *et al.* Acute vincristine neurotoxicity. *Lancet* 1985; **i**: 346.
11. Jalihal S, Roebuck N. Acute vincristine neurotoxicity. *Lancet* 1985; **i**: 637.
12. Davies CE, *et al.* Acute vincristine neurotoxicity. *Lancet* 1985; **i**: 637–8.
13. Warrier RP, Ducos R. Acute vincristine neurotoxicity. *Lancet* 1985; **i**: 980.
14. Gennery BA. Vincristine neurotoxicity. *Lancet* 1985; **ii**: 385.
15. Jackson DV, *et al.* Amelioration of vincristine neurotoxicity by glutamic acid. *Am J Med* 1988; **84**: 1016–22.

Handling and disposal. For a method for the destruction of vincristine *wastes*, see under Vinblastine Sulfate, p. 882.2.

Urine and faeces produced for up to 4 and 7 days respectively after a dose of vincristine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235**: 289–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vincristine 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 26/09/11)

Pregnancy. For a report of a healthy infant born to a woman treated with a vincristine-containing chemotherapy regimen, see Pregnancy, under Teniposide, p. 867.2.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3. Use of vincristine with drugs that inhibit cytochromes of the CYP3A subfamily may result in decreased metabolism of vincristine and increased toxicity. If vincristine is used with asparaginase it should be given 12 to 24 hours before the enzyme: giving asparaginase with or before vincristine may reduce vincristine clearance and increase toxicity. For reports of vascular toxicity and Raynaud's syndrome associated with the use of vinca alkaloids with bleomycin and other drugs see Effects on the Cardiovascular System, p. 727.2.

Antibacterials. Severe neurotoxicity has occurred when *isoniazid* was added to the regimen of a patient receiving vincristine.[1]

1. Carrión C, *et al.* Possible vincristine-isoniazid interaction. *Ann Pharmacother* 1995; **29**: 201.

Antiepileptics. A pharmacokinetic study showed that systemic clearance of vincristine was 63% higher when it was given with *phenytoin* or *carbamazepine*, two inducers of the cytochrome P450 isoenzyme CYP3A4. The clinical significance of this finding is unknown.[1]

1. Villikka K, *et al.* Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumours. *Clin Pharmacol Ther* 1999; **66**: 589–93.

Antifungals. Toxicity has been reported to be increased in children who received *itraconazole* with or without nifedipine during treatment involving vincristine.[1-4] Itraconazole is presumed to potentiate the toxicity of vincristine either by inhibition of cytochrome P450 isoenzymes, thus reducing the clearance of vincristine,[1-4] or by inhibiting the P-glycoprotein efflux pump,[2,3] and increasing intracellular concentrations of vincristine. Nifedipine also decreases the clearance of vincristine, by similar mechanisms,[1,3,4] and can theoretically further potentiate toxicity.

1. Murphy JA, *et al.* Vincristine toxicity in five children with acute lymphoblastic leukaemia. *Lancet* 1995; **346**: 443.
2. Jeng MR, Feusner J. Itraconazole-enhanced vincristine neurotoxicity in a child with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2001; **18**: 137–42.
3. Sathiapalan RK, El-Solh H. Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. *Pediatr Hematol Oncol* 2001; **18**: 543–6.
4. Kamaluddin M, *et al.* Potentiation of vincristine toxicity by itraconazole in children with lymphoid malignancies. *Acta Paediatr* 2001; **90**: 1204–7.

Nifedipine. Vincristine toxicity may be potentiated by nifedipine, see Antifungals, above.

Pharmacokinetics

Vincristine is not reliably absorbed from the gastrointestinal tract. After intravenous injection it disappears rapidly from the blood. It is extensively protein bound and is reported to be concentrated in blood platelets. It is metabolised in the liver chiefly by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5 and excreted mainly in the bile; about 70 to 80% of a dose is found in faeces, as unchanged drug and metabolites, while 10 to 20% appears in the urine. The terminal half-life is reported to be about 85 hours but may range from about 19 to 155 hours. Vincristine does not appear to cross the blood-brain barrier in significant amounts.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vincest†; ***Austral.***: Oncovin†; ***Austria***: Oncovin; ***Belg.***: Oncovin†; Vincrisin; ***Braz.***: Dabaz; Fauldvincri; Oncovin; Tecnocris; Vincizina; ***Chile***: Citomid†; ***Denm.***: Oncovin; ***Fin.***: Oncovin; ***Fr.***: Oncovin; ***Ger.***: Cellcristin; Onkocristin†; ***Gr.***: Oncovin; ***Hong Kong***: Vinracine; ***India***: Alcrist; Biocristin; Cytocristin; Neocristin†; Oncocristin; ***Malaysia***: Vinracine†; ***Mex.***: Citomid†; Crivosin†; Oncovin; Vintec; ***Philipp.***: Alcavixin; Nevexitin†; Vinsulgen; ***Rus.***: Citomid (Цитомид); ***Singapore***: Vinracine; ***Spain***: Vincrisul†; ***Swed.***: Oncovin; ***Switz.***: Oncovin; ***Thai.***: Citomid†; VCS; ***Turk.***: Oncocristin†; Oncovin; ***UK***: Oncovin; ***USA***: Marqibo; Oncovin; Vincasar PFS.

Pharmacopoeial Preparations
BP 2014: Vincristine Injection;
USP 36: Vincristine Sulfate for Injection; Vincristine Sulfate Injection.

Vindesine Sulfate *(BANM, USAN, rINNM)*

Compound 112531 (vindesine); Desacetyl Vinblastine Amide Sulfate; LY-099094; NSC-245467 (vindesine or vindesine sulfate); Sulfato de vindesina; Vindeslinisulfaatti; Vindesina, sulfato de; Vindésine, sulfate de; Vindesine Sulphate; Vindesini Sulfas; Vindesinsulfat; Vindesin-sulfát; Vindezino sulfatas; Vindezin-szulfát; Виндезина Сульфат.

3-Carbamoyl-4-*O*-deacetyl-3-de(methoxycarbonyl)vincaleukoblastine sulfate.

$C_{43}H_{55}N_5O_7,H_2SO_4$=852.0

CAS — 53643-48-4 (vindesine); 59917-39-4 (vindesine sulfate).
ATC — L01CA03.
ATC Vet — QL01CA03.
UNII — CPH2U7DNDY.

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

Ph. Eur. 8: (Vindesine Sulfate). A white or almost white, hygroscopic, amorphous substance. Freely soluble in water and in methyl alcohol; practically insoluble in cyclohexane. The pH of a 0.5% solution in water is 3.5 to 5.5. Store in airtight polypropylene containers with a polypropylene cap, at a temperature not exceeding -50 degrees.

Uses and Administration

Vindesine sulfate is an antineoplastic agent derived from vinblastine (see p. 881.3); like the other vinca alkaloids it causes mitotic arrest in metaphase by binding to microtubular protein. It is used, alone or with other antineoplastics, in the treatment of refractory acute lymphoblastic leukaemia, blast crises of chronic myeloid leukaemia, malignant melanoma unresponsive to other therapy, and advanced carcinoma of the breast, unresponsive to surgery and/or hormonal therapy. See also the cross references given below.

Vindesine sulfate is given by **intravenous** injection. Care should be taken to avoid extravasation and the intravenous injection may be given over 1 to 3 minutes into a freely-running infusion (usually sodium chloride 0.9% or glucose 5%) if preferred. However, UK guidelines recommend that for adults and adolescents, the required dose should be supplied in a 50 mL infusion bag of sodium chloride 0.9% and infused intravenously over 5 to 10 minutes. (For adolescents treated in specialised paediatric units, see Administration in Children, below.) The usual starting dose of vindesine sulfate is 3 mg/m² which may be raised by increments of 500 micrograms/m² weekly providing that the granulocyte and platelet counts do not fall below 1500 cells/mm³ and 100 000 cells/mm³, respectively (see also Bone-marrow Depression, p. 730.3), and providing the patient has no acute abdominal pain; the maximum total weekly dose is 4 mg/m².

For doses in children, see below.

Blood counts should be made before each injection. It may be necessary to reduce initial doses in patients with significantly impaired hepatic function.

Administration. Administration errors have occurred with the vinca alkaloids (see Administration Error, below). For UK guidelines on dilution of vinca alkaloids to avoid inadvertent intrathecal use, see p. 883.2.

Administration in children. An initial dose of vindesine sulfate **4 mg/m² intravenously** may be given to children for the treatment of acute lymphoblastic leukaemia (resistant to other drugs). This may be increased in weekly increments of 500 micrograms/m² providing granulocyte and platelet counts do not fall below acceptable levels and provided the patient has no acute abdominal pain. The weekly dose for children usually ranges between 4 and 5 mg/m².

UK guidelines state that doses of vinca alkaloids may be given via a syringe to children and adolescents treated in paediatric units.[1] For adolescents treated in adolescent or adult units, recommendations for administration are as for adults (see Uses and Administration, above).

1. NHS National Patient Safety Agency. Rapid Response Report NPSA/2008/RRR004 (issued 11th August, 2008): using vinca alkaloid minibags (adult/adolescent units). Available at: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60290&type=full&servicetype=Attachment (accessed 29/09/09)

Malignant neoplasms. Vindesine has been tried in refractory metastatic melanoma (p. 714.3), childhood acute lymphoblastic leukaemia (p. 692.3), chronic myeloid leukaemia in blastic crisis (p. 694.2), and neuroblastoma (p. 716.2). It is also under investigation in lung cancer, particularly non-small cell lung cancer (p. 710.2) and responses have been reported in advanced breast cancer (p. 702.1).

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p. 882.1.

The main dose-limiting effect of vindesine is granulocytopenia, with the nadir of the white cell count usually occurring 3 to 5 days after a dose and recovery after a further 4 to 5 days. Although neurotoxicity occurs it may be less severe than that seen with vincristine (see p. 883.1). Alopecia is the most common adverse effect.

Folinic acid has been suggested for the treatment of overdosage by analogy with vincristine.

Vindesine should not be given by the intrathecal route, as this may produce fatal toxicity. Care should be taken if acute abdominal pain occurs: further doses may result in paralytic ileus.

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* In a 10-year-old child accidentally given an intrathecal injection of vindesine, treatment with folinic acid and dexamethasone produced transient recovery but symptoms subsequently recurred and the patient died of progressive ascending paralysis.[1] The CNS showed changes at necropsy similar to those seen after intrathecal vincristine. Other fatal cases[2,3] have subsequently been reported. For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK recommendations on dilution of vinca alkaloids to avoid intrathecal use, see p. 883.2.

1. Robbins G. Accidental intrathecal injection of vindesine. *BMJ* 1985; **291**: 1094.
2. Tournel G, *et al.* Fatal accidental intrathecal injection of vindesine. *J Forensic Sci* 2006; **51**: 1166–8.
3. Nisse P, *et al.* Administration accidentelle intrathécale de vindésine à propos de 2 cas mortels. *Therapie* 2007; **62**: 360–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vindesine 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 26/09/11)

Interactions

As for Vinblastine Sulfate, p. 882.2.

Pharmacokinetics

The pharmacokinetics of vindesine are similar to those of the other vinca alkaloids. After intravenous doses elimination from the blood is triphasic; the drug is rapidly distributed to body tissues. The terminal half-life is reported to be about 20 hours. It is metabolised mainly in the liver and excreted in bile and urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Eldisin; ***Belg.***: Eldisine; ***China***: Ai De Xin (艾得新); Xi Ai Ke (西艾克); ***Fin.***: Eldisine; ***Fr.***: Eldisine; ***Ger.***: Eldisine; ***Gr.***: Eldisine; Enison; Gesidine; ***Irl.***: Eldisine†; ***Ital.***: Eldisine; ***Port.***: Gesidine†; ***Spain***: Enison; ***Swed.***: Eldisine; ***Switz.***: Eldisine; ***UK***: Eldisine.

Pharmacopoeial Preparations
BP 2014: Vindesine Injection.

Vinflunine *(BAN, rINN)*

F-12158; F-13840; L-0070; Vinflunina; Vinfluninum; Винфлунин.

4′-Deoxy-20′,20′-difluoro-8′-norvincaleukoblastine.

$C_{45}H_{54}F_2N_4O_8$=816.9

CAS — 162652-95-1.

ATC — L01CA05.
ATC Vet — QL01CA05.
UNII — 5BF646324K.

Vinflunine Tartrate *(rINNM)*

BMS-710485; F-12158; Tartrato de vinflunina; Vinflunine Ditartrate (BANM); Vinflunine Ditartrate (USAN); Vinflunine, Tartrate de; Vinflunini Tartras; Винфлунина Тартрат.
$C_{45}H_{54}F_2N_4O_8.2C_4H_6O_6$=1117.1
CAS — 194468-36-5.
ATC — L01CA05.
ATC Vet — QL01CA05.
UNII — 33MG53C7XW.

Uses and Administration

Vinflunine is a fluorinated vinca alkaloid derived from vinorelbine that has a similar antineoplastic action to vinblastine (p. 881.3). It is used in the treatment of advanced or metastatic bladder cancer (p. 700.2), as monotherapy after failure of a platinum-containing regimen. Vinflunine is given as the ditartrate but doses are expressed as the base; 1.37 mg of vinflunine ditartrate is equivalent to about 1 mg of vinflunine. It is given by intravenous infusion over 20 minutes, diluted in 100 mL sodium chloride 0.9% or glucose 5%, in a usual initial dose of vinflunine 320 mg/m² every 3 weeks. A lower initial dose of 280 mg/m² is given to patients with a performance status of 1 or less and prior pelvic irradiation; this can be increased thereafter to 320 mg/m² every 3 weeks in the absence of any toxicities.

Full blood counts should be monitored before each injection and the dose adjusted or delayed based on results; other toxicities may also affect the dose regimen (see Administration in Subsequent Cycles, below).

For dosage in patients with hepatic or renal impairment, see below.

Vinflunine is also being investigated in other neoplasms including non-small cell lung cancer and breast cancer.

References.

1. Bellmunt J, *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009; **27**: 4454–61. Correction. *ibid.* 2010; **28**: 182.
2. Jordan MA, *et al.* Exploring the mechanisms of action of the novel microtubule inhibitor vinflunine. *Semin Oncol* 2008; **35** (suppl 3): S6–S12.
3. Bellmunt J, *et al.* Clinical activity of vinflunine in transitional cell carcinoma of the urothelium and other solid tumors. *Semin Oncol* 2008; **35** (suppl 3): S34–S43.
4. Lobert S, Fuozzo C. Pharmacokinetics, metabolites, and preclinical safety of vinflunine. *Semin Oncol* 2008; **35** (suppl 3): S28–S33.

Administration. Administration errors have occurred with the vinca alkaloids (see Administration Error, below). For UK guidelines on dilution of vinca alkaloids to avoid inadvertent intrathecal use, see p. 883.2.

Administration in hepatic impairment. The dose of vinflunine should be reduced in patients with hepatic impairment, according to Child Pugh class or based on prothrombin time, bilirubin, transaminase, and gamma glutamyl transferase (GGT) values.

The usual intravenous dose of vinflunine 320 mg/m² every 3 weeks is given to patients with the following hepatic parameters:

- prothrombin time > 70% of the normal value
  and
- bilirubin > the upper limit of normal (ULN) and ≤ 1.5 times the ULN
  and/or
- transaminases > 1.5 times the ULN and ≤ 2.5 times the ULN
  and/or
- GGT > the ULN and ≤ 5 times the ULN

A reduced intravenous dose of 250 mg/m² every 3 weeks is given to those with hepatic impairment defined as:

- Child Pugh class A
  or
- prothrombin time ≥ 60% of the normal value
  and
- bilirubin > 1.5 times the ULN and ≤ 3 times the ULN
  and
- transaminases > the ULN
  and/or
- GGT > 5 times the ULN

A reduced intravenous dose of 200 mg/m² every 3 weeks is given to those with hepatic impairment defined as:

- Child Pugh class B
  or
- prothrombin time ≥ 50% of the normal value
  and
- bilirubin > 3 times the ULN
  and
- transaminases > the ULN
  and
- GGT > the ULN

Vinflunine has not been studied in patients with Child Pugh class C, or in those with a prothrombin time < 50% of the normal value or with bilirubin > 5 times the ULN or with transaminases > 6 times the ULN or with GGT > 15 times the ULN.

Administration in renal impairment. The dose of vinflunine should be reduced in patients with renal impairment. UK licensed product information recommends the following based on creatinine clearance (CC):

- CC > 60 mL/min: usual intravenous dose of vinflunine 320 mg/m² every 3 weeks
- CC 40 to 60 mL/min: 280 mg/m² every 3 weeks
- CC 20 to 39 mL/min: 250 mg/m² every 3 weeks
- CC < 20 mL/min: not specified

Administration in subsequent cycles. Complete blood counts should be performed in all patients given vinflunine. Patients should not begin a new cycle if their absolute neutrophil count (ANC) is < 1000 cells/mm³ or if platelets are < 100 000 cells/mm³; treatment should be delayed until blood counts reach these levels or above. If recovery has not occurred within 2 weeks, treatment should be permanently stopped.

Dose adjustments are required for the following toxicities:

- grade 4 neutropenia (ANC < 500 cells/mm³) for > 7 days
- febrile neutropenia (ANC < 1000 cells/mm³ and fever ≥ 38.5 degrees)
- grade 2 mucositis or constipation for ≥ 5 days, or ≥ grade 3 for any duration
- any other toxicity that is ≥ grade 3, except grade 3 nausea or vomiting

If one of the above toxicities occurs in a patient whose initial intravenous dose of vinflunine was 320 mg/m² (the usual initial dose), a reduced dose of vinflunine 280 mg/m² is given. This is further reduced to 250 mg/m² if a toxicity occurs again in the next cycle; treatment should be permanently stopped for toxicities occurring in 3 consecutive cycles.

If one of the above toxicities occurs in a patient whose initial intravenous dose of vinflunine was 280 mg/m², a reduced dose of 250 mg/m² is given; treatment should be permanently stopped for toxicities occurring in 2 consecutive cycles.

For organ toxicity that is ≥ grade 2 on the day the next vinflunine dose is due, treatment should be delayed until recovery to ≤ grade 1.

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p. 882.1.

The main dose-limiting effect of vinflunine is neutropenia, and the dose should be adjusted according to regular blood counts. Use is contra-indicated in patients with a baseline absolute neutrophil count < 1500 cells/mm³ or a platelet count < 100 000 cells/mm³. Gastrointestinal adverse effects are also common; regular laxatives are recommended to prevent constipation. Other adverse effects include musculoskeletal adverse effects such as pain, myalgia, and arthralgia, and cardiovascular effects such as QT prolongation, tachycardia, ischaemia, and myocardial infarction; vinflunine should be used with caution in patients with pre-existing cardiac disease, or those with risk factors for QT prolongation. It should also not be given with other medicines that prolong the QT interval, or with potent inhibitors or inducers of the cytochrome P450 isoenzyme CYP3A4 (see under Interactions, below). Patients with hepatic or renal impairment may need a reduced dose of vinflunine (see under Uses, above and above).

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK recommendations on dilution of vinca alkaloids to avoid intrathecal use, see p. 883.2.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Vinflunine is metabolised by the cytochrome P450 isoenzyme CYP3A4; exposure to vinflunine or its active metabolite 4-*O*-deacetyl-vinflunine (DVFL) may be affected by inhibitors or inducers of this enzyme and their use with vinflunine is not recommended.

Caution is required when vinflunine is used with pegylated or liposomal doxorubicin, as exposure to vinflunine was increased and exposure to doxorubicin decreased with this combination. *In vitro* data have suggested that this could be due to adsorption of vinflunine on the liposomes and a change in the distribution of both drugs in the blood.

Vinflunine should not be given with other medicines that prolong the QT interval.

Pharmacokinetics

Vinflunine is moderately bound to plasma proteins, mainly high-density lipoproteins and serum albumin, and it is extensively distributed into the tissues. The main metabolite of vinflunine is 4-*O*-deacetyl-vinflunine (DVFL), which has some antineoplastic activity and is formed by multiple esterases. All other metabolites are inactive and are formed by the cytochrome P450 isoenzyme CYP3A4. Vinflunine has a terminal elimination half-life of about 40 hours, while DVFL is eliminated more slowly, with a half-life of about 120 hours. Excretion occurs via the faeces (about two-thirds) and the urine (about one-third).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria:*** Javlor; ***Cz.:*** Javlor; ***Denm.:*** Javlor; ***Fr.:*** Javlor; ***Ger.:*** Javlor; ***Gr.:*** Javlor; ***Irl.:*** Javlor; ***Israel:*** Javlor; ***Ital.:*** Javlor; ***Neth.:*** Javlor; ***Norw.:*** Javlor; ***Pol.:*** Javlor; ***Port.:*** Javlor; ***Spain:*** Javlor; ***Swed.:*** Javlor; ***UK:*** Javlor.

Vinorelbine Tartrate *(BANM, USAN, rINNM)*

Tartrato de vinorelbina; Vinorelbiinitartraati; Vinorelbin Bitartrat; Vinorelbina, tartrato de; Vinorelbin-ditartarát; Vinorelbine Ditartrate; Vinorelbine, tartrate de; Vinorelbini Ditartras; Vinorelbini Tartras; Vinorelbino tartratas; Vinorelbintartrat; Винорелбина Тартрат; 5'-Nor-anhydrovinblastine Tartrate.

3',4'-Didehydro-4'-deoxy-8'-norvincaleukoblastine ditartrate.

$C_{45}H_{54}N_4O_8.2C_4H_6O_6$=1079.1
CAS — 71486-22-1 (vinorelbine); 125317-39-7 (vinorelbine tartrate).
ATC — L01CA04.
ATC Vet — QL01CA04.
UNII — 253GQW851Q.

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

Ph. Eur. 8: (Vinorelbine Tartrate). A white or almost white, hygroscopic powder. Freely soluble in water and in methyl alcohol; practically insoluble in hexane. A 1.4% solution in water has a pH of 3.3 to 3.8. Store under an inert gas at a temperature not exceeding -15 degrees. Protect from light.

USP 36: (Vinorelbine Tartrate). A white to yellow or light brown amorphous powder. Freely soluble in water. pH of a 1% solution in water is between 3.3 and 3.8. Store at a temperature between -25 degrees and -10 degrees in airtight containers. Protect from light.

Uses and Administration

Vinorelbine is a semisynthetic vinca alkaloid with antineoplastic activity similar to vinblastine (p. 881.3). It is used, alone or with other antineoplastics, in the first-line treatment of non-small cell lung cancer (p. 710.2) and in the treatment of advanced breast cancer (p. 702.1) that has relapsed or is refractory to an anthracycline-containing regimen.

Vinorelbine is given as the tartrate but doses are calculated in terms of vinorelbine: vinorelbine tartrate 1.385 mg is equivalent to about 1 mg of vinorelbine. Vinorelbine may be given orally or intravenously. *Antineoplastic dose regimens may be complex and doses of a drug may differ widely. For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

It may be given by intravenous injection over 5 to 10 minutes, as a solution containing the equivalent of vinorelbine 1.5 to 3 mg/mL in glucose 5% or sodium chloride 0.9% injection, into a freely-running intravenous infusion. However, UK guidelines recommend that the required dose should be supplied in a 50 mL infusion bag of sodium chloride 0.9% or glucose 5% and infused intravenously over 5 to 10 minutes. It may also be given by intravenous infusion over 20 to 30 minutes after dilution in 125 mL of glucose 5% or sodium chloride 0.9%.

The usual initial intravenous dose in the treatment of breast cancer or non-small cell lung cancer is the equivalent of vinorelbine 25 to 30 mg/m² (maximum 60 mg) once weekly. Doses may be adjusted or delayed based on blood counts (see Administration in Subsequent Cycles, p. 886.1).

The drug is also given orally as a single agent in a dose of 60 mg/m² (maximum 120 mg) once weekly for 3 weeks. Subsequent doses may be increased to 80 mg/m² (maximum 160 mg), based on neutrophil counts (see Administration in Subsequent Cycles, p. 886.1). The dose and schedule may vary in combination regimens.

For dosage in patients with hepatic impairment or with massive liver metastases, see p. 886.1.

References.
1. Gregory RK, Smith IE. Vinorelbine—a clinical review. *Br J Cancer* 2000; 82: 1907–13.
2. Sarris AH, *et al.* Infusional vinorelbine in relapsed or refractory lymphomas. *Leuk Lymphoma* 2000; 39: 291–9.
3. Sorensen P, *et al.* Phase II study of vinorelbine in the treatment of platinum-resistant ovarian carcinoma. *Gynecol Oncol* 2001; 81: 58–62.
4. Oudard S, *et al.* Phase II study of vinorelbine in patients with androgen-independent prostate cancer. *Ann Oncol* 2001; 12: 847–52.
5. Domenech GH, Vogel CL. A review of vinorelbine in the treatment of breast cancer. *Clin Breast Cancer* 2001; 2: 113–28.
6. Aapro MS, *et al.* Developments in cytotoxic chemotherapy: advances in treatment utilising vinorelbine. *Crit Rev Oncol Hematol* 2001; 40: 251–63.
7. Preyer G, *et al.* Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 2003; 21: 35–40.
8. Gebbia V, Puozzo C. Oral versus intravenous vinorelbine: clinical safety profile. *Expert Opin Drug Safety* 2005; 4: 915–28.
9. Aapro MS, *et al.* Oral vinorelbine: role in the management of metastatic breast cancer. *Drugs* 2007; 67: 657–67.
10. Gralla RJ, *et al.* Oral vinorelbine in the treatment of non-small cell lung cancer: rationale and implications for patient management. *Drugs* 2007; 67: 1403–10.
11. Bonneterre J, Penel N. Vinorelbine in breast cancer. *Expert Opin Pharmacother* 2008; 9: 2901–10.
12. Piccirillo MC, *et al.* Vinorelbine for non-small cell lung cancer. *Expert Opin Drug Safety* 2010; 9: 493–510.

Administration. Administration errors have occurred with the vinca alkaloids (see Administration Error, below). For UK guidelines on dilution of vinca alkaloids to avoid inadvertent intrathecal use, see p. 883.2.

Administration in the elderly. UK licensed product information states that, while no relevant differences in response rates to vinorelbine have been seen in the elderly, greater sensitivity of some older patients cannot be ruled out; age is stated to not affect the pharmacokinetics of vinorelbine. A review[1] found conflicting data on the effect of age on pharmacokinetics of intravenous vinorelbine, yet concluded that no dose modification was required on the basis of age.

1. Lichtman SM, *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients—an analysis of the medical literature. *J Clin Oncol* 2007; 25: 1832–43.

Administration in hepatic impairment. Clearance of intravenous vinorelbine was markedly reduced in patients with diffuse liver metastases and hence severely altered hepatic function: a 50% dose reduction was probably appropriate in such patients even if hyperbilirubinaemia was not marked.[1] However, reduced doses were not necessary in patients with moderate liver involvement in whom liver function, as measured by lidocaine metabolism, was not markedly reduced. Others have also confirmed that doses need not be reduced in mild to moderate hepatic impairment.[2]

Licensed product information in the UK suggests that the *intravenous* dose be reduced by one-third in patients with severe hepatic impairment (defined as bilirubin greater than twice the upper limit of normal (ULN) and/or transaminases greater than five times the ULN), or in those with massive liver metastases (more than 75% of liver volume replaced by tumour cells). In the USA, licensed product information recommends that the intravenous dose of vinorelbine be reduced by 50% in patients with total bilirubin values of 2.1 to 3 mg per 100 mL and by 75% in those with total bilirubin greater than 3 mg per 100 mL.

UK licensed product information recommends the following *oral* weekly doses of vinorelbine for patients with hepatic impairment:
- mild (bilirubin less than 1.5 times the ULN and transaminases from 1.5 to 2.5 times the ULN): 60 mg/m² (the standard dose)
- moderate (bilirubin 1.5 to 3 times the ULN): 50 mg/m²
- severe: use is contra-indicated

1. Robieux I, *et al.* Pharmacokinetics of vinorelbine in patients with liver metastases. *Clin Pharmacol Ther* 1996; 59: 32–40.
2. Kitzen JJ, *et al.* Mild to moderate liver dysfunction does not require dose reduction of oral or intravenous vinorelbine: results of a pharmacokinetic study. *Eur J Cancer* 2010; 46: 266–9.

Administration in subsequent cycles. Use of vinorelbine is contra-indicated if blood counts fall below acceptable levels.

In the UK, **intravenous** use is contra-indicated if platelet counts are less than 75 000 cells/mm³, or if neutrophils are less than 1500 to 2000 cells/mm³ (this varies slightly according to manufacturer), and treatment is delayed until recovery.

In the USA, dose adjustments (expressed as a percentage of the starting dose) are based on granulocyte counts as follows:
- ⩾ 1500 cells/mm³: 100%
- 1000 to 1499 cells/mm³: 50%
- < 1000 cells/mm³: dose should be omitted. Granulocyte counts are repeated in 1 week; if 3 consecutive counts are below this value, vinorelbine therapy should be stopped

For patients who, during treatment, had fever and/or sepsis while granulocytopenic, or had 2 consecutive weekly doses not given due to granulocytopenia, subsequent doses (expressed as a percentage of the starting dose) are:
- ⩾ 1500 cells/mm³: 75%
- 1000 to 1499 cells/mm³: 37.5%
- < 1000 cells/mm³: dose should be omitted. Granulocyte counts are repeated in 1 week, and if 3 consecutive weekly doses cannot be given, vinorelbine should be stopped altogether

For **oral** therapy, use is also contra-indicated if platelet counts are less than 75 000 cells/mm³ or if neutrophil counts are less than 1500 cells/mm³. For the recommended initial 3 doses, see Uses and Administration, p. 885.3. Subsequent doses are based on neutrophil counts. The recommended dose for the fourth week based on the neutrophil count during the first 3 doses (of 60 mg/m² weekly) is as follows:
- > 1000 cells/mm³: 80 mg/m²
- ⩾ 500 and < 1000 cells/mm³ (1 episode): 80 mg/m²
- ⩾ 500 and < 1000 cells/mm³ (2 episodes): 60 mg/m²
- < 500 cells/mm³: 60 mg/m²

Similarly, for any dose thereafter planned to be given as 80 mg/m², if the neutrophil count is below 1500 cells/mm³ and/or the platelet count is between 75 000 and 100 000 cells/mm³, then the treatment should be delayed until recovery. If the neutrophil count is below 500 cells/mm³ or more than once is between 500 and 1000 cells/mm³, the dose should be delayed until recovery and the dose reduced from 80 to 60 mg/m² weekly for the next 3 doses.

It is possible to re-escalate the weekly dose from 60 to 80 mg/m² if the neutrophil count did not drop below 500 cells/mm³, or to between 500 and 1000 cells/mm³ more than once, during 3 doses given at 60 mg/m².

Adverse Effects, Treatment, and Precautions

As for Vinblastine Sulfate, p. 882.1. The main dose-limiting effect of vinorelbine is neutropenia. The nadir of the neutrophil count occurs 5 to 10 days after a dose, with recovery usually after a further 7 to 14 days. The drug should be stopped if moderate or severe neurotoxicity develops. Other common adverse effects include taste disorders, dysphagia, insomnia, visual disorders, hypotension, cough, genito-urinary disorders such as dysuria, and chills. Severe hyponatraemia may occur. Local pain and thrombophlebitis may be seen with repeated injection of vinorelbine. Gastrointestinal effects such as nausea and vomiting are common with the oral formulation; giving capsules with food may reduce the incidence, and prophylaxis with antiemetics is recommended. Capsules should not be opened or chewed as the contents are irritant.

Care should be taken when using vinorelbine in patients with a history of ischaemic heart disease. Vinorelbine should not be given with radiotherapy if the treatment field includes the liver, and its use is contra-indicated in severe hepatic impairment, see Administration in Hepatic Impairment, above.

Administration error. *Inadvertent intrathecal doses of vinca alkaloids result in ascending paralysis and death.* For reference to the successful treatment of inadvertent intrathecal dosage of vincristine, and UK recommendations on dilution of vinca alkaloids to avoid intrathecal use, see p. 883.2.

Effects on the gastrointestinal tract. For reference to a report of vinorelbine possibly exacerbating ischaemic colitis in patients receiving docetaxel, see p. 781.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies vinorelbine 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 26/09/11)

Interactions

As for Vinblastine Sulfate, p. 882.2. Vinorelbine is metabolised by the cytochrome P450 isoenzyme CYP3A4 and use with strong inhibitors or inducers of CYP3A4 may affect exposure to vinorelbine; caution is advised.

Antibacterials. A retrospective cohort study in Japan[1] found that patients given *clarithromycin* with vinorelbine were at greater risk for severe neutropenia than those given vinorelbine alone.

1. Yano R, *et al.* Evaluation of potential interaction between vinorelbine and clarithromycin. *Ann Pharmacother* 2009; 43: 453–8.

Pharmacokinetics

As with the other vinca alkaloids, vinorelbine exhibits triphasic pharmacokinetics after intravenous injection. Vinorelbine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur 1.5 to 3 hours after oral doses. The absolute bioavailability is about 40%; food does not alter exposure to vinorelbine. Comparable blood concentrations occur with oral vinorelbine doses of 60 and 80 mg/m² and intravenous doses of 25 and 30 mg/m², respectively. Vinorelbine is extensively distributed, especially into pulmonary tissues; however, it is not found in the CNS. Binding to plasma proteins is 13.5% but it is strongly bound to blood cells; binding to platelets is about 78%. Vinorelbine is metabolised via the cytochrome P450 isoenzyme CYP3A4. The metabolite 4-*O*-deacetylvinorelbine (deacetylvinorelbine), which has antineoplastic activity, is thought to be formed by carboxylesterases. The mean terminal half-life of vinorelbine is about 40 hours. Vinorelbine and its metabolites are excreted mainly in faeces via the bile but a small amount (less than 20% of a dose) is found in the urine, largely as unchanged drug.

References.
1. Levêque D, Jehl F. Clinical pharmacokinetics of vinorelbine. *Clin Pharmacokinet* 1996; 31: 184–97.
2. Marty M, *et al.* Oral vinorelbine pharmacokinetics and absolute bioavailability study in patients with solid tumors. *Ann Oncol* 2001; 12: 1643–9.
3. Bugat R, *et al.* The effects of food on the pharmacokinetic profile of oral vinorelbine. *Cancer Chemother Pharmacol* 2002; 50: 285–90.
4. Variol P, *et al.* A simultaneous oral/intravenous population pharmacokinetic model for vinorelbine. *Eur J Clin Pharmacol* 2002; 58: 467–76.
5. Wong M, *et al.* Predictors of vinorelbine pharmacokinetics and pharmacodynamics in patients with cancer. *J Clin Oncol* 2006; 24: 2148–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Filcrin; Navelbine; Neocitec; Sulcoline; Vilne; Vinarine; Vinkebir; Vinorel; Vinoryen; *Austral.*: Navelbine; *Austria*: Eberelbin; Navelbine; *Belg.*: Navelbine; *Braz.*: Evotabina; Navelbine; Neocitec; Norelbin; Oncobine; Tevavinor; *Canad.*: Navelbine; *Chile*: Navelbine; *China*: Ai Ke Ning (艾克宁); Gai Nuo (盖诺); Jie Bin (杰宾); Kang Neng (康能); LeWei (乐唯); Min Nuo Bin (民诺宾); Navelbine (诺维本); Rui Ze (瑞择); Sui Bin (穗宾); Tai Bin (泰宾); *Cz.*: Navelbine; Navirel; Nibrevin†; Oncobine; *Denm.*: Navelbine; Navirel; *Fin.*: Navelbine; Navirel; *Fr.*: Navelbine; *Ger.*: Bendarelbin; Navelbine; Navin; Navirel; *Gr.*: Eunades; Navelbine; Zaolin; *Hong Kong*: Navelbine; *Hung.*: Navelbine; *India*: Navelbine; Vinelbine; *Indon.*: Navelbine; *Irl.*: Navelbine; *Israel*: Navelbine; *Ital.*: Navelbine; *Jpn*: Navelbine; *Malaysia*: Navelbine; *Mex.*: Bagovir†; Navelbine; Navildez; Vieby; Viessia; Vinilex; *Neth.*: Navelbine; Navirel; *Norw.*: Navelbine; Navirel; *NZ*: Navelbine; *Philipp.*: Navelbine; Vinotel; *Pol.*: Navelbine; Navirel; *Port.*: Navelbine; Navirel; Vinorel; *Rus.*: Maverex (Маверекс); Navelbine (Навельбин); Velbin (Велбин); Vincatera (Винкатера); Vinelbin (Винельбин); *S.Afr.*: Carcyt; Navelbine; Vinorel; *Singapore*: Navelbine; *Spain*: Navelbine; *Swed.*: Navelbine; Navirel; *Switz.*: Navelbine; *Thai.*: Navelbine; Viessia; Vinelbine†; *Turk.*: Navelbine; Renovel; *UK*: Navelbine; *Ukr.*: Navelbine (Навельбин); *USA*: Navelbine.

Pharmacopoeial Preparations
USP 36: Vinorelbine Injection.

Vismodegib *(rINN)*

GDC-0449; RG-3616; Vismodégib; Vismodegibum; Висмодегиб.

2-Chloro-*N*-[4-chloro-3-(pyridin-2-yl)phenyl]-4-(methanesulfonyl)benzamide.

$C_{19}H_{14}Cl_2N_2O_3S$=421.3

CAS — 879085-55-9.

ATC — L01XX43.

ATC Vet — QL01XX43.

UNII — 25X868M3DS.

Uses and Administration

Vismodegib is an orally active hedgehog pathway inhibitor that is used for the treatment of basal cell carcinoma (p. 714.2).

For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.

Vismodegib is used to treat patients with metastatic basal cell carcinoma, or with locally advanced disease that has recurred after surgery or who are not candidates for surgery, and who are not candidates for radiation. It is given in a dose of 150 mg once daily until there is disease progression or unacceptable toxicity. If a dose is missed it should be omitted and the next dose taken as scheduled. Capsules should be swallowed whole, and not opened or crushed.

References.
1. De Smaele E, *et al.* Vismodegib, a small-molecule inhibitor of the hedgehog pathway for the treatment of advanced cancers. *Curr Opin Investig Drugs* 2010; 11: 707–18.
2. Graham RA, *et al.* Pharmacokinetics of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with locally advanced or metastatic solid tumors: the role of alpha-1-acid glycoprotein binding. *Clin Cancer Res* 2011; 17: 2512–20.
3. Metcalfe C, de Sauvage FJ. Hedgehog fights back: mechanisms of acquired resistance against Smoothened antagonists. *Cancer Res* 2011; 71: 5057–61.

4. Lorusso PM, *et al.* Pharmacokinetic dose-scheduling study of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with locally advanced or metastatic solid tumors. *Clin Cancer Res* 2011; 17: 5774–82.

Adverse Effects and Precautions

The most common adverse effects of vismodegib are muscle spasms, arthralgias, alopecia, fatigue, gastrointestinal disturbances, taste disturbances, reduced appetite, and weight loss. Amenorrhoea has been reported in some premenopausal women. Hyponatraemia, hypokalaemia, and azotaemia have also been found in some patients given vismodegib.

Vismodegib is expected to cause embryo-fetal death and severe birth defects, based on its mechanism of action and *animal* studies. Pregnancy should be excluded before starting vismodegib in female patients and highly effective contraception used during and for 7 months after therapy. The same potential risks apply to female partners of male patients, who can be exposed to vismodegib in semen; condoms with spermicide should be used, even after vasectomy, during and for 2 months after stopping vismodegib therapy.

Patients should also be advised not to donate blood or blood products during therapy and for 7 months after stopping vismodegib.

Interactions

The solubility of vismodegib is pH dependent and drugs that affect gastric pH, such as antacids, histamine H_2-antagonists, and proton pump inhibitors, may reduce its bioavailability. Drugs that inhibit P-glycoprotein might increase systemic exposure to vismodegib.

Pharmacokinetics

Vismodegib is absorbed from the gastrointestinal tract, but with an absolute bioavailability of only about 32% after a single dose. It is highly bound to plasma proteins. Vismodegib is excreted mainly as unchanged drug via the liver; about 82% of a dose is eliminated in the faeces and about 4.4% in the urine. The elimination half-life is about 12 days after a single dose, but 4 days after continuous once-daily dosing.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Israel*: Erivedge; *UK*: Erivedge; *USA*: Erivedge.

Vitespen *(USAN)*

gp-96; HSPPC-96.

Glucose regulated protein 94 (grp 94); Endoplasmin (human tumor rejection antigen 1).

CAS — 492448-75-6.

UNII — H3598Y1TLJ.

NOTE. The name Oncophage has been used as a trade mark for vitespen.

Profile

Vitespen is a personalised cancer vaccine (p. 757.3) prepared from heat shock glycoprotein 96 and associated peptides isolated from the patient's tumour, that stimulates an immune response to tumour cells. It is under investigation for the treatment of renal cell carcinoma, metastatic melanoma, and various other solid neoplasms.

References.
1. Wood C, *et al.* C-100-12 RCC Study Group. An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. *Lancet* 2008; 372: 145–54.
2. di Pietro A, *et al.* Oncophage: step to the future for vaccine therapy in melanoma. *Expert Opin Biol Ther* 2008; 8: 1973–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Oncophage (Онкофаг).

Vosaroxin *(USAN, rINN)*

AG-7352; SNS-595; SPC-595; Voreloxin; Vosaroxina; Vosaroxine; Vosaroxinum; Вореноксин.

(+)-7-[(3*S*,4*S*)-3-Methoxy-4-(methylamino)pyrrolidin-1-yl]-4-oxo-1-(thiazol-2-yl)-1,4-dihydro-1,8-napthyridine-3-carboxylic acid.

$C_{18}H_{19}N_5O_4S$=401.4

CAS — 175414-77-4.

UNII — K6A90IIZ19.

Profile

Vosaroxin is a quinolone derivative that inhibits topoisomerase II. It is under investigation for its antineoplastic properties in the treatment of malignant neoplasms such as acute myeloid leukemia and ovarian cancer.

References.
1. Advani RH, *et al.* Voreloxin, a first-in-class anticancer quinolone derivative, in relapsed/refractory solid tumors: a report on two dosing schedules. *Clin Cancer Res* 2010; 16: 2167–75.
2. Hawtin RE, *et al.* Voreloxin is an anticancer quinolone derivative that intercalates DNA and poisons topoisomerase II. *PLoS One* 2010; 5: e10186.
3. Krug LM, *et al.* Phase II multicenter trial of voreloxin as second-line therapy in chemotherapy-sensitive or refractory small cell lung cancer. *J Thorac Oncol* 2011; 6: 384–6.

Vorinostat *(USAN, rINN)*

SAHA; Suberoylanilide Hydroxamic Acid; Vorinostatum; Вориностат.

N-Hydroxy-*N*′-phenyl octanediamide.

$C_{14}H_{20}N_2O_3$=264.3

CAS — 149647-78-9.

ATC — L01XX38.

ATC Vet — QL01XX38.

UNII — 58IFB293JI.

Uses and Administration

Vorinostat is a histone deacetylase inhibitor used for the treatment of cutaneous T-cell lymphoma (see Non-Hodgkin's Lymphomas, p. 696.3). The recommended dose is 400 mg orally, given once daily with food. This may be reduced to 300 mg once daily, with a further reduction to 300 mg once daily for 5 consecutive days of each week, if needed. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity. *For warnings and recommendations regarding the safe prescribing, dispensing, and use of oral antineoplastic drugs, see Administration, p. 732.3.*

Vorinostat is also under investigation for the treatment of multiple myeloma and mesothelioma.

References.
1. O'Connor OA. Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. *J Clin Oncol* 2006; 24: 166–73.
2. Krug LM, *et al.* Potential role of histone deacetylase inhibitors in mesothelioma: clinical experience with suberoylanilide hydroxamic acid. *Clin Lung Cancer* 2006; 7: 257–61.
3. Richon VM. Cancer biology: mechanism of antitumour action of vorinostat (suberoylanilide hydroxamic acid), a novel histone deacetylase inhibitor. *Br J Cancer* 2006; 95 (suppl): S2–S6.
4. O'Connor OA. Clinical experience with the novel histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid) in patients with relapsed lymphoma. *Br J Cancer* 2006; 95 (suppl): S7–S12.
5. Duvic M, Zhang C. Clinical and laboratory experience of vorinostat (suberoylanilide hydroxamic acid) in the treatment of cutaneous T-cell lymphoma. *Br J Cancer* 2006; 95 (suppl): S13–S19.
6. Anonymous. Vorinostat (Zolinza) for cutaneous T-Cell lymphoma. *Med Lett Drugs Ther* 2007; 49: 23–4.
7. Duvic M, Vu J. Vorinostat: a new oral histone deacetylase inhibitor approved for cutaneous T-cell lymphoma. *Expert Opin Invest Drugs* 2007; 16: 1111–20.
8. Richon VM, *et al.* Development of vorinostat: current applications and future perspectives for cancer therapy. *Cancer Lett* 2009; 280: 201–10.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

The most common adverse effects of vorinostat are gastrointestinal disturbances, fatigue, chills, dry mouth and taste disorders. Thrombocytopenia and anaemia are also common, and are dose-related; dose reductions may be necessary and in some instances, therapy may need to be stopped. Pulmonary embolism and deep-vein thrombosis have occurred. Other adverse effects include muscle spasms, alopecia, dizziness, peripheral oedema, headache, pruritus, cough, upper respiratory-tract infection, and pyrexia. Increases in serum creatinine, hypokalaemia, and hyperglycaemia have been reported, as has prolongation of the QT interval. Blood cell counts, electrolytes, glucose, and serum creatinine should be monitored every 2 weeks during the first 2 months of therapy and monthly thereafter.

Interactions

Severe thrombocytopenia and gastrointestinal bleeding have been reported when vorinostat has been given with other histone deacetylase inhibitors such as valproic acid; platelet counts should be monitored every 2 weeks for the first 2 months of therapy. Vorinostat may prolong prothrombin time and affect the INR in patients receiving coumarin anticoagulants.

Pharmacokinetics

After an oral dose of vorinostat with a high-fat meal, mean time to peak plasma concentration was about 4 hours; this was reduced to 1.5 hours after fasting. Aside from this decrease in the rate of absorption, a high-fat meal also increased the extent of absorption. While these results were stated not to be clinically significant, licensed product information recommends that vorinostat be taken with food. Plasma protein binding is about 71%. Vorinostat is metabolised by glucuronidation and hydrolysis followed by oxidation; metabolites are pharmacologically inactive. Less than 1% of a dose is recovered in the urine as unchanged drug. The mean terminal half-life is about 2 hours for vorinostat.

References.
1. Rubin EH, *et al.* A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancer. *Clin Cancer Res* 2006; 12: 7039–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zolinza; *Canad.*: Zolinza; *Gr.*: Zolinza; *Jpn*: Zolinza; *USA*: Zolinza.

Zalutumumab *(USAN, rINN)*

2F8; HuMax-EGFr; Zalutumumabum; Залутумаб.

Immunoglobulin G1, anti-(human epidermal growth factor receptor)(human monoclonal 2F8 heavy chain), disulfide with human monoclonal 2F8 κ-chain, dimer.

CAS — 667901-13-5.

Profile

Zalutumumab is a human monoclonal antibody targeted at the epidermal growth factor receptor (EGFR). EGFR is found on the surface of many cancer cells, and activation thereof promotes tumour cell growth. Zalutumumab is under investigation for the treatment of head and neck cancer.

References.
1. Rivera F, *et al.* Current situation of zalutumumab. *Expert Opin Biol Ther* 2009; 9: 667–74.

Zibotentan *(USAN, rINN)*

ZD-4054; Zibotentán; Zibotentanum; Зиботентан.

N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide.

$C_{19}H_{16}N_6O_4S$=424.4

CAS — 186497-07-4.

UNII — 8054MM4902.

Profile

Zibotentan is an endothelin-A receptor antagonist that is under investigation for the treatment of hormone-resistant prostate cancer and other solid tumours, although initial results have been disappointing.

References.
1. Morris CD, *et al.* Specific inhibition of the endothelin A receptor with ZD4054: clinical and pre-clinical evidence. *Br J Cancer* 2005; 92: 2148–52.
2. Warren R, Liu G. ZD4054: a specific endothelin A receptor antagonist with promising activity in metastatic castration-resistant prostate cancer. *Expert Opin Invest Drugs* 2008; 17: 1237–45.

Zinostatin *(USAN, rINN)*

Neocarzinostatin; NSC-69856; NSC-157365; Zinostatina; Zinostatine; Zinostatinum; Зиностатин.

CAS — 9014-02-2.

UNII — PP082U6W1L.

Description. Zinostatin is an antineoplastic antibiotic obtained from *Streptomyces carzinostaticus*.

Pharmacopoeias. *Jpn* includes zinostatin stimalamer.

Profile

Zinostatin is an antibiotic with antineoplastic activity and has been used in the treatment of malignant neoplasms.

Zinostatin stimalamer, a conjugate of zinostatin with a styrene-maleic acid polymer, is given by hepatic intra-arterial injection for the treatment of liver cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: SMANCS.

Zorubicin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de zorubicina; NSC-164011; RP-22050 (zorubicin); Zorubicina, hidrocloruro de; Zorubicine, Chlorhydrate de; Zorubicini Hydrochloridum; Зорубицина Гидрохлорид.

Benzoic acid (2*S*-*cis*)-[1-[4-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxonaphthacen-2-yl]ethylidene]hydrazide hydrochloride.
$C_{34}H_{35}N_3O_{10}$,HCl=682.1
CAS — 54083-22-6 (zorubicin); 36508-71-1 (zorubicin hydrochloride).
ATC — L01DB05.
ATC Vet — QL01DB05.
UNII — WXM8D9M6DE.

Profile

Zorubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (see p. 782.3). It has been used as the hydrochloride in the treatment of acute leukaemias.

Antiparkinsonian Drugs

The antiparkinsonian drugs described in this chapter can be broadly divided into 2 groups; the **dopaminergics**, drugs that are used to potentiate the actions of dopamine, and the **antimuscarinics**, drugs that are used to reduce excessive central cholinergic effects.

Dopamine is a key neurotransmitter in the CNS; in particular, striatal dopamine depletion is associated with the clinical condition of parkinsonism. Dopamine also inhibits prolactin release from the pituitary and is believed to be the prolactin-release inhibiting factor (PRIF or PIF); dopamine deficiency in the pituitary is associated with conditions characterised by hyperprolactinaemia. Accordingly, drugs that replenish central dopamine or that can act as stimulants of dopamine receptors (dopamine agonists), may alleviate the symptoms of parkinsonism (see below), hyperprolactinaemia (p. 2252.2), and related disorders.

At least 5 subtypes of dopamine receptor are thought to exist: D_1 receptors appear to stimulate adenylate cyclase activity; D_2 receptors activate various systems and inhibit adenylate cyclase activity. D_3, D_4, and D_5 receptors have been less well studied but D_3 and D_4 are similar to D_2, forming the D_2-like group, whereas D_1 and D_5 form the D_1-like group. D_2 receptors have been implicated in the pathophysiology of parkinsonism and schizophrenia.

Dopaminergics, or drugs that enhance their actions, described in this chapter include:

- levodopa, which is converted by decarboxylation into dopamine in the body, and which, unlike dopamine itself, can penetrate the blood-brain barrier and supply a source of dopamine to the brain
- the peripheral dopa-decarboxylase inhibitors, benserazide and carbidopa, which have no dopaminergic action of their own but increase the availability of levodopa
- apomorphine, which is structurally related to dopamine and acts as a dopamine agonist
- the adamantanamine, amantadine, which may augment dopaminergic activity
- the ergot derivatives, bromocriptine, cabergoline, lisuride, and pergolide, which act as dopamine agonists
- various other non-ergot dopamine agonists, such as piribedil, pramipexole, ropinirole, rotigotine, talipexole, and terguride
- the specific monoamine oxidase type B inhibitors, rasagiline and selegiline, which enhance the action of dopamine and levodopa
- the catechol-*O*-methyltransferase inhibitors (COMT-inhibitors), entacapone and tolcapone, which enhance the action of levodopa

Antimuscarinic drugs are used in Parkinson's disease (idiopathic or primary parkinsonism) and, particularly, drug-induced parkinsonism. They act by reducing the excessive central cholinergic effects of dopamine deficiency. Antimuscarinics described in this chapter include the tertiary amines, such as benzatropine, orphenadrine, procyclidine, and trihexyphenidyl, which are the most commonly used in the treatment of parkinsonism.

Drugs targeting non-dopaminergic pathways are being developed to reduce the impact of the motor complications associated with dopaminergic drugs. These include istradefylline, a selective adenosine A_{2A}-receptor antagonist that is given as an adjunct to levodopa therapy.

Parkinsonism

The syndrome of parkinsonism is characterised by tremor, rigidity, akinesia or bradykinesia, and loss of postural reflexes, associated with reduced dopamine activity in the brain. It may be classified as follows:

- primary (idiopathic) parkinsonism, usually referred to as Parkinson's disease (formerly paralysis agitans)
- secondary (acquired) parkinsonism, including postencephalitic parkinsonism, drug-induced parkinsonism, and symptoms associated with manganese poisoning
- 'parkinsonism-plus' syndromes where parkinsonism is a feature of other degenerative diseases of the CNS, such as progressive supranuclear palsy and multiple system atrophy

'Arteriosclerotic parkinsonism' has been used to describe parkinsonism associated with cerebrovascular disease, although this may be confusing since vascular brain damage is not a cause of Parkinson's disease.

The term parkinsonism is often used for the idiopathic form, that is, Parkinson's disease. Parkinson's disease and postencephalitic parkinsonism have been attributed mainly to depletion of striatal dopamine in the basal ganglia as a result of the loss of neurones in the substantia nigra. Striatal dopamine deficiency results in loss of the normal functional balance between dopaminergic and cholinergic activity and the aim of treatment is to increase the former and/or decrease the latter.

The **cause** of *Parkinson's disease* is not established, although environmental and genetic factors are probably superimposed on a background of neuronal loss related to ageing. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a contaminant of an illicitly produced pethidine analogue MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), causes irreversible parkinsonism similar to Parkinson's disease. This effect appears to follow conversion by monoamine oxidase B to the neurotoxic methylphenylpyridinium ion, which is selectively concentrated in dopaminergic neurones in the substantia nigra. It has been proposed that free radicals produced during normal metabolism of dopamine in the brain by monoamine oxidase B might be similarly neurotoxic to dopaminergic neurones in the substantia nigra (the oxidant stress hypothesis). This has led to concern that use of levodopa, by increasing the supply of dopamine, might therefore exacerbate neurodegeneration and hasten the progression of Parkinson's disease but compelling evidence of such an effect is lacking.

Drug-induced parkinsonism (see Extrapyramidal Disorders, p. 1049.2) can arise from depletion of presynaptic dopamine, as with reserpine and tetrabenazine, or from blockade of postsynaptic dopamine receptors in the striatum, as by antipsychotics and some antiemetics such as metoclopramide. It is generally reversible on drug withdrawal or dose reduction and may sometimes disappear gradually despite continuous drug therapy. Although the use of levodopa to overcome antipsychotic-induced blockade of dopamine receptors might appear rational, it has generally been reported to be ineffective or to increase psychiatric symptoms. Antimuscarinics may provide relief from the extrapyramidal symptoms that occur as adverse effects of antipsychotic therapy; however, they do not relieve the symptoms of tardive dyskinesia and should be withdrawn if it develops.

There is no cure for Parkinson's disease. Although the possibility of using drug therapy to slow neurodegeneration is being investigated, no drug so far has a proven neuroprotective effect. **Treatment** is palliative and symptomatic and consists mainly of drug therapy supplemented when necessary with physical treatment such as physiotherapy and speech therapy. Surgery is occasionally used and there is growing interest in the use of transplantation and in electrical devices for the control of tremor.

Drugs used in Parkinson's disease. Drug therapy consists largely of the use of dopaminergics or antimuscarinics in an attempt to restore the normal balance between dopaminergic and cholinergic activity. Dopaminergics may act by direct replacement of dopamine, by delaying the metabolism of endogenous dopamine, by stimulation of dopamine receptors directly, or by enhancement of release of endogenous dopamine. Drugs with differing actions are often used together to achieve optimum control of symptoms.

- *Levodopa* is the most effective symptomatic treatment. It is converted by decarboxylation into dopamine and, unlike dopamine, can penetrate the blood-brain barrier and supply a source of dopamine to the brain. Levodopa is usually given with a peripheral dopa-decarboxylase inhibitor such as *benserazide* or *carbidopa*. These drugs are unable to penetrate the blood-brain barrier and therefore prevent only extracerebral conversion of levodopa to dopamine. This allows effective concentrations of dopamine to be achieved in the brain with lower doses of levodopa and also reduces nausea and vomiting and other adverse effects associated with peripheral formation of dopamine.

  The majority of patients respond initially to levodopa and its use has improved the quality and duration of life. However, after 2 years or more, benefit is reduced as the disease progresses and late complications emerge. Apart from dyskinesias and psychiatric effects, a major problem with long-term levodopa treatment is the appearance of fluctuations in mobility, the two predominant forms being 'end-of-dose' deterioration ('wearing-off' effect) and the 'on-off' phenomenon (see Complications of Treatment, below). Thus, views differ as to the best time to start treatment and the dosage to use in order to limit the long-term complications.

  Catechol-*O*-methyltransferase (COMT) inhibitors, such as *entacapone* and *tolcapone*, are selective and reversible inhibitors of COMT, with mainly peripheral actions. They are given as adjunctive therapy to patients with fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations; because of the risk of serious hepatotoxicity, tolcapone should be restricted to when other adjunctive therapy is ineffective or contra-indicated. When levodopa is used with a peripheral dopa-decarboxylase inhibitor, *O*-methylation becomes the predominant form of metabolism of levodopa; adding a peripheral COMT inhibitor can thus extend the duration and effect of levodopa in the brain, and allow lower and less frequent doses of levodopa. They therefore can help to stabilise patients, especially those with 'end-of-dose' deterioration.
- *Rasagiline* and *selegiline* are selective inhibitors of monoamine oxidase type B, an enzyme involved in the metabolism of dopamine in the brain. When used with levodopa in severe parkinsonism they have a dose-sparing effect and are of value in patients with fluctuations in mobility. Early treatment with selegiline may delay the need for levodopa and there has been much interest in the possibility that these drugs might have neuroprotective effects, but it is difficult to separate any putative effect on disease progression from symptomatic benefits, and at present there is insufficient evidence to show that any treatment can slow progression of the disease. Used alone, selegiline produces few adverse effects but when used with levodopa it can provoke or worsen dyskinesias or psychiatric symptoms and doubts have been expressed on the safety of long-term use.
- Dopamine agonists such as *bromocriptine, cabergoline, pergolide, pramipexole, ropinirole,* and *rotigotine* act by direct stimulation of remaining postsynaptic dopamine receptors. Dopamine agonists are increasingly used in the early treatment of younger patients with parkinsonism in an attempt to delay therapy with levodopa (younger patients are at an increased risk of motor complications with levodopa). However, their efficacy often decreases after a few years. In older patients they may be reserved for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. They are sometimes useful in reducing 'off' periods with levodopa and in ameliorating fluctuations in mobility in the later stages of the disease. *Apomorphine* is a potent dopamine agonist, but must be given parenterally and with an antiemetic. Although this restricts its use, it has a role in stabilising patients who suffer unpredictable 'on-off' effects. It is also used in the differential diagnosis of parkinsonism.
- *Antimuscarinics* are considered to have a weak antiparkinsonian effect compared with levodopa. They may reduce tremor but have little effect on bradykinesia. They may be of use alone or with other drugs in the initial treatment of patients with mild symptoms, especially when tremor is pronounced, or later as an adjunct to levodopa, such as in patients with refractory tremor or dystonias. Antimuscarinic adverse effects, particularly cognitive impairment, occur frequently and can limit their use. However, some antimuscarinic effects can ameliorate complications associated with Parkinson's disease; dry mouth may be an advantage in patients with sialorrhoea. There appear to be no important differences in the efficacy of antimuscarinics for Parkinson's disease but some patients may tolerate one drug better than another. Those commonly used for Parkinson's disease include *benzatropine, orphenadrine, procyclidine,* and *trihexyphenidyl.*
- *Amantadine* is a weak dopamine agonist with some antimuscarinic activity although its activity as an antagonist of *N*-methyl-D-aspartate may also have a beneficial effect in Parkinson's disease. It has mild antiparkinsonian effects compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity but only a small proportion of patients derive much benefit. It is used similarly to antimuscarinics in early disease when symptoms are mild, but tolerance to its effects can occur rapidly.
- *Istradefylline* is a selective adenosine A_{2A}-receptor antagonist given as an adjunct to levodopa therapy. Drugs targeting non-dopaminergic pathways, such as the adenosine pathway, are being developed in order to reduce the impact of the motor complications associated with dopaminergic drugs.

Choice and implementation of drug treatment. If symptoms are mild, drug therapy may not be required in the early stages of the disease. When symptoms become troublesome but are still relatively mild *amantadine* or an *antimuscarinic* may be started; antimuscarinics are useful when tremor predominates but are generally more suitable for younger patients and in drug-induced rather than idiopathic parkinsonism. Some have begun treatment with

selegiline immediately, but there have been doubts over whether it has a neuroprotective effect, as postulated, and also over long-term safety. There is no consensus on when to start dopaminergic treatment or whether to begin with *levodopa* or a *dopamine agonist*. For most patients treatment with levodopa eventually becomes necessary, but many neurologists delay initial treatment with levodopa because of the increased risk of motor complications. New patients, especially younger patients, therefore often begin treatment with a dopamine agonist, with levodopa reserved for the elderly, the frail, or those with intercurrent illness or more severe symptoms.

When levodopa does become necessary, the usual practice is to start with small doses, given with a peripheral dopa-decarboxylase inhibitor, and increase slowly to a dose which reduces disability to an acceptable level. Variations in response and diminishing efficacy over the years necessitate careful adjustment of the size and form of the dose and the dosage schedule.

Complications of treatment. Fluctuations in mobility have been reported in more than half of patients on levodopa after 5 years of therapy. They generally proceed through predictable **'end-of-dose'** deterioration to the **'on-off'** phenomenon with marked very sudden swings from mobility to immobility. The cause of the fluctuations is not known, but multiple factors including desensitisation of dopamine receptors, interference with the response to dopamine by other levodopa metabolites such as 3-*O*-methyldopa, fluctuating plasma concentrations, and erratic transport of levodopa from blood to the brain have been suggested. It appears that as the disease progresses the capacity of the nigrostriatal dopaminergic system to synthesise and store dopamine, and to act as a buffer in maintaining dopamine brain concentrations, declines. Dopamine concentrations therefore become more dependent on levodopa dosage and the pattern of response will come to reflect more closely the rise and fall in levodopa concentrations. Eventually the effect of various factors that produce even small changes in plasma concentrations of levodopa will progressively become more pronounced.

Approaches to the management of 'end-of-dose' fluctuations include more frequent but smaller doses and the use of modified-release preparations. Addition of selegiline or partial replacement of levodopa by a dopamine agonist with a more prolonged action may also be tried.

Various attempts have been made to overcome the 'on-off' phenomenon. Those speculating that long-term treatment results in altered dopamine receptor sensitivity have used controlled withdrawal of levodopa for short periods ('drug holidays') but it is a dangerous procedure of doubtful value and no longer recommended.

Others have linked the 'on-off' phenomenon to variable plasma concentrations although, since transfer of levodopa into the brain involves active transport mechanisms, concentrations in plasma may not necessarily reflect those in the brain. Continuous intraduodenal or intravenous infusion of levodopa has been shown to reduce fluctuations in mobility, which suggests that dopamine receptors are still sensitive, although this is not practical for day-to-day management (but see below). However, there is evidence that some patients may benefit from modified-release formulations of levodopa with a peripheral dopa-decarboxylase or COMT inhibitor. As levodopa competes with amino acids for uptake into the brain, attempts to lessen fluctuations in dopamine brain concentrations have included taking levodopa on an empty stomach and also delaying most of a day's protein consumption until the evening. Addition of entacapone, rasagiline, selegiline, or a dopamine agonist may also help to reduce 'on-off' phenomena. If fluctuations remain a problem subcutaneous apomorphine is often effective. In some countries a gel formulation of levodopa with carbidopa is available for continuous infusion by an ambulatory pump into the duodenum when other available combination therapy has not been satisfactory.

Other complications of treatment with levodopa can include **dyskinesia**, which may respond to dosage adjustment or partial replacement of levodopa with a dopamine agonist. Amantadine may also be considered, although evidence is lacking. Some patients with Parkinson's disease may have **severe pain** and **dystonia**; measures to increase 'on' periods can help reduce or eliminate pain in most patients.

Patients with Parkinson's disease can suffer from a range of **psychiatric effects**, such as depression, dementia, sleep disturbances, and psychosis, due to the adverse effects of drug therapy and to disease progression. It has been recommended that if patients develop psychotic reactions, an attempt to adjust their antiparkinsonian drugs should be tried before resorting to the use of antipsychotics. Although classical antipsychotics are usually contra-indicated because they can exacerbate parkinsonism, atypical antipsychotics such as clozapine and quetiapine may be used in treatment-resistant psychosis—see Disturbed Behaviour, p. 1030.2. The cholinesterase inhibitor rivastigmine is licensed in some countries for the symptomatic treatment of mild to moderately severe dementia in Parkinson's disease. **Excessive daytime sleepiness** and **sudden onset of sleep** have been reported with dopamine agonists, as have **behavioural disturbances** including intense urges to gamble and increased sexual urges, and patients should be warned of the possible risks (see Effects on Mental Function, under Adverse Effects of Levodopa, p. 905.2). **Fibrotic reactions** resulting in cardiovascular and pulmonary adverse effects have been reported with ergot derivatives and patients should be monitored (see Fibrosis, under Adverse Effects of Bromocriptine, p. 897.3). **Nausea and vomiting** induced by dopaminergics may be minimised by introducing the drug gradually and giving the dose with food, but if this is ineffective or apomorphine is being used these effects can be controlled by the antiemetic domperidone. Domperidone does not readily cross the blood-brain barrier and therefore acts mainly as a peripheral dopamine antagonist. Tolerance to the nausea usually develops after a few weeks and domperidone may then be withdrawn.

References.

1. Olanow CW, *et al.* An algorithm (decision tree) for the management of Parkinson's disease (2001)—treatment guidelines. *Neurology* 2001; **56** (suppl 5): S1–S88.
2. Miyasaki JM, *et al.* Practice parameter: initiation of treatment for Parkinson's disease—an evidence-based review. *Neurology* 2002; **58**: 11–17.
3. Clarke CE, Guttman M. Dopamine agonist monotherapy in Parkinson's disease. *Lancet* 2002; **360**: 1767–9.
4. Deleu D, *et al.* Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson's disease. *Clin Pharmacokinet* 2002; **41**: 261–309.
5. Rascol O, *et al.* Treatment interventions for Parkinson's disease: an evidence based assessment. *Lancet* 2002; **359**: 1589–98.
6. Katzenschlager R, *et al.* Anticholinergics for symptomatic management of Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 16/02/06).
7. Deane K, *et al.* Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).
8. Schapira AHV, Olanow CW. Neuroprotection in Parkinson disease: mysteries, myths, and misconceptions. *JAMA* 2004; **291**: 358–64.
9. Samii A, *et al.* Parkinson's disease. *Lancet* 2004; **363**: 1783–93.
10. Thanvi BR, Lo TCN. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgrad Med J* 2004; **80**: 452–8.
11. Stocchi F, Olanow CW. Continuous dopaminergic stimulation in early and advanced Parkinson's disease. *Neurology* 2004; **62** (suppl 1): S56–S63.
12. Barone P, *et al.* Treatment of nocturnal disturbances and excessive daytime sleepiness in Parkinson's disease. *Neurology* 2004; **63** (suppl 3): S35–S38.
13. Goetz CG, *et al.* Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease—2001 to 2004. *Mov Disord* 2005; **20**: 523–39.
14. Nyholm D. Pharmacokinetic optimisation in the treatment of Parkinson's disease: an update. *Clin Pharmacokinet* 2006; **45**: 109–36.
15. Suchowersky O, *et al.* Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **66**: 968–75. Also available at: http://www.neurology.org/cgi/reprint/66/7/968.pdf (accessed 11/08/08)
16. Suchowersky O, *et al.* Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **66**: 976–82. Correction. *ibid.*: **67**: 299. Also available at: http://www.neurology.org/cgi/reprint/66/7/976.pdf (accessed 23/08/10)
17. Pahwa R, *et al.* Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **66**: 983–95. Also available at: http://www.neurology.org/cgi/reprint/66/7/983.pdf (accessed 11/08/08)
18. Miyasaki JM, *et al.* Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **66**: 996–1002. Also available at: http://www.neurology.org/cgi/reprint/66/7/996.pdf (accessed 11/08/08)
19. Olanow CW. Rationale for considering that propargylamines might be neuroprotective in Parkinson's disease. *Neurology* 2006; **66** (suppl 4): S69–S79.
20. Bonuccelli U, Del Dotto P. New pharmacologic horizons in the treatment of Parkinson disease. *Neurology* 2006; **67** (suppl 2): S30–S38.
21. National Collaborating Centre for Chronic Conditions/NICE. Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care (issued June 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/cg035fullguideline.pdf (accessed 05/06/08)
22. Clarke CE. Parkinson's disease. *BMJ* 2007; **335**: 441–5.
23. Ahlskog JE. Beating a dead horse: dopamine and Parkinson disease. *Neurology* 2007; **69**: 1701–11.
24. Davie CA. A review of Parkinson's disease. *Br Med Bull* 2008; **86**: 109–27.
25. Stowe R, *et al.* Dopamine agonist therapy in early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 05/06/08).
26. LeWitt PA. Levodopa for the treatment of Parkinson's disease. *N Engl J Med* 2008; **359**: 2468–76.
27. Antonini A, Cilia R. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. *Drug Safety* 2009; **32**: 675–88.
28. Olanow CW, *et al.* The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology* 2009; **72** (suppl 4): S1–S136.
29. Lees AJ, *et al.* Parkinson's disease. *Lancet* 2009; **373**: 2055–66. Correction. *ibid.*: **374**: 684.
30. Hasnain M, *et al.* Pharmacological management of psychosis in elderly patients with parkinsonism. *Am J Med* 2009; **122**: 614–22.
31. Stefani A, *et al.* Therapy for dyskinesias in Parkinson's disease patients. *Future Neurol* 2010; **5**: 277–99.
32. Zesiewicz TA, *et al.* Practice parameter: treatment of nonmotor symptoms of Parkinson disease. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2010; **74**: 924–31. Also available at: http://www.neurology.org/cgi/reprint/74/11/924 (accessed 24/08/10)
33. Scottish Intercollegiate Guidelines Network. Diagnosis and pharmacological management of Parkinson's disease: a national clinical guideline (issued January 2010). Available at: http://www.sign.ac.uk/pdf/sign113.pdf (accessed 18/05/10)
34. Bronstein JM, *et al.* Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol* 2011; **68**: 165–71
35. Barone P. Treatment of depressive symptoms in Parkinson's disease. *Eur J Neurol* 2011; **18** (suppl 1): 11–15.
36. Leentjens AFG. The role of dopamine agonists in the treatment of depression in patients with Parkinson's disease: a systematic review. *Drugs* 2011; **71**: 273–86.
37. Seppi K, *et al.* The Movement Disorder Society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord* 2011; **26** (suppl 3): S42–S80.
38. Ferreira JJ, *et al.* Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. *Eur J Neurol* 2013; **20**: 5–15.
39. Berardelli A, *et al.* EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease. *Eur J Neurol* 2013; **20**: 16–34. Correction. *ibid.*; 406.

Amantadine *(BAN, pINN)*

Amantadiini; Amantadin; Amantadina; Amantadinum; Амантадин.

Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine.

$C_{10}H_{17}N$=151.3

CAS — 768-94-5.

ATC — N04BB01.

ATC Vet — QN04BB01.

UNII — BF4C9Z1J53.

Amantadine Hydrochloride

(BANM, USAN, pINNM)

1-Adamantanamine Hydrochloride; Amantadiinihydroklori; Amantadina, hidrocloruro de; Amantadine, chlorhydrate d'; Amantadin-hidroklorid; Amantadin-hydrochlorid; Amantadinhydrochlorid; Amantadinhydroklorid; Amantadini Hydrochloridum; Amantadino hidrochloridas; EXP-105-1; Hidrocloruro de amantadina; NSC-83653; Амантадина Гидрохлорид.

Tricyclo[3.3.1.1^{3,7}]dec-1-ylamine hydrochloride.

$C_{10}H_{17}N.HCl$=187.7

CAS — 665-66-7.

ATC — N04BB01.

ATC Vet — QN04BB01.

UNII — M6Q1EO9TD0.

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

Ph. Eur. 8: (Amantadine Hydrochloride). A white or almost white crystalline powder. It sublimes on heating. Freely soluble in water and in alcohol.

USP 36: (Amantadine Hydrochloride). A white or practically white crystalline powder. Soluble 1 in 2.5 of water, 1 in 5.1 of alcohol, 1 in 18 of chloroform, and 1 in 70 of macrogol 400. pH of a 20% solution in water is between 3.0 and 5.5.

Amantadine Sulfate *(pINNM)*

Amantadina, sulfato de; Amantadine, Sulfate d'; Amantadine Sulphate; Amantadini Sulfas; Sulfato de amantadina; Амантадина Сульфат.

$(C_{10}H_{17}N)_2SO_4$=398.6

CAS — 31377-23-8.

ATC — N04BB01.

ATC Vet — QN04BB01.

UNII — 992IT5P019.

Uses and Administration

Amantadine is a weak dopamine agonist with some antimuscarinic activity; it is also an antagonist at *N*-methyl-D-aspartate receptors. Amantadine has mild antiparkinsonian activity and is used in the management of parkinsonism (p. 891.2), mainly in early disease when symptoms are mild. It may improve bradykinesia, rigidity, and tremor but tolerance can develop.

Amantadine is also an antiviral that inhibits replication of influenza type A virus; it has very little or no activity against influenza type B virus. It is used prophylactically against infection with influenza type A virus and to ameliorate symptoms when given during the early stages of infection (but see p. 891.2).

Amantadine has also been used in the management of herpes zoster (see Varicella-zoster Infections, p. 956.2).

Amantadine is usually given orally as the hydrochloride and the doses below are expressed in terms of this salt.

In **parkinsonism**, treatment is usually started with 100 mg daily, increasing to 100 mg twice daily after a week or more. Doses up to a maximum of 400 mg daily have occasionally been used. The lowest effective dose should be used in patients over 65 years of age because of the potential for reduced renal clearance in this age group. Withdrawal of

amantadine treatment for parkinsonism should be gradual to avoid exacerbating the condition; UK licensed product information suggests decreasing the dose by half at weekly intervals.

The dose of amantadine in the UK for the treatment of **influenza A** is 100 mg daily, usually given for about 5 days. For the prophylaxis of influenza A the same dose is given for as long as protection from infection is required, which may be for about 6 weeks. If amantadine is being given with influenza vaccination then it is usually only given for up to 3 weeks after vaccination. Children aged 10 to 15 years may also be given 100 mg daily for the recommended period. A daily dose of less than 100 mg or 100 mg given at intervals greater than one day has been recommended for patients over 65 years of age.

Doses in the USA are higher than those in the UK: for the treatment of influenza A the daily dose is 200 mg daily as a single dose or in two divided doses, continued for 24 to 48 hours after the disappearance of symptoms. The same dose is given for the prophylaxis of influenza A for at least 10 days after exposure. If given with vaccination then amantadine should be taken for the next 2 to 4 weeks. The dose of amantadine should be reduced to 100 mg daily in patients aged 65 years and over, and in those who show intolerance to the higher dose. US licensed product information recommends that children aged 1 to 9 years may be given 4.4 to 8.8 mg/kg daily to a maximum of 150 mg daily, although the CDC suggests 5 mg/kg daily (maximum 150 mg daily) to reduce the risk of toxicity. Older children may be given 100 mg twice daily; CDC suggests that children weighing less than 40 kg should be given a dose of 5 mg/kg daily, regardless of their age.

In **herpes zoster**, treatment with 100 mg twice daily may be given for 14 days; if pain persists, treatment may be continued for a further 14 days.

The dosage of amantadine should be reduced in patients with renal impairment (see below).

Amantadine sulfate has been used similarly to the hydrochloride; it has been given orally or by intravenous infusion.

Administration. Amantadine sulfate has been used successfully in doses of up to 600 mg daily by intravenous infusion in the management of akinetic crisis in patients with Parkinson's disease.[1]

1. Gadoth N, *et al.* I.V. amantidine [sic] sulfate for extrapyramidal crisis. *Clin Pharm* 1985; 4: 146.

Administration in children. For doses of amantadine hydrochloride in the prophylaxis and treatment of influenza A in children, see p. 890.3.

Administration in renal impairment. The oral dose of amantadine hydrochloride should be reduced in patients with renal impairment by either reducing the total daily dose or by increasing the dosage interval in accordance with their creatinine clearance (CC).

In the UK the following doses are recommended:

- CC over 35 mL/min: 100 mg daily
- CC 15 to 35 mL/min: 100 mg every 2 to 3 days
- CC less than 15 mL/min: not recommended

In the USA the following doses are recommended:

- CC 30 to 50 mL/min: 200 mg on the first day followed by 100 mg daily thereafter
- CC 15 to 29 mL/min: 200 mg on the first day followed by 100 mg on alternate days
- CC less than 15 mL/min or those on haemodialysis: 200 mg every 7 days

See also under Precautions, p. 892.2.

Extrapyramidal disorders. Amantadine has been used as an alternative to antimuscarinics[1] in the short-term management of *drug-induced extrapyramidal symptoms* (p. 1049.2). US licensed product information has recommended a usual oral dose of 200 mg daily in 2 divided doses increased up to 300 mg daily if necessary. However, the development of tolerance has limited its usefulness. See also Parkinsonism, below.

Amantadine has been investigated in the management of *chorea* in patients with Huntington's disease.[2,3]

1. König P, *et al.* Amantadine versus biperiden: a double-blind study of treatment efficacy in neuroleptic extrapyramidal movement disorders. *Neuropsychobiology* 1996; 33: 80–4.
2. Magnet MK, *et al.* Amantadine in the akinetic-rigid variant of Huntington's disease. *Ann Pharmacother* 2004; 38: 1194–6.
3. Heckmann JM, *et al.* IV amantadine improves chorea in Huntington's disease: an acute randomized, controlled study. *Neurology* 2004; 63: 597–8.

Hepatitis C. Amantadine has been investigated[1-4] as an addition to interferon-based antiviral regimens in the treatment of chronic hepatitis C infection (p. 952.1). A meta-analysis[1] concluded that it was of no value in treatment-naive patients or relapsers, but that triple therapy with amantadine, ribavirin, and interferon improved sustained responses in patients previously unresponsive to therapy.

1. Delenne P, *et al.* Evaluation of amantadine in chronic hepatitis C: a meta-analysis. *J Hepatol* 2004; 41: 462–73.
2. Stauber RE, *et al.* Retreatment of patients with chronic hepatitis C not responding to interferon/ribavirin combination therapy with daily interferon plus ribavirin plus amantadine. *Wien Klin Wochenschr* 2004; 116: 530–5.
3. Herrine SK, *et al.* Peginterferon alpha-2a combination therapies in chronic hepatitis C patients who relapsed after or had a viral breakthrough on therapy with standard interferon alpha-2b plus ribavirin: a pilot study of efficacy and safety. *Dig Dis Sci* 2005; 50: 719–26.
4. Mangia A, *et al.* A randomized controlled trial of pegylated interferon alpha-2a (40 KD) or interferon alpha-2a plus ribavirin and amantadine vs interferon alpha-2a and ribavirin in treatment-naive patients with chronic hepatitis C. *J Viral Hepatitis* 2005; 12: 292–9.

Hiccup. Amantadine[1] has been reported to have produced beneficial results in patients with intractable hiccups. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3.

1. Askenasy JJM, *et al.* Persistent hiccup cured by amantadine. *N Engl J Med* 1988; 318: 711.

Influenza. Amantadine has been used similarly to rimantadine (p. 1012.2) in the prophylaxis and treatment of influenza A (p. 960.2). In adults, the two drugs are equally effective, but amantadine is associated with more adverse effects;[1] further study on their safety and efficacy in children and the elderly is considered warranted.[2] Amantadine reduced the duration of influenza A symptoms when given in a dose of 200 mg daily within 48 hours of the onset of symptoms.[3] However, although amantadine is licensed in the UK and USA for the prophylaxis and treatment of influenza A, its use for such purposes is not recommended by authorities in these countries because of resistance in circulating influenza A virus strains.[4-6]

Resistance to amantadine may occur rapidly.[7] For further information see Resistance, under Rimantadine, p. 1013.1.

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 21/06/06).
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 29/05/08).
3. Nicholson KG, Wiselka MJ. Amantadine for influenza A. *BMJ* 1991; 302: 425–6.
4. CDC. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; 60 (RR-1): 1–26. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf (accessed 09/02/11)
5. NICE. Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza—includes a review of NICE technology appraisal guidance 67: NICE Technology Appraisal Guidance 158 (issued September 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA158Guidance.pdf (accessed 20/08/09)
6. NICE. Amantadine, oseltamivir and zanamivir for the treatment of influenza—review of NICE technology appraisal guidance 58: NICE Technology Appraisal Guidance 168 (issued February 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/TA168fullguidance.pdf (accessed 20/08/09)
7. 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.

Multiple sclerosis. Amantadine has been used to alleviate fatigue associated with multiple sclerosis (p. 996.3). However, a systematic review[1] concluded that there was insufficient evidence to support its use in reducing fatigue in patients with multiple sclerosis; further large controlled studies are considered warranted.

1. Pucci E, *et al.* Amantadine for fatigue in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 29/05/08).

Neuroleptic malignant syndrome. Amantadine has been tried[1-3] in the treatment of the neuroleptic malignant syndrome (p. 1050.2).

1. McCarron MM, *et al.* A case of neuroleptic malignant syndrome successfully treated with amantadine. *J Clin Psychiatry* 1982; 43: 381–2.
2. Amdurski S, *et al.* A therapeutic trial of amantadine in haloperidol-induced malignant neuroleptic syndrome. *Curr Ther Res* 1983; 33: 225–9.
3. Woo J, *et al.* Neuroleptic malignant syndrome successfully treated with amantadine. *Postgrad Med J* 1986; 62: 809–10.

Parkinsonism. Amantadine's mechanism of action in parkinsonism (p. 889.1) is unclear but may be due to its antimuscarinic activity and alterations in dopamine release and reuptake. It has also been suggested that its action as a non-competitive antagonist of *N*-methyl-D-aspartate may have a beneficial effect.[1,2] It has mild antiparkinsonian activity compared with levodopa but is relatively free from adverse effects. It can improve bradykinesia as well as tremor and rigidity and is used in a similar manner to antimuscarinics mainly in the treatment of patients with early Parkinson's disease when symptoms are mild. It may also be useful for dyskinesias in more advanced disease.[3] However, few patients obtain much benefit and tolerance to its effects can occur. Moreover, two systematic reviews[4,5] concluded that there was insufficient evidence from randomised controlled studies on the safety and efficacy of amantadine in the treatment of both Parkinson's disease and levodopa-induced dyskinesias in late disease.

Licensed product information suggests that the efficacy of amantadine may be prolonged by withdrawing it for 3 to 4 weeks, continuing with existing antiparkinsonian therapy or starting low-dose levodopa treatment if clinically necessary in the meantime.

1. Laing P. Stroke treatment. *Lancet* 1991; 337: 1601.
2. Greenamyre JT, O'Brien CF. N-Methyl-D-aspartate antagonists in the treatment of Parkinson's disease. *Arch Neurol* 1991; 48: 977–81.
3. Thomas A, *et al.* Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004; 75: 141–3.
4. Crosby NJ, *et al.* Amantadine in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/02/06).
5. Crosby NJ, *et al.* Amantadine for dyskinesia in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 16/02/06).

Withdrawal syndromes. *COCAINE.* Despite some early promising results a systematic review[1] considered that there was no evidence to support the use of dopamine agonists, including amantadine, in the treatment of cocaine dependence (p. 1990.1).

1. Soares B, *et al.* Dopamine agonists for cocaine dependence. [Withdrawn]. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 23/08/10).

Adverse Effects

Most adverse effects associated with amantadine therapy appear to be dose-related and relatively mild; some resemble those of antimuscarinic drugs. They may be reversed by withdrawing therapy but many resolve despite continuation.

Livedo reticularis, sometimes associated with ankle oedema, is quite common in patients given very high doses of amantadine or with long-term therapy. CNS effects such as anxiety, inability to concentrate, dizziness, insomnia, nightmares, headache, and changes in mood may occur. Psychotic reactions, hallucinations, and confusion have been reported, especially in the elderly, patients with renal impairment or psychiatric disorders, and those also receiving antimuscarinics.

Other adverse effects reported have included orthostatic hypotension, palpitations, urinary retention, slurred speech, ataxia, lethargy, anorexia, nausea, vomiting, dry mouth, constipation, rash, diaphoresis, and blurred vision. There have been isolated reports of congestive heart failure, photosensitisation leucopenia, neutropenia, dyskinesias, oculogyric episodes, and convulsions.

Effects on the cardiovascular system. Congestive heart failure has been reported with amantadine;[1] the patient had been receiving combined treatment with amantadine, levodopa, and orphenadrine for 4 years. Others have considered that while amantadine sometimes causes ankle oedema, an association between amantadine and heart failure is not proven.[2] Livedo reticularis, a mottled blue discoloration of the skin due to prominence of the normal pattern of venous drainage, has been reported[2] to occur in about 50% of all elderly patients given amantadine 100 to 300 mg daily for 2 to 6 weeks and was associated with oedema in 5 to 10%. Both livedo and oedema have usually been confined to the legs and may result from the catecholamine-releasing action of amantadine in certain vascular beds; the oedema was unlikely to be due to heart failure. Angina, dyspnoea, pulmonary congestion, or distension of neck veins has also been reported[2] in 4 of 89 parkinsonian patients treated with amantadine; only 2 of these 4 had had ankle oedema before heart failure developed. No patient had been seen in whom heart failure seemed due directly to amantadine.

See also Overdosage, p. 892.1.

1. Vale JA, Maclean KS. Amantadine-induced heart-failure. *Lancet* 1977; i: 548.
2. Parkes JD, *et al.* Amantadine-induced heart-failure. *Lancet* 1977; i: 904.

Effects on electrolytes. For a report of a patient who developed hyponatraemia when given amantadine or levodopa, see Effects on Kidney Function under Levodopa, p. 905.2.

Effects on the eyes. Superficial punctate keratitis and corneal abrasion with loss of visual acuity was seen in both eyes of a 64-year-old man about 3 weeks after starting treatment with amantadine 100 mg daily.[1] Symptoms resolved on stopping amantadine but recurred when retreatment with amantadine was attempted. In another report,[2] a 14-year-old boy developed bilateral corneal oedema with visual loss associated with amantadine treatment. He had been taking amantadine 300 mg daily for several months with many other drugs; symptoms resolved when amantadine was stopped.

1. Nogaki H, Morimatsu M. Superficial punctate keratitis and corneal abrasion due to amantadine hydrochloride. *J Neurol* 1993; 240: 388–9.
2. Hughes B, *et al.* Reversible amantadine-induced corneal edema in an adolescent. *Cornea* 2004; 23: 823–4.

Effects on mental function. It has been suggested[1] that the ability of amantadine and memantine to cause psychotic

disturbances in patients with Parkinson's disease might be related to their action as *N*-methyl-D-aspartate antagonists.

For reference to disturbed behaviour including excessive gambling, and to daytime somnolence reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

1. Riederer P, *et al.* Pharmacotoxic psychosis after memantine in Parkinson's disease. *Lancet* 1991; 338: 1022–3.

Effects on the nervous system. Peripheral sensory motor neuropathy secondary to long-term (8 years) use of amantadine has been reported[1] in a 48-year-old woman with parkinsonism. Trophic skin ulcers, paraesthesias, and distal weakness resolved on stopping amantadine.

1. Shulman LM, *et al.* Amantadine-induced peripheral neuropathy. *Neurology* 1999; 53: 1862–5.

Overdosage. A patient with postencephalitic parkinsonism who had taken an estimated 2.8 g of amantadine hydrochloride in a suicide attempt developed acute toxic psychosis with disorientation, visual hallucinations, and aggressive behaviour.[1] Convulsions did not occur, possibly because he had been receiving phenytoin, which was continued. The patient was treated with hydration and chlorpromazine and recovered in 4 days.

A 2-year-old child who had ingested 600 mg of amantadine hydrochloride developed symptoms of acute toxicity, including agitation and dystonic posturing, despite emesis with 'syrup of ipecac'.[2] She responded immediately to physostigmine 500 micrograms intravenously, repeated after 10 minutes. Her pupils remained moderately dilated until about 20 hours after the ingestion; thereafter she made a full recovery.

Cardiac arrest developed 4 hours after a 37-year-old woman ingested 2.5 g of amantadine hydrochloride and was treated successfully.[3] However, ventricular arrhythmias, including torsade de pointes, continued over the ensuing 48 hours and may have been exacerbated by use of isoprenaline and dopamine. The patient was subsequently stabilised with lidocaine by intravenous infusion, but died of respiratory failure 10 days after admission.

1. Fahn S, *et al.* Acute toxic psychosis from suicidal overdosage of amantadine. *Arch Neurol* 1971; 25: 45–8.
2. Berkowitz CD. Treatment of acute amantadine toxicity with physostigmine. *J Pediatr* 1979; 95: 144–5.
3. Sartori M, *et al.* Torsade de pointe: malignant cardiac arrhythmia induced by amantadine poisoning. *Am J Med* 1984; 77: 388–91.

Precautions

Amantadine is usually contra-indicated in severe renal disease and in patients with a history of epilepsy or other seizure disorders, or gastric ulceration. It should also not be given to patients with untreated angle-closure glaucoma. Amantadine should be used with caution in patients with cardiovascular or liver disease, renal impairment, recurrent eczema, or psychiatric disorders. Suicide attempts, in some cases fatal, and suicidal ideation have been reported in patients taking amantadine. Care should be taken in all elderly patients, who may be more sensitive to antimuscarinic effects, and in whom renal clearance is likely to be reduced.

In common with other drugs having antimuscarinic properties amantadine may cause blurred vision or impair alertness; patients so affected should not drive or operate machinery.

Treatment with amantadine should not be stopped abruptly in parkinsonian patients since a sudden marked clinical deterioration may occur. There have been isolated reports of a neuroleptic malignant-like syndrome associated with abrupt withdrawal of amantadine, especially in patients also receiving antipsychotics.

Antiviral resistance. See Influenza under Uses and Administration, p. 891.2.

Breast feeding. Amantadine is distributed into breast milk and licensed product information states that adverse effects have occurred in breast-fed infants of mothers taking amantadine.

Pregnancy. Amantadine should not be used during pregnancy; embryotoxicity and teratogenicity have been reported in *rats* given high doses.[1]

A complex cardiovascular lesion occurred in an infant whose mother had taken amantadine hydrochloride 100 mg daily during the first 3 months of pregnancy.[1] In another case, tetralogy of Fallot and limb deformities were seen in the neonate of a mother who was given amantadine hydrochloride 100 mg daily for 7 days during the 4th and 6th weeks of gestation.[2] However, a report of the use of amantadine during 2 separate pregnancies by a woman with multiple sclerosis noted no abnormalities in either infant.[3]

1. Nora JJ, *et al.* Cardiovascular maldevelopment associated with maternal exposure to amantadine. *Lancet* 1975; II: 607.
2. Pandit PB, *et al.* Tibial hemimelia and tetralogy of Fallot associated with first trimester exposure to amantadine. *Reprod Toxicol* 1994; 8: 89–92.
3. Levy M, *et al.* Fetal outcome following intrauterine amantadine exposure. *Reprod Toxicol* 1991; 5: 79–81.

Renal impairment. Evidence of extremely limited excretion of amantadine was found in 12 patients who were either anephric or had negligible renal function after a single 100-mg dose of amantadine hydrochloride.[1] Only small amounts were removed by dialysis. It was suggested that amantadine should be given with caution to patients requiring maintenance haemodialysis; a single dose may provide adequate plasma concentrations for many days.[1]

Dosage regimens based on creatinine clearance[2] or fixed doses at extended intervals[3] have been published. However, both regimens have been criticised and a conservative approach to amantadine dosage in these patients recommended[4] (for the regimens in licensed product information, see Administration in Renal Impairment, p. 891.1). The need for caution in using amantadine in patients with renal impairment is highlighted by a report of a patient with end-stage renal disease who progressed from delirium to coma after receiving amantadine 100 mg twice daily for 3 days.[5]

1. Soung L-S, *et al.* Amantadine hydrochloride pharmacokinetics in hemodialysis patients. *Ann Intern Med* 1980; 93: 46–9.
2. Horadam VW, *et al.* Pharmacokinetics of amantadine hydrochloride in subjects with normal and impaired renal function. *Ann Intern Med* 1981; 94: 454–8.
3. Wu MJ, *et al.* Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. *Clin Nephrol* 1982; 17: 19–23.
4. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988; 14: 35–51.
5. Macchio GJ, *et al.* Amantadine-induced coma. *Arch Phys Med Rehabil* 1993; 74: 1119–20.

Withdrawal. Neuroleptic malignant syndrome occurred in a patient being treated for heat stroke when all his medication, including antipsychotics and amantadine, was withdrawn.[1] It is suggested that dopamine agonists should not be stopped in patients with hyperpyrexia at risk from this syndrome. In another report,[2] a 14-year-old boy being treated with amantadine for influenza A encephalopathy developed neuroleptic malignant syndrome when the drug was stopped after 5 days; the patient improved when amantadine treatment was resumed. The authors recommended a gradual reduction in dosage when stopping amantadine therapy.

Acute delirium developed in 3 elderly patients with Parkinson's disease after gradual withdrawal of long-term amantadine therapy;[3] symptoms resolved when amantadine was restarted.

1. Simpson DM, Davis GC. Case report of neuroleptic malignant syndrome associated with withdrawal from amantadine. *Am J Psychiatry* 1984; 141: 796–7.
2. Ito T, *et al.* Neuroleptic malignant syndrome following withdrawal of amantadine in a patient with influenza A encephalopathy. *Eur J Pediatr* 2001; 160: 401.
3. Factor SA, *et al.* Acute delirium after withdrawal of amantadine in Parkinson's disease. *Neurology* 1998; 50: 1456–8.

Interactions

Amantadine may enhance the adverse effects of antimuscarinics and the dose of these drugs should be reduced when used with amantadine; adverse effects of levodopa may also be exacerbated.

Licensed product information states that amantadine should be used with caution in patients receiving drugs that affect the CNS. The rate of excretion of amantadine may be reduced by drugs that raise urinary pH.

Antiarrhythmics. *Quinine* and *quinidine* have been reported to reduce the renal clearance of amantadine in healthy male, but not female, subjects.[1] Patients taking these drugs together should be observed for signs of amantadine toxicity.

1. Gaudry SE, *et al.* Gender and age as factors in the inhibition of renal clearance of amantadine by quinine and quinidine. *Clin Pharmacol Ther* 1993; 54: 23–7.

Antimalarials. For the possible effects of the use of *quinine* and *quinidine* with amantadine, see Antiarrhythmics, above.

Diuretics. A patient with Parkinson's disease, previously stabilised on amantadine hydrochloride 300 mg daily, developed symptoms of amantadine toxicity, including ataxia, myoclonus, and confusion, 7 days after starting treatment with a preparation containing *triamterene* and *hydrochlorothiazide* (*Dyazide*).[1] It was postulated that the effect was due to reduction of the tubular secretion of amantadine.

1. Wilson TW, Rajput AH. Amantadine-Dyazide interaction. *Can Med Assoc J* 1983; 129: 974–5.

MAOIs. Hypertension occurred about 48 hours after starting treatment with *phenelzine sulfate* in a patient already receiving amantadine.[1]

1. Jack RA, Daniel DG. Possible interaction between phenelzine and amantadine. *Arch Gen Psychiatry* 1984; 41: 726.

Pharmacokinetics

Amantadine hydrochloride is well absorbed from the gastrointestinal tract; peak concentrations in the plasma appear within about 4 hours after oral doses. Plasma protein binding is reported to be about 67%, with a substantial amount bound to erythrocytes; the concentration is about 2.7 times higher in erythrocytes than in plasma. It is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion although small amounts of an acetylated metabolite have also been detected in urine; the plasma elimination half-life is reported to be about 15 hours in patients with normal renal function but is significantly prolonged in the elderly and in patients with renal impairment. The rate of elimination may be increased by acidification of the urine. Amantadine crosses the placenta and the blood-brain barrier. It is also distributed into breast milk.

References.

1. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988; 14: 35–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actison; Ampakine; Virosol; *Austral.*: Symmetrel; *Austria*: Hofcomant; PK-Merz; *Belg.*: Amantan†; *Braz.*: Mantidan; *Chile*: Prayanol; *Cz.*: Amantadol†; PK-Merz; Viregyt-K; *Fin.*: Atarin†; *Fr.*: Mantadix; *Ger.*: Amantagamma†; Amixx; PK-Merz; tregor; *Gr.*: Hofcomant; PK-Merz; Symmetrel; *Hong Kong*: PK-Merz; Topharmin†; *Hung.*: PK-Merz; Viregyt; *India*: Amantrel; *Irl.*: Symmetrel†; *Israel*: Paritrel†; PK-Merz; *Ital.*: Mantadan; *Malaysia*: PK-Merz; *Mex.*: Kinestrel; PK-Merz; *Neth.*: Symmetrel; *NZ*: Symmetrel; *Philipp.*: PK-Merz; *Pol.*: Amantix; Viregyt K; *Port.*: Parkadina; PK-Merz; *S.Afr.*: Symadin; Symmetrel; *Singapore*: Symmetrel; *Switz.*: PK-Merz; Symmetrel; *Turk.*: PK-Merz; *UK*: Lysovir; Symmetrel; *Ukr.*: Neomidantan (Неомидантан); PK-Merz (ПК-Мерц); *USA*: Symmetrel.

Multi-ingredient Preparations. *China*: Bi Li Kang (必利康); Ke Li Ke (可立克); Qing Lang (清朗); Tai Ke (泰克); You Ka Dan (优卡丹); *Mex.*: Antiflu-Des; Fluviatol; Fluviatol; Rosel.

Pharmacopoeial Preparations

BP 2014: Amantadine Capsules; Amantadine Oral Solution;
USP 36: Amantadine Hydrochloride Capsules; Amantadine Hydrochloride Syrup.

Apomorphine Hydrochloride *(BANM)*

Apomorfiinihydrokloridi; Apomorfin Hidroklorür; Apomorfina, hidrocloruro de; Apomorfin-hidroklorid; Apomorfinhydrochlorid hemihydrát; Apomorfinhydroklorid; Apomorfino hidrochloridas; Apomorfiny chlorowodorek; Apomorphine, chlorhydrate d'; Apomorphinhydrochlorid; Apomorphini hydrochloridum; Apomorphini Hydrochloridum Hemihydricum; Апоморфина Гидрохлорид.

6aβ-Aporphine-10,11-diol hydrochloride hemihydrate; (*R*)-10,11-Dihydroxy-6a-aporphine hydrochloride hemihydrate; (6a*R*)-5,6,6a,7-Tetrahydro-6-methyl-4*H*-dibenzo[*de,g*]quinoline-10,11-diol hydrochloride hemihydrate.

$C_{17}H_{17}NO_2,HCl,½H_2O$=312.8

CAS — 58-00-4 (apomorphine); 314-19-2 (anhydrous apomorphine hydrochloride); 41372-20-7 (apomorphine hydrochloride, hemihydrate).

ATC — G04BE07; N04BC07.

ATC Vet — QG04BE07; QN04BC07.

UNII — F39049Y068 (apomorphine hydrochloride hemihydrate); 9K13MD7A0D (anhydrous apomorphine hydrochloride).

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

Br. also includes a form for homoeopathic preparations.

Ph. Eur. 8: (Apomorphine Hydrochloride Hemihydrate). White or slightly yellowish-brown or green-tinged greyish crystals or crystalline powder, the green tinge becoming more pronounced on exposure to air and light. Sparingly soluble in water and in alcohol; practically insoluble in toluene. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

USP 36: (Apomorphine Hydrochloride). Odourless, minute white or greyish-white, glistening crystals or white powder. It gradually acquires a green colour on exposure to light and air. Soluble 1 in 50 of water and 1 in 20 of water at 80 degrees; soluble 1 in 50 of alcohol; very slightly soluble in ether and in chloroform. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

BP 2014: (Apomorphine Hydrochloride for Homoeopathic Preparations; Apomorphinum Muriaticum for Homoeopathic Preparations).

Stability. Aqueous solutions of apomorphine hydrochloride decompose on storage and should not be used if they turn green or brown or contain a precipitate.

Uses and Administration

Apomorphine is a morphine derivative with structural similarities to dopamine. It is a potent dopamine D_1- and D_2-receptor agonist used in the management of parkinsonism (below), especially in the control of the 'on-off' effect. It has also been used in the management of erectile dysfunction. Apomorphine is given as the hydrochloride and doses are expressed in terms of this salt. The regimen for parkinsonism given below applies to the UK preparation and doses are given subcutaneously; a similar preparation is available in the USA although the licensed maximum single and daily doses are less than those in the UK.

The optimal dose of apomorphine in the management of 'off' periods in parkinsonism should be established individually under specialist care. At least 2 days of pretreatment with the antiemetic domperidone is advised before starting apomorphine. After withholding antiparkinsonian therapy overnight to provoke an 'off' period, a test dose of 1 mg is given initially, followed by a second dose of 2 mg after 30 minutes, if necessary. Subsequent incremental increases should then be given at intervals of at least 40 minutes, as necessary, to determine the lowest dose producing a satisfactory motor response. Once the patient's normal antiparkinsonian therapy is re-established, the effective dose of apomorphine hydrochloride is given at the first signs of an 'off' period.

The dose and frequency are further adjusted according to response; patients typically require 3 to 30 mg daily in divided doses but individual injections should not be greater than 10 mg. Patients who require more than 10 injections daily or those whose overall control of symptoms remains unsatisfactory with intermittent injections may benefit from continuous subcutaneous infusion. The infusion is started at a rate of 1 mg/hour and this may be increased in steps of up to 500 micrograms/hour at intervals of not less than 4 hours to a maximum rate of 4 mg/hour. It is advised that infusions should only be given during waking hours and that the infusion site should be changed every 12 hours; 24-hour infusions are not advised unless there are severe night-time symptoms. Patients usually need to supplement the infusion with intermittent bolus injections but the recommended maximum total daily dose given by infusion and/or injection is 100 mg.

Apomorphine stimulates the chemoreceptor trigger zone in the brain and can produce emesis within a few minutes of a dose. However, the use of apomorphine for the induction of emesis in poisoning is considered dangerous owing to the risk of inducing protracted vomiting and shock, and is not recommended.

Homoeopathy

Apomorphine has been used in homoeopathic medicines.

Erectile dysfunction. Apomorphine is among many drugs that have been used in the management of erectile dysfunction[1-5] (p. 2348.2) with some beneficial results. It is usually given sublingually although it has also been given subcutaneously.[1] Inhaled apomorphine is also under investigation.[6]

1. Segraves RT, *et al.* Effect of apomorphine on penile tumescence in men with psychogenic impotence. *J Urol (Baltimore)* 1991; 145: 1174–5.
2. Heaton JPW, *et al.* Recovery of erectile function by the oral administration of apomorphine. *Urology* 1995; 45: 200–6.
3. Dula E, *et al.* Efficacy and safety of fixed-dose and dose-optimization regimens of sublingual apomorphine versus placebo in men with erectile dysfunction. *Urology* 2000; 56: 130–5.
4. Martinez R, *et al.* Clinical experience with apomorphine hydrochloride: the first 107 patients. *J Urol (Baltimore)* 2003; 170: 2352–5.
5. Gontero P, *et al.* Clinical efficacy of apomorphine SL in erectile dysfunction of diabetic men. *Int J Impot Res* 2005; 17: 80–5.
6. Riley A, *et al.* Inhalation device allows novel administration of apomorphine in men with erectile dysfunction: efficacy and safety findings. *J Sex Med* 2010; 7: 1508–17.

Parkinsonism. *DIAGNOSIS.* Test doses of subcutaneous apomorphine have been used in the differential diagnosis of parkinsonian syndromes,[1-4] to distinguish forms responsive to dopaminergics from other parkinsonian syndromes such as Wilson's disease, corticobasal degeneration, and diffuse Lewy-body dementia. Oral challenge with levodopa is still the best test of dopaminergic responsiveness[5,6] but apomorphine has proved of value in re-assessing patients who have become less responsive to levodopa.[1,4]

1. Barker R, *et al.* Subcutaneous apomorphine as a diagnostic test for dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1989; i: 675.
2. Oertel WH, *et al.* Apomorphine test for dopaminergic responsiveness. *Lancet* 1989; i: 1262–3.
3. Frankel JP, *et al.* Use of apomorphine to test for dopamine responsiveness in Wilson's disease. *Lancet* 1989; ii: 801–2.
4. Hughes AJ, *et al.* Apomorphine test to predict dopaminergic responsiveness in parkinsonian syndromes. *Lancet* 1990; 336: 32–4.
5. Steiger MJ, Quinn NP. Levodopa challenge test in Parkinson's disease. *Lancet* 1992; 339: 751–2.
6. Müller T, *et al.* Repeated rating improves value of diagnostic dopaminergic challenge tests in Parkinson's disease. *J Neural Transm* 2003; 110: 603–9.

TREATMENT. Although apomorphine has produced benefit in Parkinson's disease (p. 889.1) when given orally, the high doses required to overcome extensive first-pass hepatic metabolism (up to 1.4 g daily in one study[1]), were associated with uraemia. The use of apomorphine in Parkinson's disease has therefore been limited by the need for parenteral dosage. The current main use of apomorphine in Parkinson's disease is for the stabilisation of patients with 'on-off' fluctuations unresponsive to other dopamine agonists. It is usually given subcutaneously either by injection or infusion but a review[2] of the use of apomorphine in Parkinson's disease also discussed studies of rectal, sublingual, and intranasal use. Inhaled apomorphine is also under investigation.

1. Cotzias GC, *et al.* Treatment of Parkinson's disease with apomorphines. *N Engl J Med* 1976; 294: 567–72.
2. Koller W, Stacy M. Other formulations and future considerations for apomorphine for subcutaneous injection therapy. *Neurology* 2004; 62 (suppl 4): S22–S26.

Adverse Effects

Treatment of parkinsonism. Apomorphine usually produces nausea and vomiting when given in therapeutic doses but these effects can be controlled by treatment with domperidone or trimethobenzamide. Transient sedation can be common during the first few weeks of treatment. Increased salivation and perspiration have also been reported. Apomorphine can produce neuropsychiatric disturbances including increasing cognitive impairment, personality changes, confusion, and hallucinations. Signs of CNS stimulation including euphoria, lightheadedness, restlessness, tremor, tachycardia, and tachypnoea occur less frequently. Apomorphine may induce dyskinesias during 'on' periods in patients with parkinsonism and these may be severe enough to require stopping therapy; postural instability and falls may also be a problem. Transient orthostatic hypotension may also occur infrequently. Eosinophilia has occurred rarely. The use of apomorphine with levodopa may cause haemolytic anaemia and treatment may need to be stopped if this cannot be satisfactorily controlled through dosage adjustment. Induration, nodule formation, and panniculitis, sometimes leading to ulceration, often develops at the site of subcutaneous injection.

Management of erectile dysfunction. The most common adverse effects have been nausea, headache, and dizziness. Other effects reported include yawning, rhinitis, pharyngitis, somnolence, infection, pain, increased cough, flushing, taste disturbances, and sweating. Fainting and syncope (vasovagal syndrome) have also occurred.

Overdosage with apomorphine can produce persistent vomiting, respiratory depression, bradycardia, hypotension, and coma; death may occur.

Akinesia. A 60-year-old man who was being investigated for parkinsonian symptoms became totally immobile and mute 15 minutes after receiving apomorphine 4 mg subcutaneously.[1] He remained conscious but was drowsy and sweating. Similar profound akinesia occurred on rechallenge with 2- and 6-mg doses. A diagnosis of probable nigrostriatal degeneration was made as the patient had previously shown no improvement with levodopa, but the mechanism of the idiosyncratic reaction to apomorphine was unclear.

1. Jenkins JR, Pearce JMS. Paradoxical akinetic response to apomorphine in parkinsonism. *J Neurol Neurosurg Psychiatry* 1992; 55: 414–15.

Effects on the heart. A 67-year-old man developed palpitations with cold perspiration and chest pain, in addition to asthenia, salivation, nausea and vomiting, 5 minutes after receiving 3 mg apomorphine subcutaneously. An ECG showed atrial fibrillation with a ventricular frequency of 140 beats/minute.[1]

1. Stocchi F, *et al.* Transient atrial fibrillation after subcutaneous apomorphine bolus. *Mov Disord* 1996; 11: 584–5.

Effects on mental function. Severe confusion, hallucinations, and acute psychosis were reported in 4 of 6 parkinsonian patients given subcutaneous apomorphine.[1] Three of the 4 had previously had mental disturbances while receiving lisuride. However, other studies failed to note effects on mental function in parkinsonian patients given apomorphine[2,3] and it has been suggested that the risk of psychosis in patients with no history of confusion or hallucinations is low.[3] UK licensed product information notes that apomorphine has been reported to exacerbate neuropsychiatric disturbances in patients with parkinsonism.

For reference to disturbed behaviour including excessive gambling, and to daytime somnolence reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

1. Ruggieri S, *et al.* Side-effects of subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; i: 566.
2. Stibe CMH, *et al.* Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988; i: 403–6.
3. Poewe W, *et al.* Side-effects of subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; i: 1084–5.

Hypersensitivity. Allergic reactions including contact dermatitis, severe rhinitis, and respiratory distress have been reported in 2 workers who came into contact with apomorphine powder.[1] Contact allergy has also been reported in a patient who developed a swollen nose and lips after intranasal use of apomorphine.[2] Skin testing in all these cases[1,2] gave a positive reaction to apomorphine. Biopsy of subcutaneous nodules, which develop at the site of injection in most patients using apomorphine subcutaneously, has not been able to clarify what type of reaction was responsible for the development of panniculitis.[3] Although the nodules may slowly resolve the sites are often unsuitable for reuse as absorption from them is unpredictable; concern has been expressed that this may limit long-term use of apomorphine.[3]

1. Dahlquist I. Allergic reactions to apomorphine. *Contact Dermatitis* 1977; 3: 349–50.
2. van Laar T, *et al.* Nasolabiale allergische reactie op intranasale toediening van apomorfine bij de ziekte van Parkinson. *Ned Tijdschr Geneeskd* 1992; 136 (suppl 47): 26–7.
3. Acland KM, *et al.* Panniculitis in association with apomorphine infusion. *Br J Dermatol* 1998; 138: 480–2.

Oedema. Severe reversible oedema of the lower limbs developed in a patient receiving subcutaneous apomorphine.[1] Oedema recurred when apomorphine was reintroduced, but to a lesser extent.

1. Vermersch P. Severe oedema after subcutaneous apomorphine in Parkinson's disease. *Lancet* 1989; ii: 802.

Stomatitis. Stomatitis, severe enough to warrant stopping treatment, occurred in 4 of 8 patients after 2 to 6 months of therapy with sublingual apomorphine.[1]

1. Montastruc JL, *et al.* Sublingual apomorphine in Parkinson's disease: a clinical and pharmacokinetic study. *Clin Neuropharmacol* 1991; 14: 432–7.

Treatment of Adverse Effects

In the UK, domperidone is usually given to control nausea and vomiting when apomorphine is used in the management of Parkinson's disease; pretreatment with domperidone for at least 2 days is advised before starting treatment with apomorphine. Usually domperidone can be withdrawn gradually over several weeks or longer although some patients may need to continue treatment indefinitely. In the USA, trimethobenzamide hydrochloride is used similarly, beginning 3 days before starting apomorphine treatment.

In overdosage an opioid antagonist such as naloxone has been given to treat excessive vomiting, and CNS and respiratory depression.

References.

1. Bonuccelli U, *et al.* Naloxone partly counteracts apomorphine side effects. *Clin Neuropharmacol* 1991; 14: 442–9.

Precautions

Apomorphine should not be given to patients with respiratory or CNS depression, hypersensitivity to opioids, neuropsychiatric problems, or dementia. It should be used with caution in patients prone to nausea and vomiting or when vomiting is likely to pose a risk. Apomorphine should also be used with care in patients with pulmonary, cardiovascular, or endocrine disease or with renal or hepatic impairment. Extra care is needed when starting treatment in elderly or debilitated patients and in those with a history of orthostatic hypotension. Patients who suffer dizziness, lightheadedness, or syncope should not drive or operate machinery.

Treatment of parkinsonism. Apomorphine is not suitable for use in patients who have an 'on' response to levodopa marred by severe dyskinesia, hypotonia, or psychiatric effects; it should also not be used in those with hepatic impairment. Periodic monitoring of hepatic, renal, haematopoietic, and cardiovascular function has been advised and the *BNF* recommends that patients receiving apomorphine with levodopa should be screened for haemolytic anaemia and thrombocytopenia on starting treatment and then every 6 months. Patients who develop anaemia, or those who have continuing confusion or hallucinations during treatment with apomorphine require observation and dosage adjustment under specialist supervision; treatment may need to be stopped. Excessive daytime sleepiness and sudden onset of sleep may also occur with apomorphine and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Local subcutaneous reactions can sometimes be reduced by using sodium chloride 0.9% to dilute injection solutions, by rotating injection sites, and possibly by use of ultrasound in areas of nodularity and induration.

Management of erectile dysfunction. UK licensed product information has warned that drugs for erectile dysfunction should be used with caution in patients with anatomical penile deformity.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies apomorphine as probably not porphyrinogenic when given sublingually; it may be used as a drug of first choice and no precautions are needed.[1] No classification is offered when used in injectable form.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 30/09/11)

Interactions

Apomorphine should be used with caution in patients receiving antihypertensives or organic nitrates as it may potentiate their hypotensive effects. Enhanced hypotensive effects may also occur when alcohol is given with apomorphine. The therapeutic effects of apomorphine may be antagonised by antipsychotics and other drugs that act as CNS dopamine inhibitors. The effect of apomorphine is possibly enhanced by entacapone and memantine.

Antiemetics. *Domperidone* (in the UK) and *trimethobenzamide* (in the USA) are used with apomorphine to control nausea and vomiting when it is prescribed for the management of parkinsonism. However, whether other antiemetics may safely be used is less clear. US licensed product information contra-indicates the use of *ondansetron* and related 5-HT_3 antagonists with apomorphine, on the grounds that profound hypotension and loss of consciousness have been reported in patients given this combination. However, UK licensed product information makes no mention of such a contra-indication, and licensed information for lower-dose products used in the management of erectile dysfunction notes that on the basis of interaction studies, ondansetron hydrochloride or *prochlorperazine maleate* may safely be given to patients receiving apomorphine for this indication.

Pharmacokinetics

Apomorphine is well absorbed after subcutaneous injection but undergoes extensive first-pass hepatic metabolism when given by mouth and oral bioavailability is low. However, it is readily absorbed after sublingual doses and peak plasma concentrations occur in about 40 to 60 minutes; bioavailability is reported to be about 17 to 18% compared with subcutaneous injection. Apomorphine is about 90% bound to plasma proteins, mainly to albumin.

Apomorphine is extensively metabolised in the liver, mainly by conjugation with glucuronic acid or sulfate; the major metabolite is apomorphine sulfate. It is also demethylated to produce norapomorphine. Most of a dose is excreted in urine, mainly as metabolites.

References.

1. Neef C, van Laar T. Pharmacokinetic-pharmacodynamic relationships of apomorphine in patients with Parkinson's disease. *Clin Pharmacokinet* 1999; 37: 257–71.
2. Argiolas A, Hedlund H. The pharmacology and clinical pharmacokinetics of apomorphine SL. *BJU Int* 2001; 88 (suppl 3): 18–21.
3. LeWitt PA. Subcutaneously administered apomorphine: pharmacokinetics and metabolism. *Neurology* 2004; 62 (suppl 4): S8–S11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Apokinon; *Austral.*: Apomine; *Austria*: APO-go; *Braz.*: Uprima; *Chile*: APO-go; Noc; *China*: Li Ke Ji (丽科吉); *Cz.*: APO-go; *Denm.*: APO-go; *Fin.*: APO-go; *Fr.*: Apokinon; *Ger.*: APO-go; *Gr.*: APO-go; *Hong Kong*: APO-go; *Irl.*: APO-go; *Israel*: APO-go; *Ital.*: Apofin; *Jpn*: Apokyn; Ixense†; *Mex.*: Taluvian; *Neth.*: APO-go; Dacepton; *Norw.*: Britaject; *NZ*: APO-go†; Apomine; *Port.*: APO-go; *Spain*: APO-go; *Swed.*: APO-go; *Thai.*: APO-go; Ixense; Uprima; *Turk.*: APO-go; *UK*: APO-go; *USA*: Apokyn.

Homoeopathic Preparations. *Austral.*: Travellers Relief; *Austria*: Vomitusheel; *Fr.*: Apomorphinum Complexe No 97†; Bilirum Complexe No 113; *Ger.*: Homvio-Em; Vomistop; *Switz.*: Nelsons Travella†; Vomitusheel; *UK*: Travella.

Pharmacopoeial Preparations

USP 36: Apomorphine Hydrochloride Tablets.

Benserazide *(BAN, USAN, rINN)*

Benseratsidi; Benserazid; Benserazida; Bensérazide; Benserazidum; Ro-4-4602; Бенсеразид.

DL-Serine 2-(2,3,4-trihydroxybenzyl)hydrazide; 2-Amino-3-hydroxy-2'-(2,3,4-trihydroxybenzyl)propionohydrazide.

$C_{10}H_{15}N_3O_5$=257.2

CAS — 322-35-0.

UNII — 762OS3ZEJU.

Benserazide Hydrochloride *(BANM, rINNM)*

Benseratsidihydrokloridi; Benserazida, hidrocloruro de; Bensérazide, chlorhydrate de; Benserazid-hydrochlorid; Benserazidhydrochlorid; Benserazidi Hydrochloridum; Benserazido hidrochloridas; Benszerazid-hidroklorid; Hidrocloruro de benserazida; Seraziđe Hydrochloride; Бенсеразида Гидрохлорид.

$C_{10}H_{15}N_3O_5$,HCl=293.7

CAS — 14919-77-8; 14046-64-1.

UNII — 866E5RK36Q.

NOTE. Compounded preparations of benserazide hydrochloride may be represented by the following names:

- Co-beneldopa *(BAN)*—benserazide 1 part and levodopa 4 parts (w/w).

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

Ph. Eur. 8: (Benserazide Hydrochloride). A white or yellowish-white or orange-white crystalline powder. It shows polymorphism. Freely soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 4.0 to 5.0. Protect from light.

Solubility. Benserazide is unstable in a neutral, alkaline, or strongly acidic medium.[1]

1. Schwartz DE, Brandt R. Pharmacokinetic and metabolic studies of the decarboxylase inhibitor benserazide in animals and man. *Arzneimittelforschung* 1978; 28: 302–7.

Uses and Administration

Benserazide hydrochloride is a peripheral dopa-decarboxylase inhibitor with actions similar to those of carbidopa (p. 900.3) and is used similarly as an adjunct to levodopa in the treatment of parkinsonism (p. 889.1). For details of dosage, see Levodopa, p. 902.3.

References.

1. Dingemanse J, *et al.* Pharmacodynamics of benserazide assessed by its effects on endogenous and exogenous levodopa pharmacokinetics. *Br J Clin Pharmacol* 1997; 44: 41–8.

Adverse Effects and Precautions

Early reports[1] noted developmental abnormalities of the *rat* skeleton, but others found no evidence of any disorder involving bone metabolism in man.[2] Nevertheless, licensed product information recommends that benserazide should not be given to patients under 25 years of age, nor to pregnant women or to women of child-bearing potential in the absence of adequate contraception.

1. Theiss E, Schärer K. Toxicity of L-dopa and a decarboxylase inhibitor in animal experiments. In: de Ajuriaguerra J, Gauthier G, eds. *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Geneva: Georg, 1971: 497–504.
2. Ziegler WH, *et al.* Toxicity of L-dopa and a dopa decarboxylase inhibitor in humans. In: de Ajuriaguerra J, Gauthier G, eds. *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Geneva: Georg, 1971: 505–16.

Pharmacokinetics

Pharmacokinetic and metabolic studies[1,2] in *animals* and man have shown that, after oral doses in parkinsonian patients, benserazide was rapidly absorbed to the extent of about 58%; giving it with levodopa tended to increase this slightly. Benserazide was rapidly excreted in the urine in the form of metabolites, mostly within the first 6 hours; 85% of urinary excretion had occurred within 12 hours. It is mainly metabolised in the gut and appears to protect levodopa against decarboxylation primarily in the gut, but also in the rest of the organism, mainly by way of its metabolite trihydroxybenzylhydrazine. Benserazide did not cross the blood-brain barrier in *rats*.

1. Schwartz DE, *et al.* Pharmacokinetics of the decarboxylase benserazide in man: its tissue distribution in the rat. *Eur J Clin Pharmacol* 1974; 7: 39–45.
2. Schwartz DE, Brandt R. Pharmacokinetic and metabolic studies of the decarboxylase inhibitor benserazide in animals and man. *Arzneimittelforschung* 1978; 28: 302–7.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Multi-ingredient Preparations. *Arg.*: Madopar; *Austral.*: Madopar; *Austria*: Madopar; Restex; *Belg.*: Prolopa; *Braz.*: Prolopa; *Canad.*: Prolopa; *Chile*: Melitase; Prolopa; *Cz.*: Madopar; *Denm.*: Madopar; *Fin.*: Madopar; *Fr.*: Modopar; *Ger.*: Levodopa comp B†; Levopar†; Madopar; PK-Levo†; *Gr.*: Madopar; *Hong Kong*: Madopar; *Hung.*: Madopar; *India*: Benspar; Madopar-F; *Indon.*: Leparson; Levazide; Levopar; Madopar; Pardoz; *Irl.*: Madopar; *Israel*: Levopar Plus; *Ital.*: Madopar; *Malaysia*: Madopar; *Mex.*: Madopar; *Neth.*: Madopar; Modopar†; *Norw.*: Madopar; *NZ*: Madopar; *Philipp.*: Madopar; *Pol.*: Madopar; *Port.*: Madopar; *Rus.*: Madopar (Мадопар); *S.Afr.*: Madopar; *Singapore*: Madopar; *Spain*: Madopar; *Swed.*: Madopark; *Switz.*: Madopar; *Thai.*: Madopar; Udopar-250; Vopar; *Turk.*: Madopar; *UK*: Madopar; *Ukr.*: Madopar (Мадопар); *Venez.*: Madopar.

Pharmacopoeial Preparations

BP 2014: Co-beneldopa Capsules; Dispersible Co-beneldopa Tablets; Prolonged-release Co-beneldopa Capsules.

Benzatropine Mesilate *(BANM, rINNM)*

Benzatropina, mesilato de; Benzatropine, Mésilate de; Benzatropine Methanesulfonate; Benzatropini Mesilas; Benztropine Mesylate; Mesilato de benzatropina; Бензатропина Мезилат.

(1*R*,3*r*,5*S*)-3-Benzhydryloxytropane methanesulphonate.

$C_{21}H_{25}NO,CH_4O_3S$=403.5

CAS — 86-13-5 (benzatropine); 132-17-2 (benzatropine mesilate).

ATC — N04AC01.

ATC Vet — QN04AC01.

UNII — WMJ8TL7510.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Benzatropine Mesilate). A white, odourless o almost odourless, crystalline powder. Very soluble in water freely soluble in alcohol; practically insoluble in ether.

USP 36: (Benztropine Mesylate). A white, slightly hygroscopic, crystalline powder. Very soluble in water freely soluble in alcohol; very slightly soluble in ether. Store in airtight containers.

Uses and Administration

Benzatropine mesilate is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3); it also has antihistaminic properties.

Benzatropine is used for the symptomatic treatment o parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias.

Benzatropine mesilate is given orally or, if necessary, by intramuscular or intravenous injection.

The usual oral daily dose of benzatropine mesilate in **parkinsonism** is 1 to 2 mg, with a range of 0.5 to 6 mg. In arteriosclerotic and idiopathic parkinsonism the usual initial daily dose is 0.5 to 1 mg at bedtime, although some patients may require an initial daily dose of 4 to 6 mg. Patients with post-encephalitic parkinsonism often tolerate an initial daily dose of 2 mg, given in one or more doses, although highly sensitive patients may initially be given 500 micrograms at bedtime. The actions of benzatropine are cumulative, and may not be evident for several days after beginning therapy. Doses may be gradually increased by 500 micrograms every 5 to 6 days to a maximum of 6 mg daily if necessary. Maintenance therapy may be given as a single daily dose at bedtime or in divided doses 2 to 4 times daily. Similar doses may also be given intramuscularly, if appropriate.

In the management of **drug-induced extrapyramidal symptoms** doses of 1 to 4 mg once or twice daily have been given orally or parenterally. Therapy should be stopped after 1 to 2 weeks to assess whether it is still necessary.

In an emergency such as **acute dystonia**, benzatropine mesilate may be injected intramuscularly or intravenously in a dose of 1 to 2 mg; intramuscular injection is reported to produce an effect as quickly as intravenous dosage so the latter is rarely necessary.

Benzatropine has also been given as the hydrochloride.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1. Drowsiness may be severe in some patients and patients so affected should not drive or operate machinery. Mental disturbances and excitement may occur with large doses or in susceptible patients.

Abuse. For mention of abuse of benzatropine see under Trihexyphenidyl Hydrochloride, p. 918.1.

Effects on the heart. Paradoxical sinus bradycardia in a patient with depression and psychotic symptoms was attributed to benzatropine since it persisted despite modification to other treatment and resolved only when benzatropine was withdrawn.[1]

1. Voinov H, *et al.* Sinus bradycardia related to the use of benztropine mesylate. *Am J Psychiatry* 1992; 149: 711.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies benztropine 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 30/09/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Antidepressants. A report[1] of 5 patients who developed delirium while taking an antipsychotic, an *SSRI*, and benzatropine suggested that there might be an interaction between SSRIs and benzatropine.

1. Roth A, *et al.* Delirium associated with the combination of a neuroleptic, an SSRI, and benztropine. *J Clin Psychiatry* 1994; 55: 492–5.

Antipsychotics. Fatal heat stroke after exposure to an ambient temperature of over 29 degrees has been reported[1,2] in patients receiving benzatropine with antipsychotics. Paralytic ileus, sometimes fatal, has also been seen in patients taking benzatropine with antipsychotics.[3]

1. Stadnyk AN, Glezos JD. Drug-induced heat stroke. *Can Med Assoc J* 1983; **128**: 957–9.
2. Tyndel F, Labonté R. Drug-facilitated heat stroke. *Can Med Assoc J* 1983; **129**: 680.
3. Wade LC, Ellenor GL. Combination mesoridazine- and benztropine mesylate-induced paralytic ileus: two case reports. *Drug Intell Clin Pharm* 1980; **14**: 17–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Benztrop; Cogentin; ***Austria***: Cogentin†; ***Cz.***: Apo-Benztropine†; ***Hong Kong***: Cogentin; ***NZ***: Benztrop; Cogentin; ***Singapore***: Cogentin; ***Thai.***: Cogentin; ***UK***: Cogentin; ***USA***: Cogentin.

Pharmacopoeial Preparations
BP 2014: Benztropine Injection; Benzatropine Tablets;
USP 36: Benztropine Mesylate Injection; Benztropine Mesylate Tablets.

Biperiden *(BAN, rINN)*

Biperideeni; Bipéridène; Biperideno; Biperidenum; Бипериден.

1-(Bicyclo[2.2.1]hept-5-en-2-yl)-1-phenyl-3-piperidinopropan-1-ol.

$C_{21}H_{29}NO$=311.5

CAS — 514-65-8.
ATC — N04AA02.
ATC Vet — QN04AA02.
UNII — 0FRP6G56LD.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Biperiden). A white, practically odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform. Protect from light.

Biperiden Hydrochloride *(BANM, rINNM)*

Biperideenihydrokloridi; Biperiden Hidroklorür; Bipéridène, Chlorhydrate de; Biperidén-hidroklorid; Biperidenhydrochlorid; Biperiden-hydrochlorid; Biperidenhydroklorid; Biperideni Hydrochloridum; Biperideno hidrochloridas; Biperideno, hidrocloruro de; Hidrocloruro de biperideno; Бипериден Гидрохлорид.

$C_{21}H_{29}NO,HCl$=347.9

CAS — 1235-82-1.
ATC — N04AA02.
ATC Vet — QN04AA02.
UNII — K35N76CUHF.

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

Ph. Eur. 8: (Biperiden Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol; very slightly soluble in dichloromethane. A 0.2% solution in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Biperiden Hydrochloride). A white, practically odourless, crystalline powder. Slightly soluble in water, in alcohol, in chloroform, and in ether; sparingly soluble in methyl alcohol. Protect from light.

Biperiden Lactate *(BANM, rINNM)*

Biperiden Laktat; Bipéridène, Lactate de; Biperideni Lactas; Biperideno, lactato de; Lactato de biperideno; Бипериден Лактат.

$C_{21}H_{29}NO,C_3H_6O_3$=401.5

CAS — 7085-45-2.
ATC — N04AA02.
ATC Vet — QN04AA02.
UNII — 09TD6C5147.

Pharmacopoeias. *US* includes Biperiden Lactate Injection.

Uses and Administration

Biperiden is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3) but with more potent antinicotinic properties.

Biperiden is used in the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias.

Biperiden is given orally as the hydrochloride and by injection as the lactate; doses are expressed in terms of the relevant salt.

US licensed product information gives the initial oral dose for **Parkinson's disease** as 2 mg of the hydrochloride 3 or 4 times daily which can then be increased according to response to a maximum of 16 mg daily. In some countries a much lower initial oral dose of 1 mg twice daily is recommended. In the USA the recommended oral dose for **drug-induced extrapyramidal symptoms** is 2 mg of the hydrochloride 1 to 3 times daily. In other countries a wider dose range of 1 to 4 mg 1 to 4 times daily is used. Modified-release tablets with different dose schedules are available in some countries.

In severe cases, or when biperiden cannot be given orally, the lactate can be given by intramuscular or slow intravenous injection; total daily doses of up to 10 to 20 mg daily have been used.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Parenteral use may be followed by slight transient hypotension.

Abuse. Abuse of biperiden has been reported in psychiatric patients.[1,2]

1. Pullen GP, *et al.* Anticholinergic drug abuse: a common problem? *BMJ* 1984; 289: 612–13.
2. Ozucelik DN, *et al.* Gluteal abscess following intramuscular injection of dissolved biperiden tablets. *Int J Clin Pract* 2007; 61: 1417–18.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies biperiden 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 30/09/11)

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Pharmacokinetics

Biperiden is readily absorbed from the gastrointestinal tract, but bioavailability is only about 30% suggesting that it undergoes extensive first-pass metabolism. Biperiden has an elimination half-life of about 20 hours.

References.
1. Hollmann M, *et al.* Biperiden effects and plasma levels in volunteers. *Eur J Clin Pharmacol* 1984; 27: 619–21.
2. Grimaldi R, *et al.* Pharmacokinetic and pharmacodynamic studies following the intravenous and oral administration of the antiparkinsonian drug biperiden to normal subjects. *Eur J Clin Pharmacol* 1986; 29: 735–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Akineton; Berofin; Darcipireno†; Denzolam; Sinekin; ***Austral.***: Akineton; ***Austria***: Akineton; ***Belg.***: Akineton; ***Braz.***: Akineton; Cinetol; Parkinsol; Propark; ***Chile***: Akineton†; ***Cz.***: Akineton; ***Denm.***: Akineton; ***Fin.***: Akineton; Ipsatol; ***Fr.***: Akineton; ***Ger.***: Akineton; ***Gr.***: Akineton; ***Hung.***: Akineton; ***Irl.***: Akineton; ***Israel***: Dekinet; ***Ital.***: Akineton; ***Mex.***: Akineton; Bikipen†; Kinex; ***Neth.***: Akineton; ***Norw.***: Akineton; ***Philipp.***: Aketon; Akidin; Akineton; ***Pol.***: Akineton; ***Port.***: Akineton; ***Rus.***: Akineton (Акинетон); Mendilex (Мендилекс); ***S.Afr.***: Akineton; ***Spain***: Akineton; ***Swed.***: Akineton; ***Switz.***: Akineton; ***Turk.***: Akineton; ***USA***: Akineton; ***Venez.***: Akineton.

Pharmacopoeial Preparations
USP 36: Biperiden Hydrochloride Tablets; Biperiden Lactate Injection.

Bornaprine Hydrochloride *(BANM, rINNM)*

Bornaprin Hidroklorür; Bornaprina, hidrocloruro de; Bornaprine, Chlorhydrate de; Bornaprini Hydrochloridum; Hidrocloruro de bornaprina; Борнаприна Гидрохлорид.

3-Diethylaminopropyl 2-phenylbicyclo[2.2.1]heptane-2-carboxylate hydrochloride.

$C_{21}H_{31}NO_2,HCl$=365.9

CAS — 20448-86-6 (bornaprine); 26908-91-8 (bornaprine hydrochloride).
ATC — N04AA11.
ATC Vet — QN04AA11.
UNII — R99RGW1B2Q.

Profile

Bornaprine hydrochloride is a quaternary ammonium antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3). It is used in the symptomatic treatment of **parkinsonism** (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias; it is claimed to be mainly effective against tremor. Bornaprine hydrochloride is given orally in initial doses of 2 mg daily gradually increased to 6 to 12 mg daily according to response. It is also used in the treatment of **hyperhidrosis** (p. 1685.1) in a dose of 4 to 8 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Sormodren; ***Ger.***: Sormodren; ***Gr.***: Sormodren; ***Ital.***: Sormodren; ***Turk.***: Sormodren.

Bromocriptine Mesilate *(BANM, rINNM)*

Bromocriptina, mesilato de; Bromocriptine, mésilate de; Bromocriptine Mesylate (USAN); Bromocriptine Methanesulphonate; Bromocriptini Mesilas; Bromocriptinmesilat; Bromocryptine Mesylate; 2-Bromo-α-ergocryptine Mesylate; 2-Bromoergocryptine Monomethanesulfonate; Bromokriptiinimesilaatti; Bromokriptin Mesilat; Bromokriptinmesilat; Bromokriptin-mesylát; Bromokriptin-mezilát; Bromokriptino mesilatas; CB-154 (bromocriptine); Mesilato de bromocriptina; Бромокриптина Мезилат.

(5′*S*)-2-Bromo-12′-hydroxy-2′-(1-methylethyl)-5′-(2-methylpropyl)-ergotaman-3′,6′,18-trione methanesulphonate.

$C_{32}H_{40}BrN_5O_5,CH_4O_3S$=750.7

CAS — 25614-03-3 (bromocriptine); 22260-51-1 (bromocriptine mesilate).
ATC — G02CB01; N04BC01.
ATC Vet — QG02CB01; QN04BC01.
UNII — FFP983J3OD.

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

Ph. Eur. 8: (Bromocriptine Mesilate). A white or slightly coloured fine crystalline powder. Practically insoluble in water; soluble in alcohol; sparingly soluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in a mixture of 2 parts methyl alcohol to 8 of water has a pH of 3.1 to 3.8. Store in airtight containers at a temperature not exceeding -15 degrees. Protect from light.

USP 36: (Bromocriptine Mesylate). A white or slightly coloured fine crystalline powder; odourless or having a weak characteristic odour. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Uses and Administration

Bromocriptine, an ergot derivative (p. 2137.1), is a dopamine D_2-agonist. It inhibits the secretion of prolactin (p. 2145.1) from the anterior pituitary and is used in the treatment of prolactinoma and endocrinological disorders associated with hyperprolactinaemia (p. 896.2), including amenorrhoea, galactorrhoea, hypogonadism, and infertility in both men and women. Bromocriptine is also used to suppress puerperal lactation for medical reasons (p. 896.2); it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support. Growth hormone secretion may be suppressed by bromocriptine in some patients with acromegaly (p. 896.1). Because of its dopaminergic activity bromocriptine is also used in the management of Parkinson's disease (p. 896.3). It is used in some countries as an adjunct to diet and exercise to improve glycaemic control in type 2 diabetes mellitus (p. 459.1) but its exact mode of action is unknown.

Bromocriptine is usually given orally as the mesilate; doses are expressed in terms of the base. Bromocriptine mesilate 2.87 mg is equivalent to about 2.5 mg of bromocriptine. Oral doses should be taken with food. Bromocriptine mesilate has also been given intramuscularly as a depot injection for disorders associated with hyperprolactinaemia.

For the **prevention of puerperal lactation** bromocriptine 2.5 mg is given on the day of delivery followed by 2.5 mg twice daily for 14 days. The risk of hypotension and, more rarely, hypertension must be borne in mind and it has been recommended that bromocriptine should not be given until at least 4 hours after delivery. For the **suppression of established lactation** it is given in a dose of 2.5 mg daily for 2 to 3 days subsequently increased to 2.5 mg twice daily for 14 days.

For the treatment of other conditions (see below) the dose of bromocriptine is usually increased gradually. In the UK, typically, an initial dose of 1 to 1.25 mg at night is given,

increased to 2 to 2.5 mg at night after 2 to 3 days, and subsequently increased by 1 to 2.5 mg every 2 to 3 days to a dose of 2.5 mg twice daily, or more if necessary. In the USA, a usual starting dose is 1.25 to 2.5 mg daily increased by 2.5 mg every 2 to 7 days.

In the **treatment of hypogonadism and galactorrhoea syndromes and infertility** bromocriptine is introduced gradually as described above. Most patients with hyperprolactinaemia respond to 7.5 mg daily but up to 30 mg daily may be required. Infertile patients without raised serum concentrations of prolactin are usually given 2.5 mg twice daily. In patients known to have **prolactinomas** the dose is also introduced gradually as described above and may then be increased further by 2.5 mg every 2 to 3 days to a dose of 5 mg every 6 hours but occasionally patients may require up to 30 mg daily. Although unlicensed in the UK and USA, bromocriptine is used in some countries for **cyclical benign breast and menstrual disorders**. In benign breast disease bromocriptine is introduced gradually up to a daily dosage of 5 to 7.5 mg if necessary. In the treatment of premenstrual symptoms therapy should begin on day 14 of the cycle and introduced gradually up to a usual dosage of 2.5 mg twice daily until menstruation begins.

Bromocriptine may be used as an adjunct to surgery and radiotherapy to reduce plasma-growth hormone concentrations in **acromegalic patients**. In the UK, it is introduced gradually as described above and may then be increased further by 2.5 mg every 2 to 3 days if necessary up to 5 mg every 6 hours, according to response. In the USA, the usual starting dose (see above) may be increased by 1.25 to 2.5 mg every 3 to 7 days to a maximum daily dose of 100 mg if necessary; the usual dosage range is 20 to 30 mg daily.

In **Parkinson's disease** bromocriptine has been used alone, although it is usually given as an adjunct to levodopa treatment. It should be introduced even more gradually than the regimen above, and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved. In the UK, a suggested initial dose is the equivalent of 1 to 1.25 mg of bromocriptine at night during week 1, increased to 2 to 2.5 mg at night for week 2, 2.5 mg twice daily for week 3, and for week 4, 2.5 mg three times daily; the dose may be increased thereafter by 2.5 mg every 3 to 14 days according to response. The EMEA has recommended a maximum dose of 30 mg daily. In the USA, a usual starting dose is 1.25 mg twice daily increased by 2.5 mg every 14 to 28 days to a maximum dose of 100 mg daily if necessary.

In the USA, bromocriptine is used as an adjunct in **type 2 diabetes mellitus**. An initial oral dose of 800 micrograms daily is increased in weekly steps of 800 micrograms, according to tolerance, to a daily dose of between 1.6 to 4.8 mg; doses are given once daily within 2 hours of waking in the morning.

For details of uses and associated doses in children and adolescents, see below.

Administration in children. In the UK, bromocriptine is licensed for the treatment of prolactinomas and gigantism (acromegaly), under specialist supervision, in children and adolescents aged 7 to 17 years. For prolactinomas, an initial oral dose of 1 mg is given 2 or 3 times daily. A higher starting dose of 1.25 mg given 2 or 3 times daily is suggested for gigantism. Thereafter, the dose may be gradually increased according to response; a maximum of 20 mg daily is recommended in those aged 13 years or older, regardless of indication, while younger children may be given a maximum dose of 5 mg daily for prolactinomas and 10 mg daily for gigantism.

In the USA, bromocriptine is licensed for the treatment of prolactinomas in children and adolescents aged 11 to 15 years. An initial oral dose of 1.25 to 2.5 mg daily may be gradually increased, according to response, to a usual range of 2.5 to 10 mg daily.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and bromocriptine has been used in acromegaly (p. 1921.1) as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels. While it is less effective than somatostatin analogues, it can be given orally and is therefore more convenient to administer.

Cushing's syndrome. There have been occasional reports of benefit with the use of bromocriptine in the treatment of Cushing's syndrome (p. 2559.1). Remission of ACTH-dependent Cushing's syndrome was maintained for 6 years by bromocriptine 2.5 mg twice daily in a patient who had initially received pituitary irradiation.[1] However, the same group subsequently reported that they had found that bromocriptine did not effectively reduce ACTH secretion following bilateral adrenalectomy.[2]

1. Atkinson AB, *et al.* Six year remission of ACTH-dependent Cushing's syndrome using bromocriptine. *Postgrad Med J* 1985; 61: 239–42.
2. Atkinson AB. The treatment of Cushing's syndrome. *Clin Endocrinol (Oxf)* 1991; 34: 507–13.

Hepatic encephalopathy. For the view that the evidence does not support the use of dopaminergics such as bromocriptine in the management of hepatic encephalopathy see p. 1811.2.

Hyperprolactinaemia and prolactinomas. Prolactinomas (prolactin-secreting pituitary adenomas) are among the commonest causes of hyperprolactinaemia. Raised serum-prolactin concentrations can result in reduced gonadotrophin production, which in turn may suppress gonadal function. Consequences may include oligomenorrhoea or amenorrhoea, and infertility in either sex. Galactorrhoea may also result from high prolactin levels and can occur in men as well as women.

Dopamine is the major inhibitory factor in the hypothalamus and directly inhibits the secretion of prolactin. Bromocriptine, a dopamine agonist, has been the first choice of treatment in many centres for the treatment of hyperprolactinaemia secondary to a prolactinoma although cabergoline is now preferred by some. Bromocriptine is extremely effective in controlling elevated circulating prolactin concentrations and restoring gonadal function; although it is rarely curative, it may produce considerable shrinkage of the adenoma.[1]

The sensitivity of hyperprolactinaemia to bromocriptine therapy can vary considerably between patients and this is reflected in the wide range of oral doses required to reduce prolactin concentrations to normal levels. Although beginning therapy with gradually increasing doses can minimise adverse effects it has been reported that about 5 to 10% of patients are unable to tolerate oral bromocriptine;[2] other dosage routes have therefore been investigated. Bromocriptine is well absorbed from standard oral tablets placed in the vagina and appears to be both effective in lowering prolactin concentrations and well tolerated when given by this route.[3] However, limitations are considered to be the relatively short duration of action and the relatively low dose that can be given.[2] A depot preparation given intramuscularly in a dose of 50 to 250 mg monthly has been found to be effective and well tolerated in long-term studies;[4,5] it is reported to be used in some centres to begin treatment for macroprolactinomas.[2]

For discussions of the management of hyperprolactinaemia and associated disorders see p. 2252.2 (hyperprolactinaemia), p. 2251.3 (amenorrhoea), p. 2252.3 (hypogonadism), p. 2348.2 (erectile dysfunction), and p. 2253.1 (infertility).

1. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. *Pituitary* 2002; 5: 55–65.
2. Ciccarelli E, Camanni F. Diagnosis and drug therapy of prolactinoma. *Drugs* 1996; 51: 954–65.
3. Ginsburg J, *et al.* Vaginal bromocriptine. *Lancet* 1991; 338: 1205–6.
4. Ciccarelli E, *et al.* Long term therapy of patients with macroprolactinoma using repeatable injectable bromocriptine. *J Clin Endocrinol Metab* 1993; 76: 484–8.
5. Ciccarelli E, *et al.* Double blind randomized study using oral or injectable bromocriptine in patients with hyperprolactinaemia. *Clin Endocrinol (Oxf)* 1994; 40: 193–8.

PREGNANCY. References to the management of prolactinoma during pregnancy.[1-3] Bromocriptine has been successfully used for management in pregnant women, particularly if there is symptomatic enlargement of the tumour, although there continues to be debate on the appropriateness of continuous therapy in less high-risk individuals.

1. Randeva HS, *et al.* Prolactinoma and pregnancy. *Br J Obstet Gynaecol* 2000; 107: 1064–8.
2. Bronstein MD, *et al.* Medical management of pituitary adenomas: the special case of management of the pregnant woman. *Pituitary* 2002; 5: 99–107.
3. Chiodini I, Liuzzi A. PRL-secreting pituitary adenomas in pregnancy. *J Endocrinol Invest* 2003; 26: 96–9.

Lactation inhibition. Because of its effects on prolactin, bromocriptine is a potent suppressor of lactation and has been widely used for the prevention of lactation in women who choose not to breast feed post partum. However, bromocriptine has been associated with severe adverse effects in some women, and its use to suppress a physiological state has been criticised (see p. 2130.1). Consequently, licensed product information from some countries recommends that bromocriptine should only be used to suppress puerperal lactation for medical reasons; it is also not recommended for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support.

Mastalgia. Since mastalgia (p. 2265.1) can improve spontaneously, treatment should rarely be considered unless pain has been present for about 6 months. Bromocriptine is one of the drugs that may be used to treat mastalgia.[1,2] It may improve symptoms in up to about 50% of patients with cyclical mastalgia, but is less effective in the non-cyclical form.[3,4] Adverse effects can be severe in some patients.

1. Gateley CA, Mansel RE. Management of the painful and nodular breast. *Br Med Bull* 1991; 47: 284–94.
2. Anonymous. Cyclical breast pain—what works and what doesn't. *Drug Ther Bull* 1992; 30: 1–3.
3. Pye JK, *et al.* Clinical experience of drug treatments for mastalgia. *Lancet* 1985; ii: 373–7.
4. Mansel RE, Dogliotti L. European multicentre trial of bromocriptine in cyclical mastalgia. *Lancet* 1990; 335: 190–3.

Neuroleptic malignant syndrome. Bromocriptine has been used in doses of up to 30 mg daily,[1-6] usually alone or with dantrolene, in the treatment of neuroleptic malignant syndrome (p. 1050.2) although some workers have not found it to be of use.[7]

1. Mueller PS, *et al.* Neuroleptic malignant syndrome: successful treatment with bromocriptine. *JAMA* 1983; 249: 386–8.
2. Dhib-Jalbut S, *et al.* Treatment of the neuroleptic malignant syndrome with bromocriptine. *JAMA* 1983; 250: 484–5.
3. Clarke CE, *et al.* Clinical spectrum of neuroleptic malignant syndrome. *Lancet* 1988; ii: 969–70.
4. Guerrero RM, Shifrar KA. Diagnosis and treatment of neuroleptic malignant syndrome. *Clin Pharm* 1988; 7: 697–701.
5. Lo TCM, *et al.* Neuroleptic malignant syndrome: another medical cause of acute abdomen. *Postgrad Med J* 1989; 65: 653–5.
6. Chandran GJ, *et al.* Neuroleptic malignant syndrome: case report and discussion. *Can Med Assoc J* 2003; 169: 439–42.
7. Rosebush PI, *et al.* The treatment of neuroleptic malignant syndrome: are dantrolene and bromocriptine useful adjuncts to supportive care? *Br J Psychiatry* 1991; 159: 709–12.

Parkinsonism. Dopamine agonists such as bromocriptine are often used to begin treatment of parkinsonism (p. 889.1), particularly in younger patients, in an attempt to delay therapy with levodopa. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease. However, in early disease, there is no evidence that adjunctive bromocriptine prevents or delays the onset of motor complications associated with levodopa monotherapy.

References.

1. Temlett JA, *et al.* Adjunctive therapy with bromocriptine in Parkinson's disease. *S Afr Med J* 1990; 78: 680–5.
2. Hely MA, *et al.* The Sydney Multicentre Study of Parkinson's disease: a randomised, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. *J Neurol Neurosurg Psychiatry* 1994; 57: 903–10.
3. Montastruc JL, *et al.* A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. *J Neurol Neurosurg Psychiatry* 1994; 57: 1034–8.
4. Giménez-Roldán S, *et al.* Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. *Clin Neuropharmacol* 1997; 20: 67–76.
5. Ogawa N, *et al.* Nationwide multicenter prospective study on the long-term effects of bromocriptine for Parkinson's disease: final report of a ten-year follow-up. *Eur Neurol* 1997; 38 (suppl 2): 37–49.
6. Lees AJ, *et al.* Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. *Neurology* 2001; 57: 1687–94.
7. van Hilten, *et al.* Bromocriptine versus levodopa in early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/05/08).
8. van Hilten, *et al.* Bromocriptine/levodopa combined versus levodopa alone for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/05/08).

Polycystic ovary syndrome. Bromocriptine has been tried in women with the polycystic ovary syndrome (p. 2253.3) who have mild basal hyperprolactinaemia without evidence of a pituitary tumour.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has largely been empirical but dopaminergic therapy has emerged as a common first-line choice. Bromocriptine showed some benefit in a small study.[1]

1. Walters AS, *et al.* A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. *Ann Neurol* 1988:24: 455–8.

Withdrawal syndromes. *ALCOHOL* Studies of the efficacy of bromocriptine as an aid in the maintenance of abstinence from alcohol (p. 1735.1) have yielded conflicting results.[1-4] However, it has been suggested[3] that response to bromocriptine might be linked to a specific genotype of the D_2 dopamine receptor.

1. Dongier M, *et al.* Bromocriptine in the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1991; 15: 970–7.
2. Naranjo CA, *et al.* Long-acting bromocriptine (B) does not reduce relapse in alcoholics. *Clin Pharmacol Ther* 1995; 57: 161.
3. Lawford BR, *et al.* Bromocriptine in the treatment of alcoholics with the D_2 dopamine receptor A1 allele. *Nat Med* 1995; 1: 337–41.
4. Powell BJ, *et al.* A double-blind, placebo-controlled study of nortriptyline and bromocriptine in male alcoholics subtyped by comorbid psychiatric disorders. *Alcohol Clin Exp Res* 1995; 19: 462–8.

Adverse Effects

Nausea is the most common adverse effect at the beginning of treatment with bromocriptine, but vomiting, dizziness, and orthostatic hypotension may also occur. Syncope has followed initial doses.

Adverse effects are generally dose-related and may therefore be more frequent with the higher doses that have been used in the treatment of parkinsonism and acromegaly. Reduction of the dosage, followed in a few days by a more gradual increase, may alleviate many adverse effects. Nausea may be reduced by taking bromocriptine with food; domperidone may also be given at least 1 hour before bromocriptine, for the first few days of therapy.

Bromocriptine and similar drugs are vasoconstrictors; Raynaud's syndrome or digital vasospasm, induced by cold, and leg cramps have been reported. Other cardiovascular effects have included erythromelalgia, prolonged severe hypotension, arrhythmias, and exacerbation of angina. Very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances), and psychiatric disorders have been reported in postpartum women given bromocriptine.

The use of ergot derivatives such as bromocriptine has been associated with retroperitoneal fibrosis, pleural thickening and effusions, and pericarditis and pericardial effusions.

Other adverse effects reported include headache, nasal congestion, drowsiness, dry mouth, constipation, diarrhoea, and altered liver-function tests. Dyskinesias and psychomotor excitation have occurred in patients suffering from parkinsonism. Gastrointestinal bleeding has been reported in acromegalic patients. Psychosis, with hallucinations, delusions, and confusion, occurs particularly when high doses are used to treat parkinsonism, but has also been reported with low doses. A neuroleptic malignant-like syndrome associated with abrupt withdrawal of bromocriptine has been reported very rarely.

Incidence of adverse effects. In 27 published studies of the treatment of Parkinson's disease, 217 of the 790 patients given bromocriptine had adverse effects.[1] Mental changes were noted in 90 patients, dyskinesia in 20, orthostatic hypotension in 40, and gastrointestinal effects in 40. The fewest adverse effects (9%) occurred with low-dose bromocriptine, more occurred with high-dose bromocriptine (27%) or with low-dose bromocriptine with levodopa (26%), and the most occurred with high-dose bromocriptine and levodopa (32%). However, those on high doses had more advanced disease and might have been more susceptible to mental changes and dyskinesias.

An analysis by the manufacturer of published reports on patients treated with bromocriptine for 1 to 10 years concluded that in general, adverse effects noted were no different from those associated with short-term treatment.[2]

1. Lieberman AN, Goldstein M. Bromocriptine in Parkinson disease. *Pharmacol Rev* 1985; 37: 217–27.
2. Weil C. The safety of bromocriptine in long-term use: a review of the literature. *Curr Med Res Opin* 1986; 10: 25–51.

Effects on the blood. Severe leucopenia and mild thrombocytopenia developed in a 23-year-old woman after treatment with bromocriptine 7.5 to 10 mg daily for about 3 months.[1]

1. Giampietro O, *et al.* Severe leukopenia and mild thrombocytopenia after chronic bromocriptine (CB-154) administration. *Am J Med Sci* 1981; 281: 169–72.

Effects on the cardiovascular system. An early review noted that asymptomatic **hypotension** occurred in many subjects given bromocriptine.[1] However, faintness and dizziness, sometimes accompanied by *nausea* and *vomiting*, were common at the start of treatment with bromocriptine and these symptoms rather than an anaphylactic type of reaction were likely to account for the collapse that occurred in a few sensitive patients. Two of 53 patients with Parkinson's disease fainted after an initial dose of 1.25 or 2.5 mg, but the exact incidence of shock-like syndromes was difficult to assess; the manufacturers had stated that 22 of over 10 000 subjects given bromocriptine had had hypotension and collapse, mainly at the start of treatment.

- All patients starting treatment should be warned of the possibility of fainting. The initial dose should not exceed 1.25 to 2.5 mg and should be taken with food and in bed.

If fainting does occur recovery is usually rapid and spontaneous. Tolerance to adverse effects such as hypotension and nausea may develop rapidly.

Hypertension, seizures, stroke, and *myocardial infarction* have been associated with bromocriptine therapy, notably in postpartum women.[2-4] A study involving 1813 women suggested that the risk of **postpartum hypertension** was increased in women who had pregnancy-induced hypertension and that this risk was further increased in those who took bromocriptine for suppression of lactation.[5] A case-controlled study[6] involving 43 of the women who had had postpartum seizures while taking bromocriptine found that while the initial risk of seizures appeared to be lower in patients taking bromocriptine there was a small positive association with seizures occurring more than 72 hours after delivery.

- Although a causal relationship between the use of bromocriptine and these adverse effects in postpartum women has not been established, licensed product information recommends that bromocriptine should not be used post partum or in the puerperium in women with high blood pressure, coronary artery disease or other severe cardiovascular disorders, or symptoms or history of serious psychiatric disorders.
- It is also recommended that when bromocriptine is used in postpartum women blood pressure should be carefully monitored, especially during the first few days and if hypertension, unremitting headache, or signs of CNS toxicity develop, treatment should be discontinued immediately.

Severe dilated **cardiomyopathy** has been reported in a patient being treated with bromocriptine for microprolactinoma.[7]

For details of **fibrotic reactions** resulting in cardiovascular adverse effects, see Fibrosis, below.

1. Parkes D. Side effects of bromocriptine. *N Engl J Med* 1980; 302: 749–50.
2. Anonymous. Postpartum hypertension, seizures, strokes reported with bromocriptine. *FDA Drug Bull* 1984; 14: 3.
3. Ruch A, Duhring JL. Postpartum myocardial infarction in a patient receiving bromocriptine. *Obstet Gynecol* 1989; 74: 448–51.
4. Larrazet P, *et al.* Possible bromocriptine-induced myocardial infarction. *Ann Intern Med* 1993; 118: 199–200.
5. Watson DL, *et al.* Bromocriptine mesylate for lactation suppression: a risk for postpartum hypertension? *Obstet Gynecol* 1989; 74: 573–6.
6. Rothman KJ, *et al.* Bromocriptine and puerperal seizures. *Epidemiology* 1990; 1: 232–8.
7. Kaushik P, *et al.* Acute onset of severe dilated cardiomyopathy during bromocriptine therapy. *Ann Pharmacother* 2004; 38: 1219–21.

Effects on the ears. Audiometric evidence of bilateral sensorineural hearing loss was reported in 3 patients receiving bromocriptine 15 or 20 mg daily for chronic hepatic encephalopathy.[1] Hearing improved when the dose was reduced to 10 mg daily.

1. Lanthier PL, *et al.* Bromocriptine-associated ototoxicity. *J Laryngol Otol* 1984; 98: 399–404.

Effects on electrolytes. There have been isolated reports of severe hyponatraemia associated with the use of bromocriptine.[1,2]

1. Marshall AW, *et al.* Bromocriptine-associated hyponatraemia in cirrhosis. *BMJ* 1982; 285: 1534–5.
2. Damase-Michel C, *et al.* Hyponatraemia in a patient treated with bromocriptine. *Drug Invest* 1993; 5: 285–7.

Effects on the eyes. Blurred vision and diplopia have been reported in several patients receiving bromocriptine.[1] Reversible myopia also developed in a patient with hyperprolactinaemia given bromocriptine.[2]

Licensed product information states that visual field impairment associated with macroprolactinoma usually resolves with bromocriptine treatment. However, in a patient with progressive visual loss due to compression of the optic chiasm by a large pituitary tumour, bromocriptine caused total visual loss within hours.[3] Vision slowly returned to normal when the patient was placed in the supine position; the most likely cause of the visual loss was thought to be orthostatic hypotension with resultant decrease in perfusion pressure to the visual system. Monitoring of visual fields is recommended in patients with macroprolactinoma.

Bromocriptine has been reported to cause visual cortical disturbances.[4] In some cases blurred vision and transient cortical blindness have preceded seizures and strokes.

1. Calne DB, *et al.* Long-term treatment of parkinsonism with bromocriptine. *Lancet* 1978; i: 735–7.
2. Manor RS, *et al.* Myopia during bromocriptine treatment. *Lancet* 1981; i: 102.
3. Couldwell WT, Weiss MH. Visual loss associated with bromocriptine. *Lancet* 1992; 340: 1410–11.
4. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; 26: 124–47.

Effects on mental function. High doses of bromocriptine are well known to cause **psychotic reactions** in patients with parkinsonism.[1] However, mania has also been associated with the use of bromocriptine post partum[2,3] and it has been stated that psychological symptoms can occur with doses of only 2.5 to 5 mg daily.[4] It was also noted that, unlike the relatively mild and transient symptoms associated with levodopa, bromocriptine produces a severe psychosis in which the patient is violent and aggressive, suffering from intense delusions which are often hostile and violent; complete withdrawal of bromocriptine may still leave a residue of severe psychotic illness persisting for 1 to 3 weeks. Psychosis associated with low doses of bromocriptine has often occurred in patients with a history of psychotic illness or disturbances in behaviour and mood.[5-7] Drug-related psychotic reactions have also been reported in patients with no psychiatric history;[8,9] of 600 patients given bromocriptine or lisuride for the treatment of acromegaly or prolactinoma, 8 developed symptoms including anxiety, depression, auditory hallucinations, delusions, hyperactivity, disinhibition, euphoria, and insomnia and 4 had received doses only previously associated with psychosis in susceptible patients.[9]

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including bromocriptine, see under Levodopa, p. 905.2.

1. Calne DB, *et al.* Long-term treatment of parkinsonism with bromocriptine. *Lancet* 1978; i: 735–7.
2. Vlissides DN, *et al.* Bromocriptine-induced mania? *BMJ* 1978; 1: 510.
3. Brook NM, Cookson IB. Bromocriptine-induced mania? *BMJ* 1978; 1: 790.
4. Pearce I, Pearce JMS. Bromocriptine in parkinsonism. *BMJ* 1978; 1: 1402–4.
5. Pearson KC. Mental disorders from low-dose bromocriptine. *N Engl J Med* 1981; 305: 173.
6. Le Feuvre CM, *et al.* Bromocriptine-induced psychosis in acromegaly. *BMJ* 1982; 285: 1315.
7. Procter AW, *et al.* Bromocriptine induced psychosis in acromegaly. *BMJ* 1983; 286: 50. Correction. *Ibid.*: 311.
8. Einarson TR, Turchet BN. Psychotic reaction to low-dose bromocriptine. *Clin Pharm* 1983; 2: 273–4.
9. Turner TH, *et al.* Psychotic reactions during treatment of pituitary tumours with dopamine agonists. *BMJ* 1984; 289: 1101–3.

Effects on the nervous system. CSF rhinorrhoea has been associated with bromocriptine therapy in patients with invasive prolactinomas. A report of 3 cases found 13 further cases on reviewing the literature;[1] of these, 7 patients had developed rhinorrhoea within 1 month of starting bromocriptine and 2 cases developed after 12 months.

For reference to seizures associated with the use of bromocriptine in postpartum women, see Effects on the Cardiovascular System, above.

1. Barlas O, *et al.* Bromocriptine-induced cerebrospinal fluid fistula in patients with macroprolactinomas: report of three cases and a review of the literature. *Surg Neurol* 1994; 41: 486–9.

Effects on the respiratory system. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including bromocriptine, see Fibrosis, below.

Effects on sexual function. For reports of the effects of dopamine agonists on sexual function, see under Levodopa, p. 906.1.

Effects on the urinary tract. Constant dribbling urinary incontinence developed in a woman receiving bromocriptine 2.5 mg daily for a recurrent pituitary growth; symptoms resolved on stopping the drug and recurred on rechallenge.[1] Bromocriptine has been shown to have two effects, one on the bladder outflow tract and one on the detrusor muscle, that could predispose to urinary incontinence.[2]

1. Sandyk R, Gillman MA. Urinary incontinence in patient on long-term bromocriptine. *Lancet* 1983; ii: 1260–1.
2. Caine M. Bromocriptine and urinary incontinence. *Lancet* 1984; i: 228.

Fibrosis. Fibrosis has been associated with the long-term use of ergot derivatives (see under Methysergide, p. 677.2). Fibrotic reactions such as cardiac valvulopathy and pleuropulmonary effusion have been reported with bromocriptine, cabergoline, lisuride, and pergolide therapy in patients with Parkinson's disease.

Constrictive pericarditis[1] was reported in 2 patients who had received *bromocriptine* for 2 and 4 years, respectively; the latter still had slight pleural effusion 13 months after the drug was stopped. Valvular heart disease[2] developed in another patient who had received bromocriptine for 5 years; symptoms resolved 6 months after stopping the drug. Interstitial lung disease, with dyspnoea, chest pain, cough, and pulmonary fibrosis was reported[3] in a patient after use of relatively high doses of bromocriptine (62 mg daily). Respiratory symptoms largely resolved on withdrawal of the drug, although functional respiratory changes and moderate dyspnoea persisted after 6 months. A review of the literature revealed several other reports of pleuropulmonary fibrosis associated with relatively high doses of bromocriptine which occurred after between 15 days and up to 3 years of treatment. Although the incidence of this effect did not seem to be high, similar cases have continued to be reported.[4-6] In June 2008 the EMEA recommended that for long-term use in conditions such as Parkinson's disease, the maximum dose should be 30 mg daily.[7]

A patient developed pleuropulmonary disease 16 months after starting treatment with *cabergoline*;[8] he had previously received bromocriptine for 10 years and had had a normal chest X-ray at the time of transfer to cabergoline treatment. In another report, 2 cases of pleural effusion/pulmonary fibrosis, occurring after 10 to 11 months of treatment, were described.[9] One patient had modest pretreatment lung alterations attributed to previous bromocriptine therapy. Withdrawal was associated with improvement in both cases. Congestive heart failure secondary to constrictive pericarditis, and severe pleuropulmonary fibrosis that resulted in

dyspnoea, persistent in one case,[10] have also been reported in 2 patients receiving long-term cabergoline.[10,11] Another patient developed cardiac valvulopathy after taking cabergoline for a total of 20 months;[12] her dosage was 4 mg daily for the last 7 months. Cardiac symptoms slowly improved on withdrawal of the drug, although some evidence of valvular defects was still present 23 months later. Valvular heart disease has also been reported in a 74-year-old man after 4 months of therapy with cabergoline [dosage not stated].[13] By December 2005, 86 cases of suspected adverse reactions to cabergoline had been reported to the Australian Drug Reactions Advisory Committee (ADRAC),[14] of which 15 described pleural or pulmonary fibrosis/effusion, or pneumonitis; time to onset ranged from a few days to over 3 years with a median of 4 months. There had been no reports of fibrotic complications associated with low-dose cabergoline in the treatment of lactation suppression and hyperprolactinaemia. The UK MHRA considers the risk of cardiac valvulopathy to be high and UK labelling for cabergoline has been amended accordingly (see p. 900.2) with the EMEA in June 2008 recommending a maximum dose of 3 mg daily.[7]

A woman developed bilateral pleural effusions after taking *lisuride* 4 mg daily for about 17 months.[8] Her condition improved on stopping lisuride.

The UK CSM[15] reported in 2003 that *pergolide* had been associated with cases of cardiac valvulopathy; since 1989, valvulopathy had been reported in fewer than 5 in 100 000 patients. The CSM also referred to a published case series[16] which reported on 3 patients with severe tricuspid regurgitation after long-term pergolide treatment. The authors of this case series and the CSM both considered that, based on the available evidence, there was a potential association between pergolide and cardiac valvulopathy. Subsequently, the FDA[17] stated that, up to the end of 2002, it was aware of 15 cases of valvular heart disease with pergolide treatment; this figure included the 3 cases reported in the above series and 4 cases from the UK. A later study[18] that examined 78 patients taking pergolide for Parkinson's disease found evidence of restrictive valvular heart disease in 15 of 52 (29%) patients taking doses less than 5 mg daily and in 11 of 26 (42%) receiving doses of 5 mg or more daily. Pulmonary fibrosis and retroperitoneal fibrosis have also been associated with pergolide treatment;[19-21] in most cases, symptoms improved when the drug was stopped. Duration of exposure to pergolide ranged from 6 months[20] to 11 years.[21]

In April 2002 the CSM[22] calculated crude reporting rates of fibrotic reactions associated with the ergot derivative dopamine agonists (bromocriptine, cabergoline, lisuride, and pergolide), based on data submitted to its Yellow Card scheme and estimated drug exposure. Pergolide was found to be associated with a higher reporting rate of fibrotic reactions compared with the other ergot derivatives; however, this result needed further investigation to see if it reflected a true increase in risk or was due to factors such as reporting biases. There is some evidence that the incidence of reactions to pergolide are dose-related; doses are restricted in many countries (see p. 910.3) and in June 2008 the EMEA recommended a maximum dose of 3 mg daily.[7] Pergolide was withdrawn from the market in the USA and Canada. It is recommended that baseline investigations such as erythrocyte sedimentation rate, urea and electrolyte concentrations, and a chest x-ray should be performed before starting treatment with this class of drugs.

1. Champagne S, *et al.* Chronic constrictive pericarditis induced by long-term bromocriptine therapy: report of two cases. *Ann Pharmacother* 1999; 33: 1050–4.
2. Serratrice J, *et al.* Fibrotic valvular heart disease subsequent to bromocriptine treatment. *Cardiol Rev* 2002; 10: 334–6.
3. Vergeret J, *et al.* Fibrose pleuro-pulmonaire et bromocriptine. *Sem Hop Paris* 1984; 60: 741–4.
4. Kinnunen E, Viljanen A. Pleuropulmonary involvement during bromocriptine treatment. *Chest* 1988; 94: 1034–6.
5. Macak IA, *et al.* Bromocriptine-induced pulmooary disease. *Cm J Hosp Pharm* 1991; 44: 37–8, xxiv.
6. Debove P, *et al.* Pleuropneumopathie à la bromocriptine .hez un parkinsonien: revue de la littérature à propos d'une nouvelle observation. *Ann Med Interne (Paris)* 1998; 149: 167–71.
7. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)
8. Bhatt MH, *et al.* Pleuropulmonary disease associated with dopamine agonist therapy. *Ann Neurol* 1991; 30: 613–16.
9. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; 11: 495–500.
10. Ling LH, *et al.* Constrictive pericarditis and pleuropulmonary disease linked to ergot dopamine agonist therapy (cabergoline) for Parkinson's disease. *Mayo Clin Proc* 1999; 74: 371–5.
11. Townsend M, MacIver DH. Constrictive pericarditis and pleuropulmonary fibrosis secondary to cabergoline treatment for Parkinson's disease. *Heart* 2004; 90: e47.
12. Horvath J, *et al.* Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. *Mov Disord* 2004; 19: 656–62.
13. Pinero A, *et al.* Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med* 2005; 353: 1976–7.
14. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Ergot derivatives and fibrotic reactions. *Aust Adverse Drug React Bull* 2006; 25: 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0602.pdf (accessed 30/05/08)
15. CSM/MHRA. Pergolide (Celance) and cardiac valvulopathy. *Current Problems* 2003; 29: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074506&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)
16. Pritchett AM, *et al.* Valvular heart disease in patients taking pergolide. *Mayo Clin Proc* 2002; 77: 1280–6.
17. Flowers CM, *et al.* The US Food and Drug Administration's registry of patients with pergolide-associated valvular heart disease. *Mayo Clin Proc* 2003; 78: 730–1.
18. Van Camp G, *et al.* Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet* 2004; 363: 1179–83.
19. Agarwal P, *et al.* Diagnosis and management of pergolide-induced fibrosis. *Mov Disord* 2004; 19: 699–704.
20. Simcock D, Paviour D. Rapid onset of pergolide-induced pulmonary fibrosis in a patient with corticobasal degeneration. *Hosp Med* 2004; 65: 372–3.
21. Tintner R, *et al.* Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist pergolide for Parkinson disease. *Arch Neurol* 2005; 62: 1290–3.
22. CSM/MCA. Fibrotic reactions with pergolide and other ergot-derived receptor agonists. *Current Problems* 2002; 28: 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074546&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)

Hypersensitivity. An allergic reaction developed in a 26-year-old woman being treated with bromocriptine for a prolactin-secreting microadenoma.[1] The patient reacted similarly to lisuride and treatment was continued with quinagolide.

1. Merola B, *et al.* Allergy to ergot-derived dopamine agonists. *Lancet* 1992; 339: 620.

Oedema. Oedema poorly responsive to diuretics has been reported[1] in a patient given bromocriptine as part of treatment for prolactinoma. The oedema improved on substitution of pergolide but worsened with higher doses. Oedema resolved when treatment was changed to quinagolide. The reaction was considered to be idiosyncratic since enquiries by the author of the report had revealed only one similar case. In a subsequent report[2] a patient with Parkinson's disease who had been receiving bromocriptine for 5 years developed marked lower leg oedema, and subsequently cough, dyspnoea, and chest pain associated with an exudative pleural effusion; there was no evidence of fibrosis. Both oedema and effusion had largely resolved within 4 weeks of stopping bromocriptine.

1. Blackard WG. Edema—an infrequently recognized complication of bromocriptine and other ergot dopaminergic drugs. *Am J Med* 1993; 94: 445.
2. Messiaen T, *et al.* Épanchement pleural et importants œdèmes des membres inférieurs induits par la bromocriptine. *Rev Med Interne* 1996; 17: 680–3.

Overdosage. The most striking symptom in two children aged 2 and 2½ years who accidentally ingested an estimated 25 and 7.5 mg of bromocriptine, respectively, was lethargy with altered mental status.[1] The first child vomited and became sleepy. On admission he was markedly lethargic, but combative when disturbed, and also had hypotension, shallow breathing, dilated pupils, and hyperreflexic lower extremities. Nasogastric lavage was promptly performed, and activated charcoal and then magnesium citrate given. Blood pressure and ECG were monitored, and glucose and sodium chloride solution infused. The other child vomited, became lethargic, and had dilated pupils. Ipecacuanha was given, and activated charcoal followed by magnesium citrate given by nasogastric tube. Both children recovered completely.

1. Vermund SH, *et al.* Accidental bromocriptine ingestion in childhood. *J Pediatr* 1984; 105: 838–40.

Withdrawal syndromes. Transient galactorrhoea and hyperprolactinaemia occurred in a young woman after withdrawal of bromocriptine therapy for Parkinson's disease.[1] It was suggested the effects were due to a rebound phenomenon. For discussion of a syndrome resembling neuroleptic malignant syndrome that has developed on withdrawal of bromocriptine and other antiparkinsonian drugs, see under Levodopa, p. 906.2.

1. Pentland B, Sawers JSA. Galactorrhoea after withdrawal of bromocriptine. *BMJ* 1980; 281: 716.

Precautions

Patients with hyperprolactinaemia should be investigated for the possibility of a pituitary tumour before treatment with bromocriptine. Malignancy must be excluded in patients with cyclical benign breast disorders such as mastalgia. Annual gynaecological examinations (or every 6 months for postmenopausal women) are recommended. Treatment of women with hyperprolactinaemic amenorrhoea results in ovulation; patients not wishing to conceive should be advised to use contraceptive measures although oral contraceptives should be avoided because they may increase prolactin levels. Acromegalic patients should be checked for symptoms of peptic ulceration before therapy and should immediately report symptoms of gastrointestinal discomfort during therapy.

In general, bromocriptine should be given with caution to patients with cardiovascular disease, Raynaud's syndrome, or a history of psychosis. It is contra-indicated in patients with hypersensitivity to bromocriptine or other ergot alkaloids, and in those with uncontrolled hypertension.

Bromocriptine is contra-indicated in the toxaemia of pregnancy. It should also not be used postpartum or in the puerperium in women with hypertension, coronary artery disease, or symptoms or a history of serious psychiatric disorders. When used, blood pressure should be monitored carefully, especially during the first few days in postpartum women. Particular caution is necessary in patients who are receiving or who have recently received drugs that can alter blood pressure; use with ergot alkaloids during the puerperium is not recommended. Treatment in postpartum women should be stopped immediately if hypertension, unremitting headache, or signs of CNS toxicity develop.

Hypotensive reactions may be disturbing in some patients during the first few days of treatment and those who drive or operate machinery should be warned of the possibility of dizziness and fainting during this period. Excessive daytime sleepiness and sudden onset of sleep may also occur with bromocriptine and other dopaminergic agonists, and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring. A reduction in dosage or withdrawal of the drug may be appropriate. Because of the risk of fibrosis bromocriptine is contra-indicated in patients with pre-existing valve problems.

Patients on long-term, high-dose therapy should be monitored for signs of progressive fibrotic disorders such as retroperitoneal fibrosis and bromocriptine withdrawn if fibrotic changes are diagnosed or suspected. It is recommended that baseline investigations such as erythrocyte sedimentation rate, urea and electrolyte concentrations, and a chest x-ray should be performed before starting treatment with bromocriptine. Periodic monitoring of cardiovascular, haematopoietic, hepatic, and renal function is also recommended. Monitoring of visual fields is recommended in patients with macroprolactinoma.

Breast feeding. The American Academy of Pediatrics[1] considers that bromocriptine should be given with caution to breast-feeding mothers, since it suppresses lactation and may be hazardous to the mother.

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://appolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 16/02/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bromocriptine 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 30/09/11)

Pregnancy. Details of various surveys of the effect of the use of bromocriptine during pregnancy have been published by the manufacturer.[1,2] The first survey was based on spontaneous reporting of all pregnancies between 1977 and 1980 in women who had taken bromocriptine after conception.[1] Information was obtained on 1410 pregnancies in 1335 women, the majority of whom had been treated for hyperprolactinaemic conditions, while in 256 pregnancies pituitary tumours and acromegaly were the primary diagnosis. Bromocriptine was generally taken at some time in the first 8 weeks after conception, the mean duration of treatment being 21 days. In 4 patients bromocriptine was not prescribed until late in pregnancy and in 9 with acromegaly and pituitary microadenoma it was taken continuously throughout gestation. There were 157 (11.1%) spontaneous abortions, 12 (0.9%) extrauterine pregnancies, 2 patients with 3 hydatidiform moles (0.2%) and an incidence of twin pregnancies of 1.8%. Major congenital abnormalities were detected in 12 (1%) infants at birth and minor abnormalities in 31 (2.5%). A second survey,[2] which consisted of formal monitoring of the use of bromocriptine at 33 clinics between 1979 and 1980, collected data on a further 743 pregnancies in 668 women and had similar findings. The incidence rates reported in these surveys were comparable with those quoted for normal populations and the data indicate that the use of bromocriptine in the treatment of women with infertility is not associated with an increased risk of abortion, multiple pregnancy, or congenital abnormalities. Furthermore follow-up, for up to 9 years, of 546 children exposed to bromocriptine *in utero* found no evidence that bromocriptine had any adverse effect on postnatal development.[2] Nevertheless, since the risk of abortion is not increased by interruption of treatment, licensed product information recommends that bromocriptine therapy be stopped as soon as pregnancy is confirmed unless there is a definite indication for its continuation.

See also Pregnancy, under Hyperprolactinaemia and Prolactinomas, p. 896.2.

1. Turkalj I, *et al.* Surveillance of bromocriptine in pregnancy. *JAMA* 1982; 247: 1589–91.
2. Krupp P, Monka C. Bromocriptine in pregnancy: safety aspects. *Klin Wochenschr* 1987; 65: 823–7.

Interactions

Dopamine antagonists such as the phenothiazines, butyrophenones, thioxanthenes, and metoclopramide (but see below) might be expected to reduce the prolactin-lowering and the antiparkinsonian effects of bromocriptine and domperidone might reduce its prolactin-lowering effect. Memantine may enhance the effects of bromocriptine. Stimulants of gastrointestinal motility such as macrolide antibacterials or octreotide can increase the bioavailability of bromocriptine.

Alcohol. Alcohol intolerance was noted in 5 of 73 patients receiving bromocriptine 10 to 60 mg daily for the treatment of acromegaly.[1] Two patients who had gastrointestinal adverse effects while taking low doses of bromocriptine had a marked reduction in their symptoms and were able to tolerate higher doses when they refrained completely from alcohol.[2]

1. Wass JAH, *et al.* Long-term treatment of acromegaly with bromocriptine. *BMJ* 1977; 1: 875–8.
2. Ayres J, Maisey MN. Alcohol increases bromocriptine's side effects. *N Engl J Med* 1980; 302: 806.

Antibacterials. Drowsiness, dystonia, choreoathetoid dyskinesias, and visual hallucinations occurred when *josamycin* was given to a patient receiving bromocriptine.[1]

The systemic bioavailability of a single oral dose of bromocriptine 5 mg was markedly increased in 5 healthy subjects after treatment with *erythromycin estolate* 250 mg four times daily for 4 days;[2] clearance of bromocriptine was decreased and peak plasma concentrations of bromocriptine were more than 4 times higher than when given alone.

1. Montastruc JL, Rascol A. Traitement de la maladie de Parkinson par doses élevées de bromocriptine: interaction possible avec la josamycine. *Presse Med* 1984; 13: 2267–8.
2. Nelson MV, *et al.* Pharmacokinetic evaluation of erythromycin and caffeine administered with bromocriptine. *Clin Pharmacol Ther* 1990; 47: 694–7.

Antifungals. The response to bromocriptine was blocked in a patient who was also receiving *griseofulvin*.[1]

1. Schwinn G, *et al.* Metabolic and clinical studies on patients with acromegaly treated with bromocriptine over 22 months. *Eur J Clin Invest* 1977; 7: 101–7.

Antineoplastics. *Tamoxifen* may increase the dopaminergic effect of bromocriptine; for the effect of bromocriptine on tamoxifen, see Interactions, under Tamoxifen, p. 863.2.

Antipsychotics. Serum concentrations of prolactin rose and visual fields deteriorated when *thioridazine* was given to a 40-year-old man receiving bromocriptine therapy for a large prolactinoma.[1]

For a discussion of the effect of bromocriptine on patients receiving antipsychotics, see Antiparkinsonian Drugs under Chlorpromazine on p. 1052.3.

1. Robbins RJ, *et al.* Interactions between thioridazine and bromocriptine in a patient with a prolactin-secreting pituitary adenoma. *Am J Med* 1984; 76: 921–3.

Metoclopramide. As noted in Interactions, above, there are theoretical reasons to suppose that dopamine antagonists such as metoclopramide might reduce the effects of bromocriptine. However, an early study[1] in 10 patients with Parkinson's disease given single doses of bromocriptine 12.5 to 100 mg found that pretreatment with metoclopramide 60 mg had no consistent effect upon plasma concentrations of bromocriptine or growth hormone and no consistent effect upon clinical response.

1. Price P, *et al.* Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* 1978; 6: 303–9.

Sympathomimetics. There have been isolated reports[1,2] of severe hypertension, with headache and life-threatening complications, in patients taking bromocriptine with *isometheptene mucate* or *phenylpropanolamine*.

1. Kulig K, *et al.* Bromocriptine-associated headache: possible life-threatening sympathomimetic interaction. *Obstet Gynecol* 1991; 78: 941–3.
2. Chan JCN, *et al.* Postpartum hypertension, bromocriptine and phenylpropanolamine. *Drug Invest* 1994; 8: 254–6.

Pharmacokinetics

Bromocriptine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 to 3 hours after oral doses. However, only about 30% of an oral dose is absorbed and, owing to extensive first-pass metabolism, the bioavailability is only about 6%. It has been reported to be 90 to 96% bound to serum albumin *in vitro*. It is metabolised in the liver, mainly by hydrolysis to lysergic acid and peptides. The elimination of bromocriptine is biphasic; half-lives of about 4 to 4.5 hours and 15 hours, respectively have been reported for the 2 phases. It is excreted mainly in faeces via the bile, with small amounts in urine.

In a study involving 10 patients with Parkinson's disease, single oral doses of bromocriptine 12.5, 25, 50, and 100 mg resulted in very variable peak plasma concentrations ranging from 1.3 to 5.3, 1.4 to 3.5, 2.6 to 19.7, and 6.5 to 24.6 nanograms/mL, respectively, 30 to 210 minutes (mean 102 minutes) after dosage.[1] After 4 hours plasma concentrations were about 75% of the peak values. Clinical improvement was evident within 30 to 90 minutes of a dose with peak effect at about 130 minutes and in most patients improvement persisted throughout the 4-hour study period. Peak clinical response, peak fall in blood pressure, and peak rise in plasma concentrations of growth hormone occurred about 30, 60, and 70 minutes, respectively after peak plasma-bromocriptine concentrations but there was no significant relationship between them. However, there was a significant relationship between plasma concentrations and concurrent changes in clinical response compared with pretreatment scores. Dyskinesias occurred within 90 to 180 minutes of dosage in 5 of 10 patients.

Bromocriptine is well absorbed from standard oral tablets placed in the vagina and plasma concentrations sufficient to lower plasma prolactin concentrations have been achieved using this route.[2,3]

1. Price P, *et al.* Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* 1978; 6: 303–9.
2. Vermesh M, *et al.* Vaginal bromocriptine: pharmacology and effect on serum prolactin in normal women. *Obstet Gynecol* 1988; 72: 693–8.
3. Katz E, *et al.* Successful treatment of a prolactin-producing pituitary macroadenoma with intravaginal bromocriptine mesylate: a novel approach to intolerance of oral therapy. *Obstet Gynecol* 1989; 73: 517–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Parlodel; *Austral.*: Bromohexal†; Kripton; Parlodel; *Austria*: Parlodel; Umprel; *Belg.*: Parlodel; *Braz.*: Bagren†; Parlodel; *Chile*: Criten; Grifocriptina; Kriptonal; Parlodel; Prigost; *China*: Baimoting (佰莫亭)†; Parlodel; *Cz.*: Medocriptine; Parlodel; *Denm.*: Parlodel; *Fin.*: Parlodel; *Fr.*: Bromo-Kin; Parlodel; *Ger.*: kirim gyn†; kirim; Pravidel; *Gr.*: Parlodel; Serocryptin; *Hong Kong*: Bromergon; Medocriptine; Parlodel; Syntocriptine; *India*: Briptin; Brom; Bromogen; Criptal; Encript; Kripti; Ovucript; Sicriptin; *Indon.*: Cripsa; Parlodel; *Irl.*: Parlodel; *Israel*: Parilac†; Parlodel†; *Ital.*: Parlodel; *Jpn*: Parlodel; *Malaysia*: Medocriptine; Parlodel; *Mex.*: Biodel; Broptin; Crilem†; Cryocriptina†; Kriptiser†; Mesiken; Parlodel; *Neth.*: Parlodel; *Norw.*: Parlodel; *Philipp.*: Parlodel; Provasyn; *Pol.*: Bromergon; Bromocorn; Ergolaktyna†; Parlodel; *Port.*: Parlodel; *Rus.*: Bromergon (Бромэргон); Parlodel (Парлодел); *S.Afr.*: Parlodel; *Singapore*: Brameston; Butin†; Parlodel; *Spain*: Parlodel; *Swed.*: Pravidel; *Switz.*: Parlodel; *Thai.*: Brocaden†; Bromergon; Parlodel; Suplac; *Turk.*: Galaktomin; Gynodel; Parlodel; *UAE*: Antiprotin; *UK*: Parlodel; *Ukr.*: Parlodel (Парлодел)†; *USA*: Cycloset; Parlodel; *Venez.*: Parlodel.

Pharmacopoeial Preparations

BP 2014: Bromocriptine Capsules; Bromocriptine Tablets;
USP 36: Bromocriptine Mesylate Capsules; Bromocriptine Mesylate Tablets.

Budipine *(rINN)*

Budipino; Budipinum; Будипин.
1-*tert*-Butyl-4,4-diphenylpiperidine.
$C_{21}H_{27}N$=293.5
CAS — 57982-78-2.
ATC — N04BX03.
ATC Vet — QN04BX03.
UNII — L9026OPI2Z.

Profile

Budipine is a phenylpiperidine derivative used as an adjunct in the treatment of parkinsonism (p. 889.1). It is given orally as the hydrochloride in daily doses of up to 60 mg. Budipine has been reported to prolong the QT interval.

References.
1. Spieker S, *et al.* Tremorlytic activity of budipine: a quantitative study with long-term tremor recordings. *Clin Neuropharmacol* 1995; 18: 266–72.
2. Groen H, *et al.* A study to investigate the pharmacokinetics and metabolism of budipine after administration of a single oral dose of [^{14}C]-B757-01 to six healthy volunteers. *Br J Clin Pharmacol* 1999; 48: 771P–772P.
3. Malsch U, *et al.* Monotherapie der Parkinsonschen Erkrankung mit Budipin: ein randomisierter Doppelblindvergleich mit Amantadin. *Fortschr Neurol Psychiatr* 2001; 69: 86–9.
4. Przuntek H, *et al.* Budipine provides additional benefit in patients with Parkinson disease receiving a stable optimum dopaminergic drug regimen. *Arch Neurol* 2002; 59: 803–6.
5. Reichmann H. Budipine in Parkinson's tremor. *J Neurol Sci* 2006; 248: 53–5.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Cabergoline *(BAN, USAN, rINN)*

Cabergolin; Cabergolina; Cabergolinum; FCE-21336; Kabergoliini; Kabergolin; Kabergolina; Каберголин.
1-[(6-Allylergolin-8β-yl)carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea; (8*R*)-6-Allyl-*N*-[3-(dimethylamino)propyl]-*N*-(ethylcarbamoyl)ergoline-8-carboxamide.
$C_{26}H_{37}N_5O_2$=451.6
CAS — 81409-90-7.
ATC — G02CB03; N04BC06.
ATC Vet — QG02CB03; QN04BC06.
UNII — LL60K9J05T.

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

Ph. Eur. 8: (Cabergoline). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in alcohol; very slightly soluble in *n*-hexane. It is slightly soluble in 0.1M hydrochloric acid. Protect from light.

USP 36: (Cabergoline). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol; slightly soluble in 0.1M hydrochloric acid; very slightly soluble in hexane. Store in airtight containers. Protect from light.

Uses and Administration

Cabergoline, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p. 895.3). It is a potent and long-lasting inhibitor of prolactin secretion used in the management of disorders associated with hyperprolactinaemia (p. 900.1). It is also used to suppress puerperal lactation for medical reasons (p. 900.1); it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support. Cabergoline is also used in the management of Parkinson's disease (p. 900.1) as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response; in the UK cabergoline is restricted to patients who are intolerant of, or who do not respond to, non-ergot drug treatment.

Cabergoline is given orally and should be taken with food.

To **inhibit physiological lactation**, cabergoline is given as a single 1-mg dose on the first day post partum. For **suppression of established lactation**, the dose is 250 micrograms every 12 hours for 2 days.

In the treatment of **disorders associated with hyperprolactinaemia**, the initial dose of cabergoline is 500 micrograms weekly. The dose is then increased at monthly intervals in increments of 500 micrograms weekly according to response. The weekly dose may be given on a single occasion or divided into 2 or more doses on separate days according to tolerance; doses over 1 mg should be given as divided doses although the maximum single daily dose should not exceed 3 mg. The usual dose is 1 mg weekly but up to 4.5 mg weekly has been used.

In **Parkinson's disease**, cabergoline should be introduced gradually and during this period the dose of levodopa may be reduced gradually until an optimal response is achieved. A suggested initial dose of cabergoline given as a single daily dose is 500 micrograms in monotherapy or 1 mg in adjunctive therapy. The dose may be increased in increments of 0.5 or 1 mg, at intervals of 7 or 14 days, to 2 to 3 mg daily. The EMEA has recommended a maximum dose of 3 mg daily.

Doses of cabergoline may need to be reduced in patients with severe hepatic impairment (see below).

Administration in hepatic impairment. Licensed product information recommends caution in patients with severe hepatic impairment (Child-Pugh category C), and doses of cabergoline should be adjusted accordingly.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone concentrations, although they are less effective than somatostatin analogues (p. 1921.1).

A small study comparing cabergoline with depot bromocriptine and quinagolide failed to find evidence of its efficacy.[1] However, in a later open study[2] there was a good response in about 40% of patients treated with cabergoline, which is better than the response usually reported for bromocriptine. The addition of cabergoline has

also been beneficial in acromegaly that is resistant to somatostatin analogue therapy.[3]

1. Colao A, *et al.* Effect of different dopaminergic agents in the treatment of acromegaly. *J Clin Endocrinol Metab* 1997; **82**: 518–23.
2. Abs R, *et al.* Cabergoline in the treatment of acromegaly: a study in 64 patients. *J Clin Endocrinol Metab* 1998; **83**: 374–8.
3. Cozzi R, *et al.* Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. *Clin Endocrinol (Oxf)* 2004; **61**: 209–15.

Hyperprolactinaemia and prolactinomas. Dopamine agonists are widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (see p. 2252.2). Although bromocriptine has been the first choice for this indication, some now prefer cabergoline,[1] which appears to be more effective and better tolerated.[2,3]

Further references.[4-11]

1. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* 1996; **14**: 228–38. Correction. *ibid.*, 342.
2. Pascal-Vigneron V, *et al.* Amenorrhée hyperprolactinémique: traitement par cabergoline versus bromocriptine. *Presse Med* 1995; **24**: 753–7.
3. di Sarno A, *et al.* Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. *J Clin Endocrinol Metab* 2001; **86**: 5256–61.
4. Webster J, *et al.* The efficacy and tolerability of long-term cabergoline therapy in hyperprolactinaemic disorders: an open, uncontrolled, multicentre study. *Clin Endocrinol (Oxf)* 1993; **39**: 323–9.
5. Webster J, *et al.* A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *N Engl J Med* 1994; **331**: 904–9.
6. Verhelst J, *et al.* Cabergoline in the treatment of hyperprolactinaemia: a study in 455 patients. *J Clin Endocrinol Metab* 1999; **84**: 2518–22.
7. Colao A, *et al.* Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. *J Clin Endocrinol Metab* 2000; **85**: 2247–52.
8. Colao A, *et al.* Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med* 2003; **349**: 2023–33.
9. Colao A, *et al.* Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. *J Clin Endocrinol Metab* 2004; **89**: 1704–11.
10. Ono M, *et al.* Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. *J Clin Endocrinol Metab* 2008; **93**: 4721–7.
11. Kharlip J, *et al.* Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. *J Clin Endocrinol Metab* 2009; **94**: 2428–36.

Lactation inhibition. A single 1-mg dose of cabergoline was found to be as effective as bromocriptine 2.5 mg given twice daily for 14 days for preventing puerperal lactation in a double-blind multicentre study involving 272 women.[1] It has been suggested that cabergoline would be a better choice than bromocriptine for lactation inhibition.[2] However, as discussed on p. 2130.1, the routine use of dopaminergics such as bromocriptine or cabergoline is not recommended for the suppression of physiological lactation.

1. European Multicentre Study Group for Cabergoline in Lactation Inhibition. Single dose cabergoline versus bromocriptine in inhibition of puerperal lactation: randomised, double blind, multicentre study. *BMJ* 1991; **302**: 1367–71.
2. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* 1996; **14**: 228–38. Correction. *ibid.*: 342.

Parkinsonism. Cabergoline is used as a long-acting dopamine agonist in Parkinson's disease (p. 889.1). Dopamine agonists are often used to begin treatment in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stages of the disease.

References.

1. Inzelberg R, *et al.* Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. *Neurology* 1996; **47**: 785–8.
2. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11**: 495–500.
3. Hutton JT, *et al.* Multicenter, placebo-controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. *Neurology* 1996; **46**: 1062–5.
4. Marsden CD. Clinical experience with cabergoline in patients with advanced Parkinson's disease treated with levodopa. *Drugs* 1998; **55** (suppl 1): 17–22.
5. Rinne UK, *et al.* Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications: results of a double-blind levodopa controlled trial. *Drugs* 1998; **55** (suppl 1): 23–30.
6. Clarke CE, Deane K. Cabergoline for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
7. Clarke CE, Deane K. Cabergoline versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
8. Bracco F, *et al.* The long-acting dopamine receptor agonist cabergoline in early Parkinson's disease: final results of a 5-year, double-blind, levodopa-controlled study. *CNS Drugs* 2004; **18**: 733–46. Correction. *ibid.* 2005; **19**: 633.
9. Curran MP, Perry CM. Cabergoline: a review of its use in the treatment of Parkinson's disease. *Drugs* 2004; **64**: 2125–41.
10. Odin P, *et al.* Efficacy and safety of high-dose cabergoline in Parkinson's disease. *Acta Neurol Scand* 2006; **113**: 18–24.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has been largely empirical but dopaminergic therapy has emerged as a common first-line choice. Long-acting drugs such as cabergoline may be preferred in order to avoid the complications associated with levodopa therapy. Randomised multicentre studies[1,2] in patients with idiopathic RLS concluded that a single evening dose of cabergoline for 5 weeks markedly reduced symptoms during the night and the next day compared with placebo. Results from follow-up analysis of one study[1] after 1 year of treatment suggested that cabergoline at a median dose of 2 mg daily has a high rate of remission and is well tolerated; the authors recommended an initial dose of cabergoline 500 micrograms in the evening increased in increments of 500 micrograms weekly according to response.

1. Stiasny-Kolster K, *et al.* Effective cabergoline treatment in idiopathic restless legs syndrome. *Neurology* 2004; **63**: 2272–9.
2. Oertel WH, *et al.* Efficacy of cabergoline in restless legs syndrome: a placebo-controlled study with polysomnography (CATOR). *Neurology* 2006; **67**: 1040–6.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3, although patients unable to tolerate bromocriptine may tolerate cabergoline (and vice versa).

Licensed product information states that conception should be avoided for at least one month after treatment.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including cabergoline, see under Levodopa, p. 905.2.

For reference to **pathological gambling** reported in patients with Parkinson's disease receiving dopamine agonists including cabergoline, see under Levodopa, p. 905.2.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including cabergoline, see under Bromocriptine, p. 897.3.

In 2007, based on further evidence from 3 studies,[1-3] the UK MHRA[4] considered the risk of cardiac valvulopathy to be high and clinically significant with cabergoline and pergolide, and the risks of treatment with these 2 drugs to be similar. This resulted in the following changes to UK labelling for cabergoline products in Parkinson's disease:

- restricted to second-line treatment in patients intolerant of, or who do not respond to, non-ergot drug treatment
- contra-indicated in patients with a history of pulmonary, pericardial, and retroperitoneal fibrotic disorders, or in those with anatomical evidence of cardiac valvulopathy
- monitoring for development of valvular disease or fibrosis recommended: echocardiography should be performed within 3 to 6 months of starting treatment and every 6 to 12 months thereafter

In June 2008 the EMEA further recommended that the maximum dose should be 3 mg daily.[5]

1. Yamamoto M, *et al.* Dopamine agonists and cardiac valvulopathy in Parkinson disease: a case-control study. *Neurology* 2006; **67**: 1225–9.
2. Schade R, *et al.* Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007; **356**: 29–38.
3. Zanettini R, *et al.* Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007; **356**: 39–46.
4. MHRA/CHM. Cabergoline: cardiovalvulopathy. *Drug Safety Update* 2007; 1 (1): 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2031801&RevisionSelectionMethod=LatestReleased (accessed 23/08/10)
5. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)

Oedema. Three cases of lower limb oedema after chronic treatment with cabergoline have been reported.[1] In one case the oedema was severe enough to necessitate withdrawal of therapy.

1. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11**: 495–500.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cabergoline 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 30/09/11)

Interactions

As for Bromocriptine, p. 899.1.

Pharmacokinetics

Cabergoline is absorbed from the gastrointestinal tract and mean peak plasma concentrations occur within 2 to 3 hours. It is subject to first-pass metabolism and is extensively metabolised to several metabolites that do not appear to contribute to its pharmacological activity. Plasma protein binding has been estimated to be about 40%. Cabergoline is mainly eliminated via the faeces; a small proportion is excreted in the urine. In *rats*, cabergoline has been reported to cross the placenta and to be distributed into breast milk.

General references.

1. Del Dotto P, Bonuccelli U. Clinical pharmacokinetics of cabergoline. *Clin Pharmacokinet* 2003; **42**: 633–45.

Half-life. Pharmacokinetic studies of cabergoline have been hampered by lack of an assay method sensitive enough to detect plasma concentrations of cabergoline after therapeutic doses. However, the plasma elimination half-life of cabergoline has been estimated indirectly to be 63 to 68 hours in healthy subjects and 79 to 115 hours in patients with hyperprolactinaemia.[1]

1. Rains CP, *et al.* Cabergoline: a review of its pharmacological properties and therapeutic potential in the treatment of hyperprolactinaemia and inhibition of lactation. *Drugs* 1995; **49**: 255–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cabaser; Caberpar; Cabertrix; Cieldom; Dostinex; Lac Stop; Lactamax; Triaspar; *Austria.*: Bergoline; Cabaser; Cobasol; Dostan; Dostinex; Tinexa; *Austral.*: Cabaseril; Dostinex; *Belg.*: Dostinex; Sostilar; *Braz.*: Dostinex; *Canad.*: Dostinex; *Chile*: Cabertrix; Dostinex; *Cz.*: Cabera; Dostinex; *Denm.*: Cabaser; Cabergin; Dostinex; *Fin.*: Cabase; Dostinex; *Fr.*: Dostinex; *Ger.*: Cabaseril; Cabergo-TEVA†; Dostinex; *Gr.*: Dostinex; *Hong Kong*: Dostinex; *India*: Caberlin; Cabergolin; Camforte; CB-Lin; Parcar; *Irl.*: Cabaser; Caberex; Dalzio; Dostinex; Eflavex; *Israel*: Cabaser; Cabotrim; Dostinex; *Ital.*: Actualene; Cabaser; Dostinex; *Malaysia*: Dostinex; *Mex.*: Dostinex; *Neth.*: Dostinex; *Norw.*: Cabaser; Dostinex; *NZ*: Dostinex; *Pol.*: Dostinex; *Port.*: Dostinex; *Rus.*: Agalates (Агалатес); Dostinex (Достинекс); *S.Afr.*: Arigoline; Dostinex; *Singapore*: Dostinex; *Spain*: Dostinex; Sogilen; *Swed.*: Cabaser; Dostinex; *Switz.*: Cabaser; Dostinex; *Turk.*: Cabaser; Dostinex; *UK*: Cabaser; Dostinex; *Ukr.*: Alactin (Алактин); Dostinex (Достинекс); *Venez.*: Dostinex.

Pharmacopoeial Preparations
USP 36: Cabergoline Tablets.

Carbidopa *(BAN, USAN, rINN)*

Carbidopa-Monohydrat; Carbidopum; Carbidopum Monohydricum; Karbidopa; Karbidopa monohydrát; α-Methyldopa Hydrazine; MK-486; Карбидопа.

(+)-2-(3,4-Dihydroxybenzyl)-2-hydrazinopropionic acid monohydrate; (-)-L-α-Hydrazino-3,4-dihydroxy-α-methylhydrocinnamic acid monohydrate.

$C_{10}H_{14}N_2O_4.H_2O$=244.2

CAS — 28860-95-9 (anhydrous); 38821-49-7 (monohydrate).

UNII — MNX7R8C5VO (carbidopa monohydrate); KR87B45RGH (anhydrous carbidopa).

NOTE. The synonym MK-485 has been used for the racemic mixture.

Compounded preparations of carbidopa and levodopa may be represented by the following names:

- Co-careldopa *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of carbidopa and levodopa respectively
- Co-careldopa (*PEN*)—carbidopa and levodopa

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

Ph. Eur. 8: (Carbidopa). A white or yellowish-white powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane; dissolves in dilute solutions of mineral acids. Protect from light.

USP 36: (Carbidopa). A white to creamy-white, odourless or practically odourless powder. Slightly soluble in water and in methyl alcohol; practically insoluble in alcohol, in acetone, in chloroform, and in ether; freely soluble in 3N hydrochloric acid. Protect from light.

Uses and Administration

Carbidopa is a peripheral dopa-decarboxylase inhibitor with little or no pharmacological activity when given alone in usual doses. It inhibits the peripheral decarboxylation of levodopa to dopamine and as, unlike levodopa, it does not cross the blood-brain barrier, effective brain concentrations of dopamine are produced with lower doses of levodopa. At the same time reduced peripheral formation of dopamine reduces peripheral adverse effects, notably nausea and vomiting, and cardiac arrhythmias, although the dyskinesias and adverse mental effects associated with levodopa therapy tend to develop earlier. Contrary to its effect in patients on levodopa alone, pyridoxine does not inhibit the response to levodopa in patients also receiving a peripheral dopa-decarboxylase inhibitor.

In the treatment of parkinsonism (p. 889.1) carbidopa is given with levodopa to enable a lower dosage of the latter to be used, a more rapid response to be obtained, and to decrease adverse effects. For details of administration and dosage, see Levodopa, p. 902.3.

Carbidopa also inhibits the peripheral decarboxylation of the serotonin precursor oxitriptan (p. 440.3).

General references.

1. Pinder RM, *et al.* Levodopa and decarboxylase inhibitors: a review of their clinical pharmacology and use in the treatment of parkinsonism. *Drugs* 1976; 11: 329–77.
2. Boshes B. Sinemet and the treatment of parkinsonism. *Ann Intern Med* 1981; 94: 364–70.

Adverse Effects

Hypersensitivity. Henoch-Schönlein purpura that developed in a 68-year-old patient being treated for Parkinson's disease appeared to be due to either carbidopa or an excipient of the carbidopa preparation (*Sinemet*).[1]

1. Niedermaier G, Briner V. Henoch-Schönlein syndrome induced by carbidopa/levodopa. *Lancet* 1997; 349: 1071–2.

Pharmacokinetics

Carbidopa is rapidly but incompletely absorbed from the gastrointestinal tract. It is rapidly excreted in the urine both unchanged and in the form of metabolites. It does not cross the blood-brain barrier. In *rats*, carbidopa has been reported to cross the placenta and to be distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Prikap; *Irl.*: Duodopa; *Pol.*: Nakom; *UK*: Apodespan; *USA*: Lodosyn.

Multi-ingredient Preparations. *Arg.*: Carlevod; Lebocar; Lecarge; Nervocur; Parkinel; Sinemet; Stalevo; *Austral.*: Duodopa; Kinson; Levohexal†; Sinemet; Stalevo; *Austria*: Duodopa; Levocar; Sinemet; Stalevo; *Belg.*: Duodopa; Sinemet; Stalevo; *Braz.*: Carbidol; Cronomet; Duodopa; Levocarb; Parkidopa; Parklen; Sinemet; Stalevo; *Canad.*: Apo-Levocarb; Duodopa; Novo-Levocarbidopa†; Nu-Levocarb; Pro-Levocarb; Sinemet; Stalevo; *Chile*: Grifoparkin; Levofamil; Protonis†; Saniter Compuesto; Sinemet; Stalevo; *China*: Sinemet (息宁); Xi Lai Mei (西莱美); *Cz.*: Apo-Levocarb; Dopalux†; Duodopa; Isicom; Lecardop; Nakom; Sinemet; Stalevo; *Denm.*: Duodopa; Sinemet; Stalevo; *Fin.*: Duodopa; Kardopal; Levocar; Sinemet; Stalevo; *Fr.*: Duodopa; Sinemet; Stalevo; *Ger.*: Duodopa; Isicom; Levo-C; Levobeta C; Levocarb†; Levocomp†; Levodop; Levodopa comp C†; Levodopa Comp; Nacom; Stalevo; Striaton†; *Gr.*: Duodopa; Sinemet; Stalevo; Zimox; *Hong Kong*: Apo-Levocarb; Levomed; Levomet; Sinedopa†; Sinemet; Stalevo; *Hung.*: Duellin†; Duodopa; Sinemet†; Stalevo; *India*: LCD; Levopa-C; Neocare; Syndopa; *Indon.*: Stalevo; *Irl.*: Half Sinemet; Sinemet; Stalevo; *Israel*: Dopicar; Duodopa; Sinemet; Stalevo; *Ital.*: Duodopa; Sinemet; Sirio; Stalevo; *Malaysia*: Apo-Levocarb; Levomed; Sinedopa; Sinemet; Stalevo; *Mex.*: Cloisone; Lemdopa†; Racovel; Sinemet; Stalevo; Ternovag; *Neth.*: Duodopa; Sinemet; Stalevo; *Norw.*: Duodopa; Sinemet; Stalevo; *NZ*: Apo-Levocarb†; Sindopa; Sinemet; *Philipp.*: Ledocar; Sinemet; Stalev; Tidomet; *Pol.*: Sinemet; Stalevo; *Port.*: Duodopa; Ledopsan; Sinemet; Stalevo; *Rus.*: Duellin (Дуэллин); Nakom (Наком); Sinemet (Синемет); Stalevo (Сталево); Syndopa (Синдопа); Tidomet (Тидомет); Tremonorm (Тремонорм); *S.Afr.*: Carbilev; Sinemet; Stalevo; *Singapore*: Cardopar; Credanil; Levomet; Sinemet; Stalevo; Tidomet; *Spain*: Duodopa; Ledopsan†; Sinemet; Stalevo; *Swed.*: Duodopa; Levocar; Sinemet; Stalevo; *Switz.*: Duodopa; Sinemet; Stalevo; *Thai.*: Levomed; Levomet; Sinemet; Stalevo; Syndopa; Tidomet; *Turk.*: Sinemet; Stalevo; *UK*: Duodopa; Half Sinemet; Sinemet; Stalevo; *Ukr.*: Levocarbhexal (Левокарбгексал)†; Levokom (Левоком); Nakom (Наком); Stalevo (Сталево); *USA*: Atamet; Parcopa; Sinemet; Stalevo; *Venez.*: Sinemet; Stalevo.

Pharmacopoeial Preparations

BP 2014: Co-careldopa Tablets;

USP 36: Carbidopa and Levodopa Orally Disintegrating Tablets; Carbidopa and Levodopa Tablets.

Dexetimide *(BAN, USAN, rINN)*

Dextetimida; Dexétimide; Dexetimidum; Дексэтимид.

(*S*)-2-(1-Benzyl-4-piperidyl)-2-phenylglutarimide; (*S*)-3-Phenyl-1′-(phenylmethyl)-(3,4′-bipiperidine)-2,6-dione.

$C_{23}H_{26}N_2O_2$=362.5

CAS — 21888-98-2.

ATC — N04AA08.

ATC Vet — QN04AA08.

UNII — 43477QYX3D.

Dexetimide Hydrochloride *(BANM, rINNM)*

Dexbenzetimide Hydrochloride; Dexetimida, hidrocloruro de; Dexétimide, Chlorhydrate de; Dexetimidi Hydrochloridum; Hidrocloruro de dexetimida; R-16470; Дексэтимида Гидрохлорид.

$C_{23}H_{26}N_2O_2$,HCl=398.9

CAS — 21888-96-0.

ATC — N04AA08.

ATC Vet — QN04AA08.

UNII — B987A3XX7D.

Profile

Dexetimide is a tertiary antimuscarinic with actions similar to those of trihexyphenidyl (p. 917.3). It has been used to alleviate drug-induced extrapyramidal symptoms (see under Chlorpromazine, p. 1049.2), but, like other antimuscarinics, is of no value against tardive dyskinesias. Dexetimide hydrochloride has been given orally and by intramuscular injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Tremblex†.

Diethazine Hydrochloride *(BANM, rINNM)*

Diaethazinium Chloratum; Dietazina, hidrocloruro de; Diéthazine, Chlorhydrate de; Diethazini Hydrochloridum; Eazamine Hydrochloride; Hidrocloruro de dietazina; RP-2987; Диэтазина Гидрохлорид.

10-(2-Diethylaminoethyl)phenothiazine hydrochloride.

$C_{18}H_{22}N_2S$,HCl=334.9

CAS — 60-91-3 (diethazine); 341-70-8 (diethazine hydrochloride).

UNII — S88072126Q.

Profile

Diethazine hydrochloride is an antimuscarinic with actions similar to those of profenamine hydrochloride (p. 912.3), but it is more toxic and bone-marrow depression may occur. It has been used in the treatment of parkinsonism.

Droxidopa *(USAN, rINN)*

DOPS; Droxidopum; L-DOPS; L-*threo*-DOPS; L-*threo*-3,4-Dihydroxyphenylserine; Дроксидопа.

(-)-*threo*-3-(3,4-Dihydroxyphenyl)-L-serine.

$C_9H_{11}NO_5$=213.2

CAS — 23651-95-8.

UNII — J7A92W69L7.

Profile

Droxidopa is a precursor of noradrenaline that is used in the treatment of parkinsonism (p. 889.1) and some forms of orthostatic hypotension (p. 1634.3). The usual oral maintenance dose is 600 mg daily for the treatment of parkinsonism and 300 to 600 mg daily in orthostatic hypotension; daily doses should be divided.

The racemic form (DL-*threo*-3,4-dihydroxyphenylserine) has also been studied for orthostatic hypotension.

References.

1. Iida N, *et al.* Treatment of dialysis-induced hypotension with L-threo-3, 4-dihydroxyphenylserine. *Nephrol Dial Transplant* 1994; 9: 1130–5.
2. Freeman R, *et al.* The treatment of neurogenic orthostatic hypotension with 3,4-DL-threo-dihydroxyphenylserine: a randomized, placebo-controlled, crossover trial. *Neurology* 1999; 10: 2151–7.
3. Akizawa T, *et al.* Clinical effects of L-threo-3,4-dihydroxyphenylserine on orthostatic hypotension in hemodialysis patients. *Nephron* 2002; 90: 384–90.
4. Kaufmann H, *et al.* Norepinephrine precursor therapy in neurogenic orthostatic hypotension. *Circulation* 2003; 108: 724–8.
5. Goldstein DS, *et al.* Clinical pharmacokinetics of the norepinephrine precursor L-threo-DOPS in primary chronic autonomic failure. *Clin Auton Res* 2004; 14: 363–8.
6. Kaufmann H. L-dihydroxyphenylserine (Droxidopa): a new therapy for neurogenic orthostatic hypotension: the US experience. *Clin Auton Res* 2008; 18 (suppl 1): 19–24.
7. Mathias CJ. L-dihydroxyphenylserine (Droxidopa) in the treatment of orthostatic hypotension: the European experience. *Clin Auton Res* 2008; 18 (suppl 1): 25–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Dops.

Entacapone *(BAN, USAN, rINN)*

Entacapona; Entacaponum; Entakapon; Entakaponi; OR-611; Энтакапон.

(*E*)-α-Cyano-*N*,*N*-diethyl-3,4-dihydroxy-5-nitrocinnamamide; (*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylacrylamide.

$C_{14}H_{15}N_3O_5$=305.3

CAS — 130929-57-6.

ATC — N04BX02.

ATC Vet — QN04BX02.

UNII — 4975G9NM6T.

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

Ph. Eur. 8: (Entacapone). A greenish-yellow or yellow powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in anhydrous ethanol; soluble or sparingly soluble in acetone. Protect from light.

USP 36: (Entacapone). A greenish yellow to yellow powder. Practically insoluble in water; slightly soluble in alcohol; in chloroform, in ether, and in isopropyl alcohol; sparingly soluble in acetone and in methyl alcohol; very slightly soluble in toluene. Store in airtight containers.

Uses and Administration

Entacapone is a selective, reversible, peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of dopamine and levodopa. It is used as an adjunct to combination preparations of levodopa and dopa-decarboxylase inhibitors, in patients with Parkinson's disease (below) and 'end-of-dose' motor fluctuations who cannot be stabilised on levodopa combinations alone. Entacapone is given orally in a dosage of 200 mg at the same time as each dose of levodopa with dopa-decarboxylase inhibitor, up to a maximum of 200 mg ten times daily. It is often necessary to gradually reduce the dosage of levodopa by about 10 to 30% within the first few weeks after starting treatment with entacapone; this effect may be more marked in the presence of benserazide than of carbidopa.

Entacapone may also be given as a combination preparation with carbidopa and levodopa; for dosage details, see Levodopa, p. 902.3.

Parkinsonism. Entacapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT), with mainly peripheral actions. It is given as adjunctive therapy to patients with Parkinson's disease (p. 889.1) having fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations. When levodopa is given with a peripheral dopa-decarboxylase inhibitor, *O*-methylation then becomes the predominant form of metabolism of levodopa; therefore adding a peripheral COMT inhibitor such as entacapone potentially extends the duration and effect of levodopa in the brain, and thus allows levodopa to be given less often and in lower doses.

References.

1. Holm KJ, Spencer CM. Entacapone: a review of its use in Parkinson's disease. *Drugs* 1999; 58: 159–177.
2. Anonymous. Entacapone for Parkinson's disease. *Med Lett Drugs Ther* 2000; 42: 7–8.
3. Chong BS, Mersfelder TL. Entacapone. *Ann Pharmacother* 2000; 34: 1056–65.
4. Myllylä VV, *et al.* Twelve-month safety of entacapone in patients with Parkinson's disease. *Eur J Neurol* 2001; 8: 53–60.
5. Poewe WH, *et al.* Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). *Acta Neurol Scand* 2002; 105: 245–55.
6. Brooks DJ, *et al.* Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. *J Neurol Neurosurg Psychiatry* 2003; 74: 1071–9.
7. Fenelon G, *et al.* Efficacy and tolerability of entacapone in patients with Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearing-off motor fluctuations: a randomized, double-blind, multicentre study. *J Neurol Transm* 2003; 110: 239–51.
8. Olanow CW, Stocchi F. COMT inhibitors in Parkinson's disease: can they prevent and/or reverse levodopa-induced motor complications? *Neurology* 2004; 62 (suppl 1): S72–S81.
9. Deane K, *et al.* Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).
10. Poewe W. The role of COMT inhibition in the treatment of Parkinson's disease. *Neurology* 2004; 62 (suppl 1): S31–S38.
11. Schrag A. Entacapone in the treatment of Parkinson's disease. *Lancet Neurol* 2005; 4: 366–70.

Adverse Effects

The most frequent adverse effects produced by entacapone relate to increased dopaminergic activity and occur most commonly at the start of treatment: reduction of the levodopa dosage may reduce the severity and frequency of such effects. Adverse effects may include nausea, vomiting, abdominal pain, constipation, diarrhoea, colitis, dry mouth, and dyskinesias. Other commonly reported adverse effects include dizziness, insomnia, nightmares, hallucinations, confusion, fatigue, and increased sweating. Behavioural disturbances including intense urges to gamble and increased sexual urges have also been reported (see Effects on Mental Function, in Levodopa, p. 905.2). There have been rare reports of agitation, urticaria, erythematous or maculopapular rash, anorexia, and weight decrease. Increases in liver enzyme values have been reported rarely; there have also been isolated cases of cholestatic hepatitis. Isolated cases of neuroleptic malignant syndrome have been reported after abrupt reduction or withdrawal of entacapone; there have also been isolated cases of rhabdomyolysis. It may produce a harmless reddish-brown discoloration of the urine. Skin, hair, beard, and nail discolorations have been reported.

References.

1. Brooks DJ. Safety and tolerability of COMT inhibitors. *Neurology* 2004; 62 (Suppl 1): S39–S46.

Carcinogenicity. The FDA[1] reported that it is continuing to review data from the STRIDE-PD study, which suggested that parkinsonian patients who were taking the combination preparation containing entacapone, carbidopa, and levodopa (*Stalevo; Novartis, USA*) had an increased risk of prostate cancer when compared with those who were taking carbidopa with levodopa. The FDA commented that previous studies of shorter duration did not find such an association with entacapone, and that prostate cancer is most commonly diagnosed in men of the same age as those in the STRIDE-PD study.

1. FDA. FDA drug safety communication: ongoing safety review of Stalevo (entacapone/carbidopa/levodopa) and possible development of prostate cancer (issued 31st March, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm206363.htm (accessed 14/05/10)

Effects on the cardiovascular system. The FDA[1] is continuing to evaluate data from clinical studies that initially suggest that patients taking a combination preparation containing entacapone, carbidopa, and levodopa (*Stalevo; Novartis, USA*) are at an increased risk of cardiovascular events compared with those taking carbidopa with levodopa. The FDA commented that most patients had pre-existing risk factors for cardiovascular disease.

1. FDA. FDA drug safety communication: ongoing safety review of Stalevo and possible increased cardiovascular risk (issued 20th August, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm223060.htm (accessed 24/08/10)

Precautions

Entacapone is contra-indicated in patients with phaeochromocytoma and in patients with a history of neuroleptic malignant syndrome or nontraumatic rhabdomyolysis. It should be avoided in patients with hepatic impairment, and given with caution to patients with biliary obstruction. A general medical evaluation, including liver function, should be considered in those who develop progressive anorexia, asthenia, and weight decrease within a relatively short period of time. Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, under Adverse Effects of Levodopa, p. 905.2) and again, caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Treatment with entacapone should not be stopped abruptly; when necessary withdrawal should be made gradually, increasing the dose of levodopa as required.

Genetic polymorphism. For reference to slow metabolisers being more susceptible to COMT-inhibitor induced hepatotoxicity, see under Tolcapone, p. 917.2.

Interactions

Use of entacapone with a non-selective MAOI is contra-indicated. Entacapone should be used with caution in patients receiving drugs metabolised by catechol-*O*-methyltransferase (COMT) including adrenaline, apomorphine, dobutamine, dopamine, isoprenaline, methyldopa, noradrenaline, paroxetine, and rimiterol. Caution is also advised when used with certain antidepressants including the tricyclics, reversible inhibitors of monoamine oxidase type A, and noradrenaline reuptake inhibitors such as venlafaxine.

Entacapone may aggravate levodopa-induced orthostatic hypotension and should be used cautiously in patients who are taking other drugs that may cause orthostatic hypotension.

Entacapone may form chelates with iron preparations in the gastrointestinal tract; the two drugs should be taken at least 2 to 3 hours apart.

Pharmacokinetics

There are large intra- and interindividual variations in the absorption of entacapone. Peak plasma concentrations occur about one hour after oral doses. Entacapone undergoes extensive first-pass metabolism and oral bioavailability is about 35%. Absorption is not affected significantly by food. Entacapone is about 98% bound to plasma proteins. It is eliminated mainly in the faeces with about 10 to 20% being excreted in the urine, mainly as glucuronide conjugates. Entacapone is thought to be distributed into breast milk on the basis of studies in *rats*.

Entacapone is rapidly absorbed from the gastrointestinal tract and bioavailability after oral doses has been reported to range from 29 to 46%. It does not cross the blood-brain barrier. Over half of a dose appears in the faeces with smaller amounts being excreted in the urine as glucuronides of entacapone and its (*Z*)-isomer. Elimination half-lives of about 1.6 to 3.4 hours have been reported for entacapone.

References.
1. Wikberg T, *et al.* Identification of major metabolites of the catechol-O-methyltransferase inhibitor entacapone in rats and humans. *Drug Metab Dispos* 1993; 21: 81–92.
2. Keränen T, *et al.* Inhibition of soluble catechol-O-methyltransferase and single-dose pharmacokinetics after oral and intravenous administration of entacapone. *Eur J Clin Pharmacol* 1994; 46: 151–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Comtan; *Austral.*: Comtan; *Austria*: Comtan; *Belg.*: Comtan; *Braz.*: Comtan; Entarkin; *Canad.*: Comtan; *China*: Comtan (珂丹); *Cz.*: Comtan; Comtess; *Denm.*: Comtan†; Comtess; *Fin.*: Comtess; *Fr.*: Comtan; *Ger.*: Comtess; *Gr.*: Comtan; *Hong Kong*: Comtan; *Hung.*: Comtan; *India*: Adcapone; Entacom; *Indon.*: Comtan; *Irl.*: Comtan; Comtess; *Israel*: Comtan; *Ital.*: Comtan; *Malaysia*: Comtan; *Mex.*: Comtan; *Neth.*: Comtan; Comtess; *Norw.*: Comtess; *NZ*: Comtan; *Philipp.*: Comtan; *Pol.*: Comtan; Comtess; *Port.*: Comtan; Comtess; *S.Afr.*: Comtan; *Singapore*: Comtan; *Spain*: Comtan; *Swed.*: Comtess; *Switz.*: Comtan; *Thai.*: Comtan; *Turk.*: Comtan; *UK*: Comtess; *Ukr.*: Comtan (Комтан)†; *USA*: Comtan; *Venez.*: Comtan.

Multi-ingredient Preparations. *Arg.*: Stalevo; *Austral.*: Stalevo; *Austria*: Stalevo; *Belg.*: Stalevo; *Braz.*: Stalevo; *Canad.*: Stalevo; *Chile*: Stalevo; *Cz.*: Stalevo; *Denm.*: Stalevo; *Fin.*: Stalevo; *Fr.*: Stalevo; *Ger.*: Stalevo; *Gr.*: Stalevo; *Hong Kong*: Stalevo; *Hung.*: Stalevo; *Indon.*: Stalevo; *Irl.*: Stalevo; *Israel*: Stalevo; *Ital.*: Stalevo; *Malaysia*: Stalevo; *Mex.*: Stalevo; *Neth.*: Stalevo; *Norw.*: Stalevo; *Philipp.*: Stalev; *Pol.*: Stalevo; *Port.*: Stalevo; *Rus.*: Stalevo (Сталево); *S.Afr.*: Stalevo; *Singapore*: Stalevo; *Spain*: Stalevo; *Swed.*: Stalevo; *Switz.*: Stalevo; *Thai.*: Stalevo; *Turk.*: Stalevo; *UK*: Stalevo; *Ukr.*: Stalevo (Сталево); *USA*: Stalevo; *Venez.*: Stalevo.

Pharmacopoeial Preparations
USP 36: Entacapone Tablets.

Istradefylline *(USAN, rINN)*

Istradefilina; Istradéfylline; Istradefyllinum; KW-6002; Истрадефиллин.

8-[(1*E*)-2-(3,4-Dimethoxyphenyl)ethenyl]-1,3-diethyl-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione.

$C_{20}H_{24}N_4O_4$=384.4

CAS — 155270-99-8.

UNII — 2GZ0UK7T4.

Profile

Istradefylline is a selective adenosine A_{2A}-receptor antagonist given to reduce 'end-of-dose' deterioration with levodopa therapy in the treatment of Parkinson's disease (p. 889.1). Istradefylline is given orally in a usual dose of 20 mg once daily, which can be increased to 40 mg daily if necessary.

References.
1. Park A, Stacy M. Istradefylline for the treatment of Parkinson's disease. *Expert Opin Pharmacother* 2012; 13: 111–14.
2. Chen W, *et al.* Istradefylline, an adenosine A_{2A} receptor antagonist, for patients with Parkinson's disease: a meta-analysis. *J Neurol Sci* 2013; 324: 21–8.
3. Dungo R, Deeks ED. Istradefylline: first global approval. *Drugs* 2013; 73: 875–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Nouriast.

Levodopa *(BAN, USAN, rINN)*

Dihydroxyphenylalanine; L-Dopa; 3-Hydroxy-L-tyrosine; Laevo-dopa; Lévodopa; Levodopum; Леводопа.

(-)-3-(3,4-Dihydroxyphenyl)-L-alanine.

$C_9H_{11}NO_4$=197.2

CAS — 59-92-7.

ATC — N04BA01.

ATC Vet — QN04BA01.

UNII — 46627O600J.

NOTE. Compounded preparations of levodopa may be represented by the following names:
- Co-beneldopa (*BAN*)—benserazide 1 part and levodopa 4 parts (w/w)
- Co-careldopa *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of carbidopa and levodopa, respectively
- Co-careldopa (*PEN*)—carbidopa and levodopa

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

Ph. Eur. 8: (Levodopa). A white or slightly cream-coloured, crystalline powder. Slightly soluble in water; freely soluble in 1M hydrochloric acid but sparingly soluble in 0.1M hydrochloric acid; practically insoluble in alcohol. A 1% suspension in water has a pH of 4.5 to 7.0. Protect from light.

USP 36: (Levodopa). A white to off-white, odourless, crystalline powder. In the presence of moisture, it is rapidly oxidised by atmospheric oxygen and darkens. Slightly soluble in water; freely soluble in 3N hydrochloric acid; insoluble in alcohol. Store in a dry place in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Stability. Extemporaneously prepared oral liquid dosage forms may be unstable and manufacturers' formulations should be used where possible.[1] Water dispersible formulations of levodopa with benserazide are available in some countries but a method that can be used by patients to prepare daily solutions of levodopa with carbidopa has been suggested:[2] one litre of a solution in potable water may be prepared with ten crushed standard tablets of levodopa 100 mg with carbidopa 25 mg and 2 g of ascorbic acid added to stabilise the levodopa.

1. Walls TJ, *et al.* Problems with inactivation of drugs used in Parkinson's disease. *BMJ* 1985; 290: 444–5.
2. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; 14: 365–74.

Uses and Administration

Levodopa, a naturally occurring amino acid, is the immediate precursor of the neurotransmitter dopamine. The actions of levodopa are mainly those of dopamine (p. 1367.2).

Unlike dopamine, levodopa readily enters the CNS and is used in the treatment of conditions, such as Parkinson's disease (p. 904.1), that are associated with depletion of dopamine in the brain. Levodopa is rapidly decarboxylated by peripheral enzymes so that very little unchanged drug is available to cross the blood-brain barrier for central conversion into dopamine. Consequently, levodopa is usually given with a peripheral dopa-decarboxylase inhibitor such as benserazide (p. 894.1) or carbidopa (p. 900.3) to increase the proportion of levodopa that can enter the brain. This enables the dosage of levodopa to be reduced and may diminish peripheral adverse effects, such as nausea and vomiting and cardiac arrhythmias, by blocking the peripheral production of dopamine. It may also provide a more rapid response at the start of therapy.

The majority of patients with Parkinson's disease benefit from levodopa therapy, but after 2 years or more, improvement in disability is gradually lost as the disease progresses and fluctuations in mobility emerge. Postencephalitic parkinsonism responds to levodopa, but a higher incidence of adverse effects has been reported than in the idiopathic form so smaller doses are generally used. Levodopa has also been used to control the neurological symptoms of chronic manganese poisoning, which resemble those of parkinsonism. It should not be used in antipsychotic-induced parkinsonism.

Levodopa has an effect on pituitary function as a result of its conversion to dopamine. It may enhance growth hormone secretion and has been used diagnostically as a provocative test for growth hormone deficiency. Levodopa also inhibits prolactin secretion.

Response to levodopa varies considerably between patients. **Treatment of parkinsonism** should begin with small doses increased gradually, ideally to a dose that improves mobility without producing adverse effects. Levodopa should be taken with or after meals, although in later disease, it may be preferable to take it on an empty stomach (see Precautions, p. 906.3). Once established, maintenance doses may need to be reduced as the patient ages. When given **without a peripheral dopa-decarboxylase inhibitor** (which is rare) a suggested initial oral dose is 125 mg twice daily increased gradually every 3 to 7 days, according to response, to up to 8 g daily in divided doses. The intervals between doses should be adjusted to meet individual needs; many patients find 4 or 5 divided doses daily to be satisfactory although some may require smaller, more frequent doses in order to control fluctuations in mobility. Maximum improvement may take up to 6 months or longer to occur.

When given **with a peripheral dopa-decarboxylase inhibitor** lower doses of levodopa are used. As high central dopamine concentrations can be achieved more quickly, both beneficial and adverse effects tend to occur more rapidly than with levodopa alone and patients should be monitored carefully. In those already receiving levodopa the drug should be stopped and benserazide or carbidopa with levodopa started on the next day or after 24 hours if the patient was receiving a modified-release preparation of levodopa.

Benserazide is given as the hydrochloride but doses are expressed in terms of the base. Benserazide hydrochloride 28.5 mg is equivalent to about 25 mg of benserazide. Benserazide is usually given with levodopa in the ratio of 1 part of benserazide base to 4 parts of levodopa (co-beneldopa) and the doses for co-beneldopa that follow are expressed in terms of the levodopa component.

- An initial oral dose for *patients not previously treated with levodopa* is levodopa 50 mg three or four times daily increased gradually in increments of levodopa 100 mg once or twice weekly, according to response. If the disease is at an advanced stage, the initial starting dose may be increased to levodopa 100 mg three times daily. For some elderly patients, an initial dose of levodopa 50 mg once or twice daily, increased by 50 mg every third or fourth day, may be suitable. Maintenance doses usually lie within the range of levodopa 400 to 800 mg daily in divided doses, although most patients require no more than 600 mg daily. If optimal improvement has not been achieved after several weeks at the average dose, further increases may be made with caution; it is rarely necessary to give more than 1 g of levodopa daily.
- The initial dose of levodopa given with benserazide in *patients previously treated with levodopa alone* should be about 10 to 15% of the dose previously being taken, thus levodopa 300 mg would be appropriate for a patient previously taking levodopa 2 g daily. For *patients previously treated with other levodopa/dopa-decarboxylase inhibitor combinations* an initial dose is levodopa 50 mg given three or four times daily. In either situation, the dose may then be adjusted in a similar manner as described for previously untreated patients.
- Modified-release capsules containing the equivalent of benserazide 25 mg with levodopa 100 mg are available to reduce fluctuations in response to immediate-release preparations. For *patients not already receiving levodopa* the initial dose is one capsule three times daily adjusted every 2 to 3 days according to response; it is recommended that initial dosages should not exceed 600 mg of levodopa daily. For *patients already receiving an immediate-release preparation* of levodopa with benserazide, initially one capsule should be substituted for every 100 mg of levodopa and should be given at the same dosage frequency as before; increases in dosage can then be made every 2 to 3 days according to response. An average of 50% more levodopa may be required compared with previous therapy and titration may take up to 4 weeks. *Supplementary doses* of an immediate-release preparation of benserazide with levodopa may also be required with the first morning dose.

Carbidopa is usually given with levodopa (co-careldopa) as tablets in the ratio of 1 to 4 or 1 to 10, which allows dosage adjustments of either drug for individual patients. Carbidopa is given as the hydrous base although doses are expressed in terms of the anhydrous base; hydrous carbidopa 10.8 mg is equivalent to about 10 mg of anhydrous carbidopa. Full inhibition of peripheral dopa-decarboxylase is reported to be achieved with 70 to 100 mg of carbidopa daily.

- A suggested initial oral dose for *patients not previously treated with levodopa* is carbidopa 25 mg with levodopa 100 mg three times daily, increased gradually, in increments of carbidopa 12.5 mg with levodopa 50 mg or carbidopa 25 mg with levodopa 100 mg every day or on alternate days, as necessary, until a total daily dose of carbidopa 200 mg with levodopa 800 mg is reached. Maintenance therapy should be individualised and adjusted gradually according to response. Carbidopa doses greater than 200 mg daily are not generally exceeded.
- The initial dose of levodopa with carbidopa in *patients previously treated with levodopa alone* should be about 20 to 25% of the dose previously being taken, thus for patients taking less than 1.5 g of levodopa daily a suggested initial dose is carbidopa 25 mg with levodopa 100 mg given three or four times daily; a suggested initial dose for patients taking more than 1.5 g of levodopa daily is carbidopa 25 mg with levodopa 250 mg given three or four times daily. For *patients previously treated with other levodopa/dopa-decarboxylase inhibitor combinations* an initial dose should provide a similar daily amount of levodopa.
- Modified-release tablets containing carbidopa with levodopa in the ratio of 1 to 4 are available to reduce fluctuations in response to immediate-release preparations. For *patients not already receiving levodopa* therapy, or for *those currently receiving levodopa alone*, the initial dose is carbidopa 50 mg with levodopa 200 mg twice daily, adjusted according to response, at intervals of not less than 3 days. It is recommended that for patients who are not already receiving levodopa initial dosages should not exceed 600 mg of levodopa daily. For *patients already receiving an immediate-release preparation* of carbidopa with levodopa, the initial dose of the modified-release preparation should provide a similar daily amount of levodopa, but the dosing intervals should be prolonged and are normally between 4 to 12 hours. The initial substitution dose of the modified-release preparation should provide no greater than 10% more levodopa than was previously given for doses of levodopa exceeding 900 mg daily. Doses and intervals may then be altered according to clinical response, allowing at least 3 days between adjustments. Up to 30% more levodopa may be required in the modified-release preparation than was previously given in the immediate-release preparation. Average maintenance doses of modified-release preparations lie within the range of carbidopa 100 mg with levodopa 400 mg to carbidopa 400 mg with levodopa 1.6 g daily in divided doses. *Supplementary doses* of an immediate-release preparation of carbidopa with levodopa may be required in some patients.

Combination preparations of levodopa with carbidopa and the catechol-*O*-methyltransferase (COMT) inhibitor **entacapone** are also available; each tablet contains levodopa and carbidopa in a ratio of 4 to 1 with entacapone 200 mg. Such preparations are indicated for patients with end-of-dose motor fluctuations not stabilised on levodopa/peripheral dopa-decarboxylase inhibitor treatment. Patients should only take one combination tablet for each dose.

- *Patients previously treated with an immediate-release preparation of levodopa with a peripheral dopa-decarboxylase inhibitor and separate entacapone* should be transferred to the combination preparation at a dose that provides similar or slightly higher amounts of levodopa.
- For *patients not currently taking entacapone*, the dose of the combination preparation should normally provide a similar or slightly lower dose of levodopa to that previously taken. However, patients with *dyskinesia* or taking *levodopa in doses above 800 mg daily* should start entacapone as a separate medication before being transferred to the combination preparation, as a 10 to 30% reduction in their levodopa dose may be needed when starting combination therapy, especially if levodopa is being given with benserazide.

In some countries a gel formulation of levodopa 20 mg/mL with carbidopa 5 mg/mL is available for *continuous infusion* by an ambulatory pump into the duodenum. It is indicated for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations when other available combination therapy has not been satisfactory. A positive test of the clinical response via a temporary nasoduodenal tube is required before a permanent tube is inserted into the duodenum or upper jejunum. The total daily dose comprises of 3 individually-adjusted doses, which are expressed in terms of the levodopa component as follows:

- the *morning bolus dose*, based on the patient's previous morning intake of levodopa, is usually 100 to 200 mg and should not exceed 300 mg in total; the therapeutic dose level is achieved within 10 to 30 minutes
- the *continuous maintenance dose*, based on the patient's previous daily intake of levodopa, is usually 40 to 120 mg/hour infused over 16 hours, adjustable in steps of 2 mg/hour to within a range of 20 to 200 mg/hour; higher doses may be needed in exceptional cases
- *extra bolus doses*, given when required, are usually between 10 to 40 mg although higher doses may be needed in exceptional cases; the maintenance dose should be increased if more than 5 bolus doses are needed daily

After the initial dose setting, further dose adjustments should be made over a few weeks. If medically justified, it may be administered during the night.

Melevodopa, the methyl ester of levodopa, has been used orally as the hydrochloride with carbidopa in some countries for parkinsonism. The ethyl ester of levodopa, etilevodopa, has also been studied.

Administration. A small crossover study involving 24 patients with severe Parkinson's disease found that daytime intraduodenal infusion of a levodopa and carbidopa gel preparation for 3 weeks was clinically superior to individually optimised conventional regimens.[1] Another small case series of 5 patients found that continuous 24-hour intraduodenal infusion was also generally well-tolerated and improved motor fluctuations without the development of clinically significant tolerance to its effects.[2] Long-term experience (up to 7 years) in a limited number of patients has suggested that intraduodenal infusion is a good alternative for those with advanced disease and disabling motor fluctuations.[3] A gel formulation of levodopa 20 mg/mL with carbidopa 5 mg/mL is available in some countries for intraduodenal infusion.

1. Nyholm D, *et al.* Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; **64**: 216–23.
2. Nyholm D, *et al.* Long-term 24-hour duodenal infusion of levodopa: outcome and dose requirements. *Neurology* 2005; **65**: 1506–7.
3. Nilsson D, *et al.* Duodenal levodopa infusion in Parkinson's disease: long-term experience. *Acta Neurol Scand* 2001; **104**: 343–8.

Administration in children. Although unlicensed, levodopa has been tried for various conditions in neonates, children, and adolescents. For further details and suggested doses, see Amino Acid Metabolic Disorders (below), Dystonias (below), and Pituitary and Hypothalamic Disorders (p. 904.2).

Amino acid metabolic disorders. Although not licensed for the treatment of defects in tetrahydrobiopterin synthesis and dihydrobiopterin reductase deficiency, the *BNFC* suggests that neonates, children, and adolescents up to the age of 18 years may be given initial oral doses of 250 to 500 micrograms/kg of levodopa (with carbidopa in the ratio of 4 to 1) four times daily increased according to response every 4 to 5 days to a maintenance dose of 2.5 to 3 mg/kg four times daily. Preparations containing levodopa with carbidopa in the ratio of 10 to 1 should be considered at higher doses. Treatment should be reviewed regularly every 3 to 6 months during early childhood.

Drug-induced extrapyramidal disorders. The management of drug-induced extrapyramidal disorders is discussed under the Adverse Effects of Chlorpromazine on p. 1049.2. Although the use of dopamine agonists, especially levodopa, to overcome antipsychotic-induced blockade of dopamine receptors might appear rational, levodopa has generally been reported to be ineffective or to increase psychiatric symptoms.

Dysphagia. Results of a small study[1] have suggested that levodopa may improve the impaired swallowing reflex in patients with basal ganglia infarctions and thereby help to prevent aspiration pneumonia.

1. Kobayashi R, *et al.* Levodopa and swallowing reflex. *Lancet* 1996; **348**: 1320–1.

Dystonias. A dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures; it may also have additional myoclonic or tremulous components. Typically it starts as a focal dystonia localised in one part of the body and to begin with may appear only during a specific motor act (action dystonia). If the syndrome is progressive the dystonias may become apparent at rest and spread first to more than one part of the body (segmental dystonia) and may eventually affect most or all of the body (generalised dystonia). Progression of the dystonia appears to be related to age of onset. Dystonia beginning in childhood usually starts in the legs and progresses to become segmental or generalised, whereas in adults the dystonia usually starts in other parts of the body and rarely becomes generalised. Examples of focal dystonias are blepharospasm (affecting the eye and surrounding facial muscles), writer's cramp (hand and arm), spasmodic torticollis (neck), spasmodic dysphonia, or dystonic dysphagia (larynx or pharynx), and leg dystonias. Some dystonias may be associated with metabolic disorders such as Wilson's disease or Lesch-Nyhan syndrome; with neurological disorders such as Huntington's disease; or with other causes including head trauma, manganese or carbon disulfide toxicity, or the adverse effects of antipsychotics or antiparkinsonian drugs. However, in the majority of cases the disease is idiopathic.

There are no cures for most types of dystonia, but with appropriate **management** symptomatic relief is possible in many patients.[1-5]

- It has been suggested that all children and adolescents presenting with dystonia, particularly starting in the legs, should first be given a trial with *levodopa*.[1,3,5] Although not licensed for children in the UK, the *BNFC* states that children aged 3 months and older with dopamine-sensitive dystonias, including dystonic cerebral palsy, may be given 250 micrograms/kg of levodopa (with carbidopa in the ratio of 4 to 1) orally two or three times daily increased according to response every 2 to 3 days to a maximum of 1 mg/kg of levodopa three times daily. Another suggested regimen is to gradually build up to a dose of levodopa 200 mg with carbidopa 50 mg given three times daily and to maintain this dose for 3 months; if there is no useful response in this period the drug is withdrawn.[1] Where there is benefit it is usually dramatic and is sustained as long as the drug is taken, which may be more than 10 years in some cases, in general without the long-term problems associated with levodopa for parkinsonism (see p. 889.1).
- In children and adolescents who fail to respond to levodopa an *antimuscarinic* such as trihexyphenidyl is second choice; the *BNFC* also suggests using procyclidine. Adverse effects are minimised by starting with a low dose which is then gradually increased. General experience indicates that about half of all children and adolescents benefit from antimuscarinics; adults tolerate the drug less well and only about a fifth of adult patients with focal dystonia benefit.
- In patients who do not respond to levodopa or high-dose antimuscarinics other drugs may be used. Many benefit from *benzodiazepines* such as diazepam; a few have responded to *baclofen* or *carbamazepine*. *Antipsychotics* are sometimes useful but carry the risk of inducing tardive dyskinesia. *Tetrabenazine* carries less risk of tardive dyskinesia but may induce depression. In very severe dystonia combination therapy may be required: tetrabenazine with pimozide and trihexyphenidyl is sometimes effective.

- In patients refractory to oral therapy *intrathecal* baclofen, or surgery may be tried.
- The response in patients with adult onset focal dystonia is usually poor. However, the use of *botulinum A toxin* can produce relief in blepharospasm, spasmodic torticollis, and spasmodic dysphonia, and is under investigation for writer's cramp and other occupational dystonias. In some patients with generalised and segmental dystonia, botulinum A toxin injected into the most disabling or painful muscles has been used as adjunctive therapy. Local injections into the affected muscles produce weakness over the next week or so, thereby reducing or abolishing dystonic spasms. The effect lasts some 2 to 4 months. *Botulinum B toxin* has also been used in the management of spasmodic torticollis.

Further details of the management of blepharospasm and spasmodic torticollis can be found under Botulinum Toxins on p. 2018.1 and p. 2019.2, respectively. For a discussion of the management of antipsychotic-induced dystonic reactions, see Extrapyramidal Disorders, under Adverse Effects of Chlorpromazine, p. 1049.2.

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; 300: 139–44.
2. Williams A. Consensus statement for the management of focal dystonias. *Br J Hosp Med* 1993; 50: 655–9.
3. Bressman SB. Dystonia update. *Clin Neuropharmacol* 2000; 23: 239–51.
4. Tarsy D, Simon DK. Dystonia. *N Engl J Med* 2006; 355: 818–29.
5. Jankovic J. Treatment of dystonia. *Lancet Neurol* 2006; 5: 864–72.

Hepatic encephalopathy. For the view that the evidence does not support the use of dopaminergics such as levodopa in the management of hepatic encephalopathy see p. 1811.2.

Neuroleptic malignant syndrome. There have been isolated reports[1-4] that levodopa used alone or with bromocriptine has been successful in the treatment of patients with neuroleptic malignant syndrome (p. 1050.2). However, bromocriptine is usually preferred when a dopaminergic is required for the treatment of this condition.

1. Knezevic W, *et al.* Neuroleptic malignant syndrome. *Med J Aust* 1984; 140: 28–30.
2. Clarke CE, *et al.* Clinical spectrum of neuroleptic malignant syndrome. *Lancet* 1988; ii: 969–70.
3. Lo TCN, *et al.* Neuroleptic malignant syndrome: another medical cause of acute abdomen. *Postgrad Med J* 1989; 65: 653–5.
4. Shoop SA, Cernek PK. Carbidopa/levodopa in the treatment of neuroleptic malignant syndrome. *Ann Pharmacother* 1997; 31: 119.

Parkinsonism. Levodopa is the mainstay in the treatment of Parkinson's disease (p. 889.1) but opinion varies on when it should be used in the course of the disease. Most patients respond to levodopa initially but after a few years benefit may be reduced. There may be problems with dyskinesias and psychiatric effects and fluctuations in mobility necessitating careful dosage adjustment or the use of adjunctive drugs. For most patients treatment with levodopa eventually becomes necessary, but many neurologists delay initial treatment with levodopa because of the increased risk of motor complications. New patients, especially younger patients, therefore often begin treatment with a dopamine agonist, with levodopa reserved for the elderly, the frail, or those with intercurrent illness or more severe symptoms. Levodopa should be given with a peripheral dopa-decarboxylase inhibitor; a peripheral catechol-*O*-methyltransferase (COMT) inhibitor may also be necessary for patients with fluctuations in disability related to levodopa and dopa-decarboxylase inhibitor combinations. The various methods used for the pharmacokinetic optimisation of levodopa therapy as Parkinson's disease progresses include timing of doses, the use of modified-release formulations, oral solutions (but see Stability, p. 902.3) and dispersible formulations for immediate absorption, the timing of food intake, and the use of other drugs to increase the absorption of levodopa. In some countries a gel formulation of levodopa with carbidopa is available for intraduodenal infusion.

References.

1. Giroi LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; 14: 365–74.
2. Contin M, *et al.* Pharmacokinetic optimisation in the treatment of Parkinson's disease. *Clin Pharmacokinet* 1996; 30: 463–81.
3. Murer MG, *et al.* Levodopa in Parkinson's disease: neurotoxicity issue laid to rest? *Drug Safety* 1999; 21: 339–52.
4. Furlanut M, *et al.* Monitoring of L-dopa concentrations in Parkinson's disease. *Pharmacol Res* 2001; 43: 423–7. Correction. *ibid.*; 44: 149.
5. Carlsson A. Treatment of Parkinson's with L-DOPA: the early discovery phase, and a comment on current problems. *J Neural Transm* 2002; 109: 777–87.
6. Katzenschlager R, Lees AJ. Treatment of Parkinson's disease: levodopa as the first choice. *J Neurol* 2002; 249 (suppl 2): II19–II24.
7. van Laar T. Levodopa-induced response fluctuations in patients with Parkinson's disease: strategies for management. *CNS Drugs* 2003; 17: 475–89.
8. LeWitt PA, Nyholm D. New developments in levodopa therapy. *Neurology* 2004; 62 (suppl 1): S9–S16.
9. Stocchi F, Olanow CW. Continuous dopaminergic stimulation in early and advanced Parkinson's disease. *Neurology* 2004; 62 (suppl 1): S56–S63.
10. Nyholm D, *et al.* Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; 64: 216–23.
11. LeWitt PA. Levodopa for the treatment of Parkinson's disease. *N Engl J Med* 2008; 359: 2468–76.

Pituitary and hypothalamic disorders. *DIAGNOSIS AND TESTING.* Diminished growth hormone reserve is one of the earliest functional abnormalities in anterior pituitary failure and, since dopamine is believed to stimulate growth hormone secretion, levodopa has been used as a provocative test for the diagnosis of growth hormone deficiency.[1,2] Levodopa 500 mg has been given orally after an overnight fast and serum concentrations of growth hormone measured hourly at 0 to 3 hours; children may be given 10 mg/kg to a maximum of 500 mg. Transient nausea, vomiting, vertigo, and hypotension may occur and the patient should be kept recumbent during the test. A normal response is an increase in serum concentration of growth hormone of more than 5 nanograms/mL or to a level of more than 10 nanograms/mL, although 10 to 15% of normal subjects may not respond. However, there is some dispute as to whether stimulated growth hormone secretion tests are superior to measurements of circulating somatomedins in detecting growth hormone deficiency.[3-5] For a discussion of the management of growth retardation, including the problems of accurate diagnosis, see p. 1921.3.

1. Abboud CF. Laboratory diagnosis of hypopituitarism. *Mayo Clin Proc* 1986; 61: 35–48.
2. Möller EE, *et al.* Involvement of brain catecholamines and acetylcholine in growth hormone deficiency states: pathophysiological, diagnostic and therapeutic implications. *Drugs* 1991; 41: 161–77.
3. Hoffmann DM, *et al.* Diagnosis of growth-hormone deficiency in adults. *Lancet* 1994; 343: 1064–8. Correction. *ibid.*, 344: 206.
4. de Boer H, *et al.* Diagnosis of growth hormone deficiency in adults. *Lancet* 1994; 343: 1645–6.
5. Rosenfeld RG, *et al.* Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. *J Clin Endocrinol Metab* 1995; 80: 1532–40.

Sleep-associated movement disorders. The aetiology of *restless legs syndrome* and *periodic limb movements in sleep* is obscure and treatment has been largely empirical (p. 1034.2). Few of the treatments tried in these often co-existent disorders have been studied in a controlled manner but small controlled studies[1-6] have reported beneficial effects such as improved sleep quality and reduced leg movements from levodopa used with a peripheral dopa-decarboxylase inhibitor. Most patients received a bedtime dose of 50 to 200 mg of levodopa with possible additional doses during the night. A 1-year open-label extension study[7] confirmed the continued efficacy and safety of levodopa in patients with restless legs syndrome; the authors recommended a maximum daily dose of 400 mg levodopa to decrease the risk of exacerbation or rebound symptoms during the day. However, long-acting dopaminergic agonists are preferred in order to avoid the complications associated with levodopa.

Levodopa has also been reported to have been of benefit in a study of 10 patients with *sleep bruxism*.[8]

1. von Scheele C. Levodopa in restless legs. *Lancet* 1986; ii: 426–7.
2. Brodeur C, *et al.* Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind controlled study. *Neurology* 1988; 38: 1845–8.
3. Kaplan PW, *et al.* A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep* 1993; 16: 717–23.
4. Trenkwalder C, *et al.* L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind crossover trial. *Sleep* 1995; 18: 681–8.
5. Benes H, *et al.* Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. *Sleep* 1999; 22: 1073–81.
6. Janzen L, *et al.* An overview of levodopa in the management of restless legs syndrome in a dialysis population: pharmacokinetics, clinical trials, and complications of therapy. *Ann Pharmacother* 1999; 33: 86–92.
7. Trenkwalder C, *et al.* One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? *Mov Disord* 2003; 18: 1184–9.
8. Lobbezoo F, *et al.* The effect of the catecholamine precursor L-dopa on sleep bruxism: a controlled clinical trial. *Mov Disord* 1997; 12: 73–8.

Strabismus. Experimental studies have shown that centrally acting drugs such as levodopa may improve vision in patients with amblyopia (see Strabismus, p. 2000.3). However, their role in clinical practice is not established.[1]

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; 2: 91–100.

Tourette's syndrome. Levodopa has been studied in the management of Tourette's syndrome (see Tics, p. 1030.1). A small pilot study[1] has produced encouraging results.

1. Black KJ, *et al.* Response to levodopa challenge in Tourette syndrome. *Mov Disord* 2000; 15: 1194–8.

Adverse Effects

Gastrointestinal effects, notably nausea, vomiting, and anorexia are common early in treatment with levodopa, particularly if the dosage is increased too rapidly. Gastrointestinal bleeding has been reported in patients with a history of peptic ulcer disease.

The commonest cardiovascular effect is orthostatic hypotension, which is usually asymptomatic, but may be associated with faintness and dizziness. Cardiac arrhythmias have been reported and hypertension has occasionally occurred.

Psychiatric symptoms occur in a high proportion of patients, especially the elderly, and include agitation, anxiety, euphoria, nightmares, insomnia or sometimes drowsiness, and depression. More serious effects, usually requiring a reduction in dosage or withdrawal of levodopa, include aggression, paranoid delusions, hallucinations, delirium, severe depression, with or without suicidal behaviour, and unmasking of psychoses. Psychotic reactions are more likely in patients with postencephalitic parkinsonism or a history of mental disorders. Excessive daytime sleepiness and sudden onset of sleep have been reported very rarely, as have pathological gambling, increased libido, and hypersexuality.

Abnormal involuntary movements or dyskinesias are the most serious dose-limiting adverse effects of levodopa and are very common at the optimum dose required to control parkinsonism; their frequency increases with duration of treatment. Involuntary movements of the face, tongue, lips, and jaw often appear first and those of the trunk and extremities later. Severe generalised choreoathetoid and dystonic movements may occur after prolonged use. Muscle twitching and blepharospasm may be early signs of excessive dosage. Exaggerated respiratory movements and exacerbated oculogyric crises have been reported in patients with postencephalitic parkinsonism. Bradykinesia and akinesia, in the form of 'end-of-dose' deterioration and the 'on-off' phenomenon, may re-emerge in patients with parkinsonism as a complication of long-term treatment, but may be due to progression of the disease rather than to levodopa (see also Parkinsonism, p. 889.1).

A positive response to the direct Coombs' test may occur, usually without evidence of haemolysis although autoimmune haemolytic anaemia has occasionally been reported. Transient leucopenia and thrombocytopenia have occurred rarely. The effects of levodopa on liver and kidney function are generally slight; transient increases in liver enzymes, and in blood-urea nitrogen and serum-uric acid concentrations, have been reported. Levodopa may cause discoloration of the urine; reddish at first then darkening on standing. Other body fluids may also be discoloured.

Some of the adverse effects reported may not be attributable directly to levodopa, but rather to the use of antimuscarinics, to increased mobility, or to the unmasking of underlying conditions as parkinsonism improves. Use with a peripheral dopa-decarboxylase inhibitor may reduce the severity of peripheral symptoms such as gastrointestinal and cardiovascular effects, but central effects such as dyskinesias and mental disturbances may occur earlier in treatment.

Incidence of adverse effects. The major adverse effects of levodopa are dyskinesia in 75% of patients and psychiatric disturbances in 25%.[1] Nausea and vomiting in 40 to 50% gradually regress and hypotension in 25 to 30% is generally asymptomatic. Less common adverse effects include cardiac arrhythmias, particularly atrial and ventricular ectopic beats and less commonly atrial flutter and fibrillation; palpitations and flushing often accompanied by excessive sweating; hypertension; polyuria, incontinence and urinary retention, although antimuscarinic drugs often contribute to problems with micturition; and dark coloration of the urine and saliva. Rare adverse effects include abdominal pain, constipation, and diarrhoea, mydriasis, blurred vision, diplopia, and precipitation of glaucoma; headache; stridor; tachypnoea; and paraesthesias.

1. Caine DB, Reid JL. Antiparkinsonian drugs: pharmacological and therapeutic aspects. *Drugs* 1972; 4: 49–74.

Abnormal coloration. Black pigmentation of rib cartilage has been noted at necropsy in patients treated with levodopa.[1,2] Abnormal pigmentation is generally not seen at other sites[2] but there have been isolated reports[2,3] of patients who also had pigmentation of the intervertebral discs. Although the pigmentation appears to be irreversible it was considered to be probably harmless.[2] It has been suggested that the pigmentation was due to deposition of dihydroxyphenylalanine (DOPA) in the cartilage.[1] It is known that DOPA will readily auto-oxidise *in vitro* in the presence of oxygen to a black pigment and this can also happen *in vivo* since black urine is a well known adverse effect of levodopa. Dark sweat and pigmentation of the skin and teeth are also known adverse effects.

See also Effects on the Skin and Hair, p. 906.1.

1. Connolly CE, *et al.* Black cartilage associated with levodopa. *Lancet* 1986; i: 690.
2. Rausing A, Rosén U. Black cartilage after therapy with levodopa and methyldopa. *Arch Pathol Lab Med* 1994; 118: 531–5.
3. Keen CE. *BMJ* 1998; 316: 240.

Dysgeusia. A change in taste sensation was reported[1] in 23 of 514 patients treated with levodopa and a peripheral dopa-decarboxylase inhibitor; 2 of the 23 had total loss of taste initially. The altered taste, often described as insipid, metallic, or plastic, was first noted 3 to 32 weeks after

beginning treatment, and lasted for 2 to 40 weeks. In an earlier report, 22 of 100 patients receiving levodopa alone had had changes in taste.[2]

1. Siegfried J, Zumstein H. Changes in taste under L-DOPA therapy. *Z Neurol* 1971; **200**: 345–8.
2. Barbeau A. L-DOPA therapy: past, present and future. *Arit Med* 1970; **27**: 1–4.

Effects on the blood. Reports of effects of levodopa on the blood are mostly confined to individual case reports. A study in 365 patients, receiving levodopa in a mean daily dosage of 4.04 g, found that 32 developed a positive direct Coombs' test, the majority after between 3 and 12 months of therapy, but none developed haemolytic anaemia.[1] However, occasional cases of auto-immune haemolytic anaemia have been reported;[2-4] in one case, dosage reduction and addition of a peripheral dopa-decarboxylase inhibitor largely abolished haemolysis,[3] but in another, haemolysis recurred on re-institution of levodopa with carbidopa and required corticosteroid treatment.[4] A case of severe acute non-haemolytic anaemia related to levodopa therapy has also been reported.[5]

Levodopa is widely stated to produce leucopenia in some patients; however, there are few published reports. Transient minor decreases in total leucocyte counts were reported in 3 of a group of 80 patients receiving levodopa.[6]

Severe thrombocytopenia has been reported in 2 patients who had received levodopa for 3 and 2 years respectively;[7,8] the condition was apparently an auto-immune response and responded to prednisone therapy and withdrawal of levodopa.

1. Joseph C. Occurrence of positive Coombs test in patients treated with levodopa. *N Engl J Med* 1972; **286**: 1401–2.
2. Territo MC, *et al.* Autoimmune hemolytic anemia due to levodopa therapy. *JAMA* 1973; **226**: 1347–8.
3. Lindström FD, *et al.* Dose-related levodopa-induced haemolytic anaemia. *Ann Intern Med* 1977; **86**: 298–300.
4. Bernstein RM. Reversible haemolytic anaemia after levodopa-carbidopa. *BMJ* 1979; **1**: 1461–2.
5. Alkalay I, Zipoli T. Levodopa-induced acute non-hemolytic anemia. *Ann Allergy* 1977; **39**: 191.
6. Barbeau A. L-Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Can Med Assoc J* 1969; **101**: 791–800.
7. Wanamaker WM, *et al.* Thrombocytopenia associated with long-term levodopa therapy. *JAMA* 1976; **235**: 2217–19.
8. Giner V, *et al.* Thrombocytopenia associated with levodopa treatment. *Arch Intern Med* 2003; **163**: 735–6.

Effects on the cardiovascular system. There have been conflicting reports on the effects of peripheral dopa-decarboxylase inhibitors on orthostatic hypotension attributed to levodopa therapy. In a study,[1] supine and erect systolic blood pressure was found to be significantly higher in parkinsonian patients given levodopa with carbidopa than in those receiving levodopa alone, suggesting that the peripheral actions of dopamine contribute to levodopa-induced hypotension. However, another study[2] found no change in the incidence and degree of orthostatic hypotension after giving levodopa with carbidopa and, similarly, no difference in the frequency of ventricular arrhythmias.

See also Effects on Kidney Function, below and Cardiovascular Disorders, under Precautions, p. 907.1.

1. Calne DB, *et al.* Action of L-α-methyldopahydrazine on the blood pressure of patients receiving levodopa. *Br J Pharmacol* 1972; **44**: 162–4.
2. Leibowitz M, Lieberman A. Comparison of dopa decarboxylase inhibitor (carbidopa) combined with levodopa and levodopa alone on the cardiovascular system of patients with Parkinson's disease. *Neurology* 1975; **25**: 917–21.

Effects on electrolytes. See Effects on Kidney Function, below.

Effects on the endocrine system. Single doses of levodopa given to healthy subjects cause an increase in plasma concentrations of glucose, insulin, and glucagon, as well as of growth hormone[1] and there has been concern over the potential endocrine effects of levodopa therapy in patients with Parkinson's disease.[2] A study of carbohydrate metabolism in 24 patients with Parkinson's disease indicated that these patients had abnormally low rates of **glucose utilisation** when untreated, apparently due to impaired insulin release, and this was not altered when levodopa therapy was given.[3] However, a similar study completed by 19 patients[2] noted increased impairment of glucose utilisation after levodopa therapy for 1 year with a delayed hypersecretion of insulin in response to a glucose load similar to the metabolic changes of acromegaly. It was considered that patients given levodopa for parkinsonism should be monitored for evidence of diabetes mellitus or frank acromegaly.[2]

Postmenopausal bleeding occurred in varying degrees in 12 of 47 women treated with levodopa.[4] In one case bleeding was severe enough to warrant interrupting treatment and subsequent dosage reduction.

1. Rayfield EJ, *et al.* L-Dopa stimulation of glucagon secretion in man. *N Engl J Med* 1975; **293**: 589–91.
2. Sirtori CR, *et al.* Metabolic responses to acute and chronic L-dopa administration in patients with parkinsonism. *N Engl J Med* 1972; **287**: 729–33.
3. Van Woert MH, Mueller PS. Glucose, insulin, and free fatty acid metabolism in Parkinson's disease treated with levodopa. *Clin Pharmacol Ther* 1971; **12**: 360–7.
4. Wajsbort J. Post-menopausal bleeding after L-dopa. *N Engl J Med* 1972; **286**: 784.

Effects on the eyes. Both miosis[1] and mydriasis[2] have been reported with levodopa.

For a report of the exacerbation of oculogyric crises by levodopa, see under Extrapyramidal Effects, p. 906.2.

1. Spiers ASD, *et al.* Miosis during L-dopa therapy. *BMJ* 1970; **2**: 639–40.
2. Weintraub ML, *et al.* Pupillary effects of levodopa therapy: development of anisocoria in latent Horner's syndrome. *N Engl J Med* 1970; **283**: 120–3.

Effects on the gastrointestinal tract. Although gastrointestinal bleeding has more commonly been reported in patients with a history of peptic ulceration, there is a rare report[1] of acute melaena and non-specific gastritis associated with levodopa therapy in a 56-year-old man without any previous evidence of a gastric disorder.

See also Dysgeusia, p. 904.3.

1. Riddoch D. Gastritis and L-dopa. *BMJ* 1972; **1**: 53–4.

Effects on kidney function. Levodopa 1 to 2 g given to 7 patients with idiopathic or postencephalitic Parkinson's disease produced significant increases in renal plasma flow, glomerular filtration rate, and sodium and potassium excretion.[1] It was considered that the natriuretic effects could contribute to the orthostatic hypotension commonly seen in patients receiving levodopa. There is a report of a patient who developed hyponatraemia when given levodopa with carbidopa.[2] The patient had previously had a similar reaction with amantadine. On each occasion symptoms disappeared when dopaminergic medication was withdrawn and recurred on rechallenge. Inappropriate secretion of antidiuretic hormone was suggested as a possible mechanism.

Levodopa has also been reported to have a kaliuretic effect, resulting in hypokalaemia, in some parkinsonian patients;[3] the effect could be prevented by also giving a peripheral dopa-decarboxylase inhibitor.

1. Pinlay GD, *et al.* Augmentation of sodium and potassium excretion, glomerular filtration rate and renal plasma flow by levodopa. *N Engl J Med* 1971; **284**: 865–70.
2. Lammers GJ, Roos RAC. Hyponatraemia due to amantadine hydrochloride and L-dopa/carbidopa. *Lancet* 1993; **342**: 439.
3. Granérus A-K, *et al.* Kaliuretic effect of L-dopa treatment in parkinsonian patients. *Acta Med Scand* 1977; **201**: 291–7.

Effects on mental function. Psychiatric complications were the single commonest reason for stopping levodopa treatment in a follow-up study of 178 patients with idiopathic Parkinson's disease, 81 of whom were still taking levodopa after 6 years.[1] Within 2 years, levodopa was withdrawn because of toxic confusional states (21 patients), paranoid psychosis (6 patients), unipolar depression (2 patients), and mania (1 patient). The incidence of visual hallucinations increased as treatment continued but, as with toxic confusional states, patients generally improved when levodopa was withdrawn. Before treatment, 40 patients had suffered severe depression and levodopa produced sustained improvement in only 2. After 6 years, 20 of the 81 patients remaining were moderately or severely depressed and were rarely improved by withdrawal or reduction in dosage of levodopa. Increasing dementia affected 26 of the 81 patients after 6 years; withdrawal of levodopa in 5 failed to improve cognitive disabilities, but increased parkinsonism.

Another study[2] reported that 141 of 400 patients being treated for Parkinson's disease developed mental disorders. In this study certain acute states, particularly anxiety, on-off hallucinations, and fits of delirium were linked to treatment with levodopa, whereas dementia and depression were not.

Long-term use of levodopa and dopamine agonists has been associated with various **behavioural disturbances**, including hypersexuality (see Effects on Sexual Function, p. 906.1), punding (purposeless repetitive acts), excessive gambling or shopping (see below), and other obsessive behaviour such as compulsive eating.[3-5] Risk factors include male gender, young age at onset of Parkinson's disease, underlying personality traits, and a personal or family history of addictive disorders.[4] Reduction in dopaminergic therapy can lead to cessation or improvement in symptoms. Some patients may develop dopamine dysregulation syndrome (see Abuse, under Precautions, p. 906.3).

A 12-month study of 1281 patients in the USA treated with dopamine agonists for Parkinson's disease found that 9 were suffering from **excessive gambling.**[6] All patients had received levodopa, 8 pramipexole, and the remaining patient pergolide. The rate of pathological gambling was 1.5% in the 529 patients taking pramipexole. The authors considered that this was not unexpected given the general availability of casinos in the local area and an incidence in the general US population of 0.3 to 1.3%. An analysis[7] of 11 patients who began pathological gambling after starting therapy with pramipexole (9 cases) or ropinirole (2 cases) found that in 8 patients such behaviour resolved when the drug was tapered or stopped; follow-up was not available in the other 3. In 7 patients the symptoms had developed within 1 to 3 months of achieving maintenance dose or after dose increases of dopamine agonist therapy. Of the 11 patients, 3 had not received levodopa. Cabergoline therapy has also been associated with pathological gambling.[8] Similar behaviour described as being markedly increased in "on" periods has been reported in other patients treated with levodopa.[9] Pathological gambling has also been associated with misuse of dopaminergics.[10]

Sleep-related complaints have occurred and were reported by 74 of 100 patients with Parkinson's disease.[11] All 74 were on levodopa and the prevalence of symptoms increased with the duration of treatment. Symptoms included insomnia, excessive daytime somnolence, altered dream phenomena, nocturnal vocalisation, involuntary myoclonic movements, and rarely, sleepwalking. Sleep fragmentation, which includes insomnia and somnolence, was the most common symptom overall. It has been suggested[12] that in patients with mild to moderate disease levodopa and dopamine agonists could cause sleep disruption. However, these drugs produce beneficial effects on nocturnal disabilities in patients with more severe disease. Reports[13-19] of daytime somnolence or sudden onset of sleep with various other dopamine agonists, including apomorphine, bromocriptine, cabergoline, lisuride, pergolide, piribedil, pramipexole, quinagolide, and ropinirole, suggest that this is a class effect of dopaminergic antiparkinsonian therapy, and patients should be warned of the possible risks (see Precautions, p. 906.3). The risk of somnolence may be increased in those patients taking combinations of dopaminergics.[18,20]

1. Shaw KM, *et al.* The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980; **49**: 283–93.
2. Rondot P, *et al.* Mental disorders in Parkinson's disease after treatment with L-Dopa. *Adv Neurol* 1984; **40**: 259–69.
3. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 2004; **17**: 172–80.
4. Antonini A, Cilia R. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. *Drug Safety* 2009; **32**: 475–88.
5. *MHRA. Public Assessment Report—Dopamine agonists:* pathological gambling and increased libido (Issued 7th November, 2006). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2025150&RevisionSelectionMethod=LatestReleased (accessed 23/08/10)
6. Driver-Dunckley E, *et al.* Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 2003; **61**: 422–3.
7. Dodd ML, *et al.* Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005; **62**: 1377–81.
8. Adverse Drug Reactions Advisory Committee (ADRAC). Pathological gambling with cabergoline. *Aust Adverse Drug React Bull* 2005; **24**: 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0508.pdf (accessed 16/02/06)
9. Molina JA, *et al.* Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov Disord* 2000; **15**: 869–72.
10. Gschwandtner U, *et al.* Pathologic gambling in patients with Parkinson's disease. *Clin Neuropharmacol* 2001; **24**: 170–2.
11. Nausieda PA, *et al.* Psychiatric complications of levodopa therapy of Parkinson's disease. *Adv Neurol* 1984; **40**: 271–7.
12. van Hilten B, *et al.* Sleep disruption in Parkinson's disease: assessment by continuous activity monitoring. *Arch Neurol* 1994; **51**: 922–8.
13. Frucht S, *et al.* Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999; **52**: 1908–10.
14. Schapira AHV. Sleep attacks (sleep episodes) with pergolide. *Lancet* 2000; **355**: 1332–3.
15. Ferreira JJ, *et al.* Sleep attacks and Parkinson's disease treatment. *Lancet* 2000; **355**: 1333–4.
16. Pirker W, Happe S. Sleep attacks in Parkinson's disease. *Lancet* 2000; **356**: 597–8.
17. Houmann CN, *et al.* Sleep attacks in patients taking dopamine agonists: review. *BMJ* 2002; **324**: 1483–7.
18. *CSM/MHRA.* Dopaminergic drugs and sudden sleep onset. *Current Problems* 2003; **29**: 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)
19. Plowman BK, *et al.* Sleep attacks in patients receiving dopamine-receptor agonists. *Am J Health-Syst Pharm* 2005; **62**: 537–40.
20. Etminan M, *et al.* Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease: a meta-analysis of randomised controlled trials. *Drug Safety* 2001; **24**: 863–8.

Effects on respiration. Respiratory crises, including attacks of gasping, panting, sniffing, puffing, and breath-holding, occurred in 12 of 25 patients with postencephalitic parkinsonism during treatment with levodopa.[1] A further 8 developed respiratory and phonatory tics, including sudden deep breaths, yawns, coughs, giggles, sighing, grunting, and moaning. All 20 patients also suffered tachypnoea, bradypnoea, and asymmetrical movement of both sides of the chest, paradoxical diaphragmatic movements, and reversal of inspiratory and expiratory phases. The induction of respiratory crises may be prompt or greatly delayed; 3 patients only developed crises after more than 9 months of treatment with levodopa. Crises were readily precipitated by psychophysiological arousals such as rage and exertion. Most of the patients who developed marked respiratory disorders had shown slight irregularities of respiratory rhythm, rate, and force before receiving levodopa.

In another report a distressing dose-related irregularity in the rate and depth of breathing occurred when a patient with Parkinson's disease was given levodopa with benserazide.[2] The respiratory abnormality was completely suppressed by use of tiapride, with no reduction in the efficacy of levodopa.

1. Sacks OW, *et al.* Side-effects of L-dopa in postencephalitic parkinsonism. *Lancet* 1970; I: 1006.
2. De Keyser J, Vincken W. L-Dopa-induced respiratory disturbance in Parkinson's disease suppressed by tiapride. *Neurology* 1985; 35: 235–7.

Effects on sexual function. An increase in libido, over and above the effects of improved mobility and well-being, has been reported in parkinsonian patients receiving levodopa or dopamine agonists. One report noted increased libido but no improvement in sexual performance in 4 of 80 patients receiving levodopa[1] while another reported a moderate increase in sexual interest in 4 of 7 male patients.[2] There have also been reports of hypersexuality and deviant sexual behaviour in patients with Parkinson's disease receiving levodopa or dopamine agonists.[3-6] In some cases this was associated with increased dosage and possibly abuse of the drugs. Symptoms often improved on dosage reduction or withdrawal. Hypersexual behaviour and hypergenitalism have also been reported in a pre-pubertal boy given levodopa for behavioural disturbances.[7]

Some workers[8] have commented that dopaminergics such as cabergoline are being promoted illegally on the Internet for male sexual enhancement and warn of the potential for abuse and serious adverse effects.

Clitoral tumescence and increased libido has been noted in a woman receiving bromocriptine to suppress lactation[9] but there has been a report of sexual dissatisfaction and decreased libido in 3 women receiving bromocriptine for hyperprolactinaemia.[10]

1. Barbeau A. L-Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Can Med Assoc J* 1969; 101: 791–9.
2. Brown R, *et al.* Sexual function and affect in parkinsonian men treated with L-dopa. *Am J Psychiatry* 1978; 135: 1552–5.
3. Vogel HP, Schiffter R. Hypersexuality—a complication of dopaminergic therapy in Parkinson's disease. *Pharmacopsychiatry* 1983; 16: 107–10.
4. Jiménez-Jiménez FJ, *et al.* Possible zoophilia associated with dopaminergic therapy in Parkinson disease. *Ann Pharmacother* 2002; 36: 1178–9.
5. Kaňovský P, *et al.* Penile erections and hypersexuality induced by pergolide treatment in advanced, fluctuating Parkinson's disease. *J Neurol* 2002; 249: 112–14.
6. Berger C, *et al.* Sexuelle Delinquenz und Morbus Parkinson. *Nervenarzt* 2003; 74: 370–5.
7. Korten JJ, *et al.* Undesirable prepubertal effects of levodopa. *JAMA* 1973; 226: 355.
8. Pinero A, *et al.* Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med* 2005; 353: 1976–7.
9. Blin O, *et al.* Painful clitoral tumescence during bromocriptine therapy. *Lancet* 1991; 337: 1231–2.
10. Saleh AK, Mousse MAA. Sexual dysfunction in women due to bromocriptine. *BMJ* 1984; 289: 228.

Effects on the skin and hair. Two women who were given levodopa, up to 3 g daily, developed diffuse alopecia in addition to other adverse effects.[1] Repigmentation of hair has occurred in a white-bearded man after being treated with levodopa 1.5 g daily for 8 months.[2] Vitiligo has been reported[3] in a patient with Parkinson's disease following addition of tolcapone to his levodopa/carbidopa regimen. The development of vitiligo was attributed to the increase in plasma-levodopa concentrations brought about by concomitant use of tolcapone.

See also Melanoma, under Precautions, p. 907.1.

1. Marshall A, Williams MJ. Alopecia and levodopa. *BMJ* 1971; 2: 47.
2. Grainger KM. Pigmentation in Parkinson's disease treated with levodopa. *Lancet* 1973; I: 97–8.
3. Sabaté M, *et al.* Vitiligo associated with tolcapone and levodopa in a patient with Parkinson's disease. *Ann Pharmacother* 1999; 33: 1228–9.

Extrapyramidal effects. Choreiform movements were the major dose-limiting complication of long-term treatment with levodopa in a follow-up study of 178 patients with idiopathic Parkinson's disease, 81 of whom were still taking levodopa after 6 years.[1] Dyskinesias usually appeared in the first year and became more severe and generalised with time. Certain distinctive patterns of involuntary movements occurred as follows:

- peak-dose movements affected 65 of the 81 patients and were dose-related. Movements were usually choreic, affecting the face and limbs, but dystonic and ballistic movements were also seen; characteristically they began 20 to 90 minutes after an oral dose and lasted from 10 minutes to 4 hours with a tendency to be more severe mid-way through the interdose period
- biphasic movements presenting as 2 distinct episodes of chorea or dystonia within each interdose period occurred in only 3 patients
- early morning and 'end-of-dose' dystonia was present in 15 patients after 6 years of treatment with levodopa, but rarely developed during the first 3 years
- nocturnal myoclonus occurred in 12 patients

The frequency, intensity, and complexity of spontaneous fluctuations in performance were greatly enhanced by long-term levodopa therapy. Two clinically distinct types of fluctuation, 'end-of-dose' deterioration and the 'on-off' phenomenon, were related to treatment. 'End-of-dose' deterioration or the 'wearing-off' effect affected 52 patients after 6 years of treatment and was characterised by progressive reduction in the duration of benefit from each dose with a gradual return of nocturnal and early morning disability in some patients. The 'on-off' phenomenon affected 14 patients who had completely unpredictable swings from relative mobility, usually accompanied by involuntary movements, to periods of profound bradykinesia and hypotonia. In addition, 'freezing episodes' and abrupt falls became increasingly common and affected 50 patients after 6 years compared with 33 before therapy.

1. Shaw KM, *et al.* The impact of treatment with levodopa on Parkinson's disease. *Q J Med* 1980; 49: 283–93.

OCULOGYRIC CRISIS. After initial remission, oculogyric crises in 5 of 25 patients with postencephalitic parkinsonism recurred and were subsequently severely exacerbated during treatment with levodopa.[1] One patient, who previously had not had oculogyric crises, developed severe crises in the fourth month of therapy with levodopa. During these crises forced gaze deviation was always accompanied by severe neurological and mental symptoms, some of which were scarcely tolerable.

1. Sacks OW, Kohl M. L-Dopa and oculogyric crises. *Lancet* 1970; II: 215–16.

Gout. There have been reports of elevated serum uric acid concentrations in patients receiving levodopa, but some of these are of doubtful significance since levodopa has been shown to give falsely-elevated uric acid concentrations by colorimetric methods.[1] However, hyperuricaemia as measured by more specific methods,[2,3] with a few cases of overt gout,[2,3] has also been reported.

1. Cawein MJ, Hewins J. False rise in serum uric acid after L-dopa. *N Engl J Med* 1969; 281: 1489–90.
2. Honda H, Gindin RA. Gout while receiving levodopa for parkinsonism. *JAMA* 1972; 219: 55–7.
3. Calne DB, Fermaglich J. Gout induced by L-dopa and decarboxylase inhibitors. *Postgrad Med J* 1976; 52: 232–3.

Hypersensitivity. Reports of hypersensitivity reactions to levodopa have included a vasculitis characterised by neuromyopathy, periarteriolitis with eosinophilia,[1] and a lupus-like auto-immune syndrome.[2]

1. Wolf S, *et al.* Neuromyopathy and periarteriolitis in a patient receiving levodopa. *Arch Intern Med* 1976; 136: 1055–7.
2. Massarotti G, *et al.* Lupus-like autoimmune syndrome after levodopa and benserazide. *BMJ* 1979; 2: 553.

Overdosage. Adverse effects after ingestion of 80 to 100 g of levodopa over a 12-hour period by a parkinsonian patient included hypertension initially, followed by hypotension of a few hours' duration, sinus tachycardia, and symptomatic orthostatic hypotension for more than a week.[1] Marked confusion, agitation, insomnia, and restlessness were the most prominent clinical symptoms and did not disappear completely for over a week; severe anorexia and insomnia persisted for 2 to 3 weeks. After the overdose the patient had virtually no signs of parkinsonism and received no levodopa or antimuscarinic medication for 6 days; rigidity and akinesia began to recur on the fourth day.

1. Hoehn MM, Rutledge CO. Acute overdose with levodopa: clinical and biochemical consequences. *Neurology* 1975; 25: 792–4.

Withdrawal syndromes. Withdrawal of antiparkinsonian drugs, particularly levodopa, has been implicated in the development of a syndrome resembling the neuroleptic malignant syndrome,[1-6] characterised by fever, muscle rigidity, profuse sweating, tachycardia, tachypnoea, and elevated muscle enzyme values.[2] Several fatalities have occurred.[1,2] It has been suggested that the neuroleptic malignant syndrome is associated with blockade of dopamine receptors in the striatum, leading to increased rigidity and heat production, and in the hypothalamus, resulting in impaired thermoregulation[7] and it seems reasonable that withdrawal of levodopa might have a similar effect in patients with depleted central dopamine concentrations. Thus, the use of a 'drug holiday' to manage fluctuations in response to levodopa (see Parkinsonism, p. 889.1) is no longer recommended.

Fever, extrapyramidal symptoms and raised creatine kinase concentrations, resembling a very mild form of the neuroleptic malignant syndrome, have also been reported in parkinsonian patients exposed to stress such as dehydration or infection but without any change in medication.[8]

1. Sechi GP, *et al.* Fatal hyperpyrexia after withdrawal of levodopa. *Neurology* 1984; 34: 249–51.
2. Friedman JH, *et al.* A neuroleptic malignantlike syndrome due to levodopa therapy withdrawal. *JAMA* 1985; 254: 2792–5.
3. Figà-Talamanca L, *et al.* Hyperthermia after discontinuance of levodopa and bromocriptine therapy: impaired dopamine receptors a possible cause. *Neurology* 1985; 35: 258–61.
4. Gibb WRG, Griffith DNW. Levodopa withdrawal syndrome identical to neuroleptic malignant syndrome. *Postgrad Med J* 1986; 62: 59–60.
5. Serrano-Dueñas M. Neuroleptic malignant syndrome-like, or—dopaminergic malignant syndrome—due to levodopa therapy withdrawal: clinical features in 11 patients. *Parkinsonism Relat Disord* 2005; 9: 175–8.
6. Mizuno Y, *et al.* Malignant syndrome in Parkinson's disease: concept and review of the literature. *Parkinsonism Relat Disord* 2003; 9 (suppl 1): 53–59.
7. Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? *Neurology* 1981; 31: 132–7.
8. Mezaki T, *et al.* Benign type of malignant syndrome. *Lancet* 1989; I: 49–50.

Treatment of Adverse Effects

Reduction in dosage reverses most of the adverse effects of levodopa. Nausea and vomiting may be diminished by increasing the dose of levodopa gradually, and/or by taking with or after meals, although taking levodopa on a full stomach may lead to lower plasma concentrations. Gastrointestinal effects may also be reduced by giving an antiemetic such as cyclizine or domperidone but not a phenothiazine (see Antipsychotics, under Interactions, p. 907.3). Use with a peripheral dopa-decarboxylase inhibitor reduces peripheral but not central adverse effects. Orthostatic hypotension may respond to the use of elastic stockings.

The benefits of gastric decontamination after an overdose of levodopa are uncertain. However, activated charcoal should be considered in adults who have ingested more than 2 g (or more than the total daily dose, whichever is greater), and in children who have taken more than 200 mg, if they present within 1 hour of ingestion. Supportive measures should also be instituted. Pyridoxine may increase the metabolism of levodopa (see Nutritional Agents, under Interactions, p. 908.1) but its value in overdosage has not been established; it does not reduce the effects of levodopa given with a peripheral dopa-decarboxylase inhibitor.

Nausea and vomiting. For reference to the use of domperidone in the management of nausea and vomiting associated with levodopa in patients with Parkinson's disease, see under Uses and Administration of Domperidone, p. 1841.2.

Psychosis. Atypical antipsychotics such as clozapine (p. 1058.1) have been tried in the management of psychosis occurring as a complication of parkinsonism and of drugs such as levodopa used in its treatment.

Precautions

Levodopa is contra-indicated in patients with angle-closure glaucoma and should be used with caution in open-angle glaucoma. Caution is also required in patients with cardiovascular disease, pulmonary disease, endocrine disorders, psychiatric disturbances, osteomalacia, hepatic or renal disease, or a history of peptic ulceration. Periodic evaluations of hepatic, psychiatric, haematological, renal and cardiovascular functions have been advised.

Since an association between levodopa and activation of malignant melanoma has been suspected (although not confirmed), it is generally recommended that levodopa should not be given to patients with (or with a history of) the disease or with skin disorders suggestive of it.

Parkinsonian patients who benefit from levodopa therapy should be warned to resume normal activities gradually to avoid the risk of injury. Treatment with levodopa should not be stopped abruptly.

Excessive daytime sleepiness and sudden onset of sleep may occur with levodopa and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Levodopa inhibits prolactin secretion and may therefore interfere with lactation.

Food interferes with the absorption of levodopa, though levodopa is usually given with or immediately after meals to reduce nausea and vomiting. However, patients with the 'on-off' phenomenon may benefit from dosage on an empty stomach (see Parkinsonism, p. 889.1).

Abuse. Abuse of levodopa and dopamine agonists in patients with Parkinson's disease has been reported.[1-6] The term dopamine dysregulation syndrome, has been used to describe a condition where there is a compulsive and dysregulated use of dopaminergic drugs beyond that needed to achieve relief of motor symptoms and which is harmful to the patient.[7] Patients have progressively increased the dosage of levodopa to obtain psychotropic effects such as euphoria despite accompanying dystonia and other extrapyramidal adverse effects. Withdrawal often led to craving, drug-seeking behaviour, and mood disturbances such as depression, features resembling a psychological dependence syndrome. Abuse in patients without parkinsonism has also occurred.[8]

See also Effects on Sexual Function, under Adverse Effects, above.

1. Nausieda PA. Sinemet "abusers". *Clin Neuropharmacol* 1985; 8: 318–27.

2. Soyka M, Huppert D. L-dopa abuse in a patient with former alcoholism. *Br J Addict* 1992; **87**: 117–18.
3. Spigset O, von Schéele C. Levodopa dependence and abuse in Parkinson's disease. *Pharmacotherapy* 1997; **17**: 1027–30.
4. Merims D, *et al.* Is there addiction to levodopa in patients with Parkinson's disease? *Mov Disord* 2000; **15**: 1014–16.
5. Müller U, *et al.* Levodopa-Abhängigkeit bei Parkinsonkrankheit: Fallbericht und Literaturübersicht. *Nervenarzt* 2002; **73**: 887–91.
6. Borek LL, Friedman JH. Levodopa addiction in idiopathic Parkinson disease. *Neurology* 2005; **65**: 1508.
7. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. *J Geriatr Psychiatry Neurol* 2004; **17**: 172–80.
8. Steiner I, Wirguin I. Levodopa addiction in non-parkinsonian patients. *Neurology* 2003; **61**: 1451.

Cardiovascular disorders. A high incidence of cardiovascular adverse effects was reported in early studies of levodopa, but both Parkinson's disease and heart disease are common in the elderly and adverse cardiac effects of levodopa may be less prevalent than was first thought. A study in 40 patients[1] concluded that, apart from those with severe orthostatic hypotension or unstable coronary disease, levodopa may be used safely in parkinsonian patients with heart disease. Others[2] noted that levodopa and bromocriptine cause cardiac arrhythmias in less than 1% of all patients, the incidence for levodopa with a peripheral dopa-decarboxylase inhibitor being lower still. Nevertheless, caution is advised in patients with cardiovascular disease.

1. Jenkins RB, *et al.* Levodopa therapy of patients with parkinsonism and heart disease. *BMJ* 1972; **3**: 512–14.
2. Parkes JD, *et al.* Amantadine-induced heart failure. *Lancet* 1977; **i**: 904.

Diabetes mellitus. For reference to concern over the potential of levodopa to impair glucose utilisation, see Effects on the Endocrine System under Adverse Effects, p. 905.1.

Melanoma. There has been concern over the effects of levodopa on melanoma in view of the ability of malignant melanoma cells to convert levodopa to melanin and isolated reports of melanoma developing or being exacerbated during levodopa therapy continue to appear. However, in a survey of 1099 patients with primary cutaneous malignant melanoma only one had taken levodopa.[1] It was concluded that levodopa therapy is not an important factor in the induction of malignant melanoma. Furthermore, use of levodopa in daily doses of up to 4 g with carbidopa in 17 patients with metastatic melanoma failed to provide any evidence that levodopa accelerated the progression of the disease.[2] Reviews[3,4] of these and later reports concluded that the purported link between levodopa and malignant melanoma was tenuous.

For a report of antineoplastic chemotherapy used for the treatment of melanoma reducing the efficacy of levodopa, see under Interactions, below.

1. Sober AJ, Wick MM. Levodopa therapy and malignant melanoma. *JAMA* 1978; **240**: 534–5.
2. Gurney H, *et al.* The use of L-dopa and carbidopa in metastatic malignant melanoma. *J Invest Dermatol* 1991; **96**: 85–7.
3. Siple JF, *et al.* Levodopa therapy and the risk of malignant melanoma. *Ann Pharmacother* 2000; **34**: 382–5.
4. Fiala KH, *et al.* Malignant melanoma and levodopa in Parkinson's disease: causality or coincidence? *Parkinsonism Relat Disord* 2003; **9**: 321–7.

Pregnancy. Levodopa alone and with carbidopa has been associated with fetal abnormalities in *animals* given high doses; no teratogenic effect has been noted with carbidopa alone. However, 2 women with parkinsonism who received levodopa with carbidopa or levodopa alone throughout their pregnancies gave birth to normal infants.[1]

1. Cook DG, Klawans HL. Levodopa during pregnancy. *Clin Neuropharmacol* 1985; **8**: 93–5.

Withdrawal. For adverse effects associated with withdrawal of levodopa, see under Adverse Effects, p. 906.2.

Interactions

The therapeutic or adverse effects of levodopa may be affected by interactions with a variety of drugs. Mechanisms may include effects on catecholamine metabolising enzymes, neurotransmitters, or receptor sites, effects on the endocrine system, and effects on gastrointestinal absorption. Drugs that modify gastric emptying may affect the absorption of levodopa.

Antibacterials. A study[1] in 7 healthy subjects showed that use of *spiramycin* with levodopa and carbidopa resulted in reduced plasma-levodopa concentrations and an increase in its peripheral metabolism.

A hypertensive reaction and severe tremor occurred when *isoniazid* was given to a patient receiving levodopa;[2] it was not certain whether isoniazid was acting as an MAOI.

1. Brion N, *et al.* Effect of a macrolide (spiramycin) on the pharmacokinetics of L-dopa and carbidopa in healthy volunteers. *Clin Neuropharmacol* 1992; **15**: 229–35.
2. Morgan JP. Isoniazid and levodopa. *Ann Intern Med* 1980; **92**: 434.

Antidepressants. *BUPROPION.* Caution has been advised with bupropion because of reports of a higher incidence of adverse effects during use with levodopa.

MAOIS. Giving levodopa with non-specific MAOIs such as *phenelzine, nialamide,* or *tranylcypromine* may cause dangerous hypertension;[1-4] it is recommended that levodopa should not be given with, or within at least 14 days of stopping, an MAOI. Hypertensive reactions to levodopa with tranylcypromine were inhibited by carbidopa,[5] but licensed product information for preparations containing levodopa with carbidopa or benserazide still contra-indicates their use with MAOIs. The incidence of adverse effects may be increased if levodopa is used with *moclobemide,* a monoamine oxidase type A inhibitor (see Dopaminergics, p. 438.2). *Selegiline,* a monoamine oxidase type B inhibitor, is used to enhance the antiparkinsonian effect of levodopa, see p. 914.3.

1. Hodge JV. Use of monoamine oxidase inhibitors. *Lancet* 1965; **i**: 764–5.
2. Friend DG, *et al.* The action of L-dihydroxyphenylalanine in patients receiving nialamide. *Clin Pharmacol Ther* 1965; **6**: 362–6.
3. Hunter KR, *et al.* Monoamine oxidase inhibitors and L-dopa. *BMJ* 1970; **3**: 388.
4. Sharpe J, *et al.* Idiopathic orthostatic hypotension treated with levodopa and MAO inhibitor: a preliminary report. *Can Med Assoc J* 1972; **107**: 296–300.
5. Teychenne PF, *et al.* Interactions of levodopa with inhibitors of monoamine oxidase and L-aromatic amino acid decarboxylase. *Clin Pharmacol Ther* 1975; **18**: 273–7.

SSRIS. There was some evidence from a prescribing study that *SSRIs might* exacerbate parkinsonism resulting in increased doses of levodopa or addition of adjunctive drugs.[1]

1. van de Vijver DAMC, *et al.* Start of a selective serotonin reuptake inhibitor (SSRI) and increase of antiparkinsonian drug treatment in patients on levodopa. *Br J Clin Pharmacol* 2002; **54**: 168–70.

TRICYCLIC ANTIDEPRESSANTS. Although tricyclic antidepressants have generally been used safely with levodopa,[1] hypertensive crises have occurred in some rare cases. Such events have been reported in patients receiving *amitriptyline* or *imipramine* and levodopa with carbidopa.[2,3] Imipramine has been reported to impair the rate of levodopa absorption,[4] presumably due to its antimuscarinic properties (for the effect of antimuscarinics on the absorption of levodopa, see below).

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii**: 1283–5.
2. Rampton DS. Hypertensive crisis in a patient given Sinemet, metoclopramide, and amitriptyline. *BMJ* 1977; **2**: 607–8.
3. Edwards M. Adverse interaction of levodopa with tricyclic antidepressants. *Practitioner* 1982; **226**: 1447–8.
4. Morgan JP, *et al.* Imipramine-mediated interference with levodopa absorption from the gastrointestinal tract in man. *Neurology* 1975; **25**: 1029–34.

TRYPTOPHAN. See Amino Acids under Nutritional Agents, below.

Antiepileptics. *Phenytoin* has been shown to diminish the therapeutic effect of levodopa in patients with parkinsonism or chronic manganese poisoning.[1] The mechanism of the interaction was considered uncertain.

1. Mendez JS. Diphenylhydantoin: blocking of levodopa effects. *Arch Neurol* 1975; **32**: 44–6.

Antihypertensives. Use of levodopa with *guanethidine* may cause increased hypotension.[1] *Clonidine* has been reported to inhibit the therapeutic effect of levodopa, possibly by stimulating central alpha-adrenoceptors.[2] *Methyldopa* and levodopa may enhance each other's therapeutic or adverse effects, although there has been mention of the inhibitory effect of methyldopa on the therapeutic response to levodopa.[3,4] *Reserpine and other rauwolfia alkaloids* may oppose the antiparkinsonian effects of levodopa by central depletion of dopamine; UK licensed product information advises that use together should be avoided.

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii**: 1283–5.
2. Shoulson I, Chase TN. Clonidine and the anti-parkinsonian response to L-dopa or piribedil. *Neuropharmacology* 1976; **15**: 25–7.
3. Cotzias GC, *et al.* L-Dopa in Parkinson's syndrome. *N Engl J Med* 1969; **281**: 272.
4. Kofman O. Treatment of Parkinson's disease with L-dopa: a current appraisal. *Can Med Assoc J* 1971; **104**: 483–7.

Antimuscarinics. Antimuscarinic antiparkinsonian drugs may enhance the therapeutic effects of levodopa but by delaying gastric emptying they may also reduce its absorption.[1]

1. Algeri S, *et al.* Effect of anticholinergic drugs on gastro-intestinal absorption of L-dopa in rats and in man. *Eur J Pharmacol* 1976; **35**: 293–9.

Antineoplastics. A patient with Parkinson's disease noted[1] that the efficacy of levodopa was reduced each time he received *dacarbazine* for the treatment of melanoma. As serum-dopamine concentrations were unchanged it was suggested[1] that dacarbazine might compete with levodopa at the blood-brain barrier.

1. Merello M, *et al.* Impaired levodopa response in Parkinson's disease during melanoma therapy. *Clin Neuropharmacol* 1992; **15**: 69–74.

Antipsychotics. The therapeutic effects of levodopa may be diminished by CNS dopamine inhibitors including phenothiazine derivatives[1] such as *prochlorperazine.*[2] Butyrophenones such as *haloperidol* and thioxanthenes such as *flupentixol* might be expected to have a similar effect due to their antidopaminergic properties.

1. Yahr MD, Duvoisin RC. Drug therapy of parkinsonism. *N Engl J Med* 1972; **287**: 20–4.
2. Duvoisin RC. Diphenidol for levodopa induced nausea and vomiting. *JAMA* 1972; **221**: 1408.

Anxiolytics. Reversible deterioration of parkinsonism has been reported in patients receiving levodopa who were also given *benzodiazepines* such as *diazepam,*[1,2] *nitrazepam*[1] (although the evidence was equivocal), or *chlordiazepoxide.*[3] In one case parkinsonian symptoms resolved without alteration in the medication.[1]

1. Hunter KR, *et al.* Use of levodopa with other drugs. *Lancet* 1970; **ii**: 1283–5.
2. Wodak J, *et al.* Review of 12 months' treatment with L-dopa in Parkinson's disease, with remarks on unusual side effects. *Med J Aust* 1972; **2**: 1277–82.
3. Yosselson-Superstine S, Lipman AG. Chlordiazepoxide interaction with levodopa. *Ann Intern Med* 1982; **96**: 259–60.

Baclofen. Adverse effects including hallucinations, confusion, headache, and nausea and worsening of symptoms have been reported[1,2] in patients with Parkinson's disease taking levodopa when also given baclofen.

1. Skausig OB, Korsgaard S. Hallucinations and baclofen. *Lancet* 1977; **i**: 1258.
2. Lees AJ, *et al.* Baclofen in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1978; **41**: 707–8.

Gastrointestinal drugs. *ANTACIDS.* Some studies have suggested that taking an antacid before a dose of levodopa enhances the absorption of levodopa, apparently by enhancing gastric emptying and reducing metabolism of levodopa in the stomach.[1,2] This was particularly marked in a case report in a patient with prolonged gastric emptying time.[1] However, another study in 8 patients with presumably normal gastric motility, only 3 of whom had Parkinson's disease, found no significant increase in overall absorption of levodopa when given with an antacid although there was some evidence of increased absorption in some of the patients.[3] UK licensed product information (*Madopar CR; Roche*) states that antacids reduce the absorption of levodopa from the modified-release preparation by 32%.

1. Rivera-Calimlim L, *et al.* L-Dopa treatment failure: explanation and correction. *BMJ* 1970; **4**: 93–4.
2. Pocelinko R, *et al.* The effect of an antacid on the absorption and metabolism of levodopa. *Clin Pharmacol Ther* 1972; **13**: 149.
3. Leon AS, Spiegel HE. The effect of antacid administration on the absorption and metabolism of levodopa. *J Clin Pharmacol* 1972; **12**: 263–7.

ANTIEMETICS. Metoclopramide is a dopamine antagonist and may cause extrapyramidal symptoms including parkinsonism; however, it accelerates gastric emptying and has been reported[1] to increase the rate of levodopa absorption. The importance of timing has been noted[2] since levodopa delays gastric emptying and metoclopramide antagonises this effect. Licensed product information advises caution when using metoclopramide with levodopa. *Domperidone* has been reported to increase the bioavailability of levodopa slightly.[3]

1. Morris JGL, *et al.* Plasma dopa concentrations after different preparations of levodopa in normal subjects. *Br J Clin Pharmacol* 1976; **3**: 985–90.
2. Berkowitz DM, McCallum RW. Interaction of levodopa and metoclopramide on gastric emptying. *Clin Pharmacol Ther* 1980; **27**: 414–20.
3. Shindler JS, *et al.* Domperidone and levodopa in Parkinson's disease. *Br J Clin Pharmacol* 1984; **18**: 959–62.

PROKINETICS. Maximum plasma concentrations of levodopa are increased by *cisapride.*[1]

See also Metoclopramide and Domperidone, under Antiemetics, above.

1. Neira WD, *et al.* The effects of cisapride on plasma L-dopa levels and the clinical response in Parkinson's disease. *Mov Disord* 1995; **10**: 66–70.

General anaesthetics. The general anaesthetics *cyclopropane* and *halothane* lower the threshold for ventricular arrhythmias to sympathomimetic amines, including dopamine, and should probably not be used within 6 to 8 hours of levodopa.[1,2] Although other general anaesthetics are now usually preferred, it was suggested that, in any case, levodopa could safely be taken before surgery when given with a peripheral dopa-decarboxylase inhibitor.[3]

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* 1971; **12**: 376–82.
2. Bianchine JR, Sunyapridakul L. Interactions between levodopa and other drugs: significance in the treatment of Parkinson's disease. *Drugs* 1973; **6**: 364–88.
3. Anonymous. Surgery and long-term medication. *Drug Ther Bull* 1984; **22**: 73–6.

Nutritional agents. *AMINO ACIDS.* The transport of levodopa into the brain is subject to competition from chemically related L-amino acids, especially the other aromatic amino acids *phenylalanine, tyrosine, tryptophan,* and *histidine.*[1] A high-protein diet or the large neutral amino acids pheny-

lalanine, *leucine*, or *isoleucine* have been shown to reduce the therapeutic effect of levodopa given by intravenous infusion to parkinsonian patients; such alterations in the absorption and transport of levodopa may contribute to the fluctuating responses seen in Parkinson's disease, the so-called 'on-off' phenomenon[2] (see also Parkinsonism, p. 889.1). In contrast, a study in healthy subjects[3] found that while a low-protein meal appeared to cause a small reduction in levodopa absorption, a high-protein meal had no such effect. Other reported interactions with amino acids include *methionine*-antagonism of the therapeutic effect of levodopa in parkinsonism[4] and *tryptophan*-reduced blood concentrations of levodopa.[5]

1. Daniel PM, *et al.* Do changes in blood levels of other aromatic aminoacids influence levodopa therapy? *Lancet* 1976; i: 95.
2. Nutt JG, *et al.* The "on-off" phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med* 1984; 310: 483–8.
3. Robertson DRC, *et al.* The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. *Br J Clin Pharmacol* 1991; 31: 413–17.
4. Pearce LA, Waterbury LD. L-methionine: a possible levodopa antagonist. *Neurology* 1974; 24: 640–1.
5. Weitbrecht W-U, Weigel K. Der Einfluss von L-Tryptophan auf die L-Dopa-Resorption. *Dtsch Med Wochenschr* 1976; 101: 20–2.

IRON SALTS. Levodopa forms complexes with iron salts and *ferrous sulfate* has reduced bioavailability of levodopa by about 50% in healthy subjects.[1] Giving ferrous sulfate to 9 patients with Parkinson's disease receiving levodopa with carbidopa reduced the area under the concentration-time curve for levodopa by 30%; the reduction was greater than 75% for carbidopa. Although this was associated with deterioration in some patients' disability, the average reduction in efficacy of therapy did not achieve statistical significance.[2]

1. Campbell NRC, Hasinoff BB. Iron supplements: a common cause of drug interactions. *Br J Clin Pharmacol* 1991; 31: 251–5.
2. Campbell NRC, *et al.* Sinemet-ferrous sulphate interaction in patients with Parkinson's disease. *Br J Clin Pharmacol* 1990; 30: 599–605.

PYRIDOXINE. The enzyme responsible for the decarboxylation of levodopa, L-amino acid decarboxylase, is dependent on pyridoxine and pyridoxine supplements have been reported to enhance the peripheral metabolism of levodopa to dopamine leaving less available to cross the blood-brain barrier for central conversion to dopamine;[1-4] pyridoxine therefore inhibits the action of levodopa but this can be stopped by use of a peripheral dopa-decarboxylase inhibitor.[2,3]

1. Leon AS, *et al.* Pyridoxine antagonism of levodopa in parkinsonism. *JAMA* 1971; 218: 1924–7.
2. Cotzias GC, Papavasiliou PS. Blocking the negative effects of pyridoxine on patients receiving levodopa. *JAMA* 1971; 215: 1504–5.
3. Yahr MD, Duvoisin RC. Pyridoxine, levodopa, and L-α-methyldopa hydrazine regimen in parkinsonism. *JAMA* 1971; 216: 2141.
4. Carter AB. Pyridoxine and parkinsonism. *BMJ* 1973; 4: 236.

Papaverine. Antagonism of the beneficial effects of levodopa in parkinsonism has been reported when patients were also given papaverine,[1,2] and it was recommended that the combination should be avoided. However, a later study[3] in 9 patients receiving levodopa with a peripheral dopa-decarboxylase inhibitor found no changes in the control of Parkinson's disease when they were also given papaverine for 3 weeks.

1. Duvoisin RC. Antagonism of levodopa by papaverine. *JAMA* 1975; 231: 845.
2. Posner DM. Antagonism of levodopa by papaverine. *JAMA* 1975; 233: 768.
3. Montastruc JL, *et al.* Does papaverine interact with levodopa in Parkinson's disease? *Ann Neurol* 1987; 22: 558–9.

Penicillamine. Isolated case reports suggest that penicillamine increases plasma-levodopa concentrations.[1]

1. Mizuta E, *et al.* Effect of D-penicillamine on pharmacokinetics of levodopa in Parkinson's disease. *Clin Neuropharmacol* 1993; 16: 448–50.

Sympathomimetics. It has been suggested that sympathomimetics such as *adrenaline* or *isoprenaline* may enhance the cardiac adverse effects of levodopa.[1]

1. Goldberg LI, Whitsett TL. Cardiovascular effects of levodopa. *Clin Pharmacol Ther* 1971; 12: 376–82.

Pharmacokinetics

Levodopa is rapidly absorbed from the gastrointestinal tract by an active transport system. Most absorption takes place in the small intestine; absorption is very limited from the stomach, and since decarboxylation may take place in the stomach wall, delays in gastric emptying may reduce the amount of levodopa available for absorption. Peak plasma concentrations occur within 2 hours of oral doses. Levodopa is about 10 to 30% bound to plasma proteins.

Levodopa is rapidly decarboxylated by the enzyme aromatic L-amino acid decarboxylase, mostly in the gut, liver, and kidney, to dopamine, which is metabolised in turn, principally to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Other routes of metabolism include *O*-methylation, transamination, and oxidation, producing a variety of minor metabolites including noradrenaline and 3-*O*-methyldopa; the latter may accumulate in the CNS due to its relatively long half-life. The elimination half-life of levodopa itself is reported to be about 30 to 60 minutes.

Unlike dopamine, levodopa is actively transported across the blood-brain barrier, but because of the extent of peripheral decarboxylation very little is available to enter the CNS unless it is given with a peripheral dopa-decarboxylase inhibitor. In the presence of a peripheral dopa-decarboxylase inhibitor the major route of metabolism of levodopa becomes the formation of 3-*O*-methyldopa by the enzyme catechol-*O*-methyltransferase.

About 80% of an oral dose of levodopa is excreted in the urine within 24 hours, mainly as dihydroxyphenylacetic and homovanillic acids. Only small amounts of levodopa are excreted unchanged in the faeces.

Levodopa crosses the placenta and is distributed into breast milk.

General references.

1. Nutt JG, Fellman JH. Pharmacokinetics of levodopa. *Clin Neuropharmacol* 1984; 7: 35–49.
2. Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. *Clin Pharmacokinet* 1987; 13: 141–78.
3. Robertson DRC, *et al.* The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa. *Br J Clin Pharmacol* 1989; 28: 61–9.
4. Robertson DRC, *et al.* The influence of levodopa on gastric emptying in man. *Br J Clin Pharmacol* 1990; 29: 47–53.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Prikap; *China*: Symblyopia (思利巴); *Ger.*: Restex; *India*: Bidopal; *Irl.*: Duodopa; *Jpn*: Doparl†; *Pol.*: Nakom; *UK*: Apodespan.

Multi-ingredient Preparations. *Arg.*: Carlevod; Lebocar; Lecarge; Madopar; Nervocur; Parkinel; Sinemet; Stalevo; *Austral.*: Duodopa; Kinson; Levohexal†; Madopar; Sinemet; Stalevo; *Austria*: Duodopa; Levocar; Madopar; Restex; Sinemet; Stalevo; *Belg.*: Duodopa; Prolopa; Sinemet; Stalevo; *Braz.*: Carbidol; Cronomet; Duodopa; Levocarb; Parkidopa; Parklen; Prolopa; Sinemet; Stalevo; *Canad.*: Apo-Levocarb; Duodopa; Novo-Levocarbidopa†; Nu-Levocarb; Pro-Levocarb; Prolopa; Sinemet; Stalevo; *Chile*: Grifoparkin; Levofamil; Melitase; Prolopa; Protonis†; Saniter Compuesto; Sinemet; Stalevo; *China*: Sinemet (息宁); Xi Lai Mei (西莱美); *Cz.*: Apo-Levocarb; Dopalux†; Duodopa; Isicom; Lecardop; Madopar; Nakom; Sinemet; Stalevo; *Denm.*: Duodopa; Madopar; Sinemet; Stalevo; *Fin.*: Duodopa; Kardopal; Levocar; Madopar; Sinemet; Stalevo; *Fr.*: Duodopa; Modopar; Sinemet; Stalevo; *Ger.*: Duodopa; Isicom; Levo-C; Levobeta C; Levocarb†; Levocomp†; Levodop; Levodopa comp B†; Levodopa comp C†; Levodopa Comp; Levopar†; Madopar; Nacom; PK-Levo†; Stalevo; Striaton†; *Gr.*: Duodopa; Madopar; Sinemet; Stalevo; Zimox; *Hong Kong*: Apo-Levocarb; Levomed; Levomet; Madopar; Sinedopa†; Sinemet; Stalevo; *Hung.*: Duellin†; Duodopa; Madopar; Sinemet†; Stalevo; *India*: Benspar; LCD; Levopa-C; Madopar-F; Neocare; Syndopa; *Indon.*: Leparson; Levazide; Levopar; Madopar; Pardoz; Stalevo; *Irl.*: Half Sinemet; Madopar; Sinemet; Stalevo; *Israel*: Dopicar; Duodopa; Levopar Plus; Sinemet; Stalevo; *Ital.*: Duodopa; Madopar; Sinemet; Sirio; Stalevo; *Malaysia*: Apo-Levocarb; Levomed; Madopar; Sinedopa; Sinemet; Stalevo; *Mex.*: Cloisone; Lemdopa†; Madopar; Racovel; Sinemet; Stalevo; Ternovag; *Neth.*: Duodopa; Madopar; Modopar†; Sinemet; Stalevo; *Norw.*: Duodopa; Madopar; Sinemet; Stalevo; *NZ*: Apo-Levocarb†; Madopar; Sindopa; Sinemet; *Philipp.*: Ledocar; Madopar; Sinemet; Stalev; Tidomet; *Pol.*: Madopar; Sinemet; Stalevo; *Port.*: Duodopa; Ledopsan; Madopar; Sinemet; Stalevo; *Rus.*: Duellin (Дуэллин); Madopar (Мадопар); Nakom (Наком); Sinemet (Синемет); Stalevo (Сталево); Syndopa (Синдопа); Tidomet (Тидомет); Tremonorm (Тремонорм); *S.Afr.*: Carbilev; Madopar; Sinemet; Stalevo; *Singapore*: Cardopar; Credanil; Levomet; Madopar; Sinemet; Stalevo; Tidomet; *Spain*: Duodopa; Ledopsan†; Madopar; Sinemet; Stalevo; *Swed.*: Duodopa; Levocar; Madopark; Sinemet; Stalevo; *Switz.*: Duodopa; Madopar; Sinemet; Stalevo; *Thai.*: Levomed; Levomet; Madopar; Sinemet; Stalevo; Syndopa; Tidomet; Udopar-250; Vopar; *Turk.*: Madopar; Sinemet; Stalevo; *UK*: Duodopa; Half Sinemet; Madopar; Sinemet; Stalevo; *Ukr.*: Levocarbhexal (Левокарбгексал)†; Levokom (Левоком); Madopar (Мадопар); Nakom (Наком); Stalevo (Сталево); *USA*: Atamet; Parcopa; Sinemet; Stalevo; *Venez.*: Madopar; Sinemet; Stalevo.

Pharmacopoeial Preparations

BP 2014: Co-beneldopa Capsules; Co-careldopa Tablets; Dispersible Co-beneldopa Tablets; Levodopa Capsules; Levodopa Tablets; Prolonged-release Co-beneldopa Capsules;
USP 36: Carbidopa and Levodopa Orally Disintegrating Tablets; Carbidopa and Levodopa Tablets; Levodopa Capsules; Levodopa Tablets.

Lisuride Maleate *(BANM, rINNM)*

Lisurid Maleat; Lisurida, maleato de; Lisuride, Maléate de; Lisuridi Hydrogenomaleas; Lisuridi Maleas; Lisuridivetymaleaatti; Lisuridvätemaleat; Lysuride Maleate; Maleato de lisurida; Methylergol Carbamide Maleate; Лизурида Малеат.
3-(9,10-Didehydro-6-methylergolin-8α-yl)-1,1-diethylurea hydrogen maleate; 8-Decarboxamido-8-(3,3-diethylureido)-D-lysergamide maleate.
$C_{20}H_{26}N_4O.C_4H_4O_4$=454.5

CAS — 18016-80-3 (lisuride); 19875-60-6 (lisuride maleate).
ATC — G02CB02; N02CA07.
ATC Vet — QG02CB02; QN02CA07.
UNII — UV1635N8XW.

Uses and Administration

Lisuride maleate, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p. 895.3). It is also reported to have serotonergic activity. It is used similarly in the management of Parkinson's disease (p. 909.1) and has been used in disorders associated with hyperprolactinaemia (below), including amenorrhoea, galactorrhoea, and infertility. It is also used to suppress puerperal lactation for medical reasons; it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that can be adequately relieved with simple analgesics and breast support. Lisuride has been used in some countries for the treatment of acromegaly, and for the prophylaxis of migraine. It is normally given orally; doses should be taken with food.

In the management of **Parkinson's disease**, lisuride maleate has been added to treatment with levodopa or other antiparkinsonian drugs. Initially 100 micrograms is taken at bedtime and additional doses of 100 micrograms may be added, at intervals of one week, first in the morning and then at midday. Further increases are made, until an optimum response is obtained, by adding 100 micrograms each week using the same sequence of increases, starting with the bedtime dose; dosage should not normally exceed 2 mg daily given in 3 or 4 divided doses.

When used to **suppress lactation**, the usual dose of lisuride maleate is 200 micrograms two or three times daily for 14 days; treatment should be started within the first 24 hours of delivery.

In the treatment of disorders associated with **hyperprolactinaemia**, 100 micrograms of lisuride maleate may be given in the evening of the first day, followed by 100 micrograms at midday and in the evening of the second day, and 100 micrograms in the morning, at midday, and in the evening of the third day; thereafter doses may be adjusted according to prolactin levels. Similar doses are also used in **acromegaly** with adjustments made according to growth hormone levels (see also below).

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p. 1921.1). While bromocriptine and cabergoline have been the main dopamine agonists used, lisuride has been used in some countries.

Hyperprolactinaemia and prolactinomas. Dopamine agonists have been widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p. 2252.2). Lisuride has been used as an alternative to bromocriptine. There is a report of plasma-prolactin concentrations being reduced to normal in 4 female patients with macroprolactinomas given lisuride 400 to 800 micrograms daily for 2 years.[1] Subsequent dosage reduction in 3 was followed by a rise in prolactin values. In the fourth patient prolactin remained in the normal range when the dose was progressively reduced from 400 to 50 micrograms daily, although complete withdrawal was followed by an increase in prolactin concentration within 3 months.

Vaginal dosage of lisuride has been studied in an attempt to avoid adverse effects associated with oral therapy. In a study[2] involving 40 women with hyperprolactinaemia a 200-microgram standard oral tablet placed in the vagina at night produced a similar reduction in prolactin concentrations to that obtained with 400 micrograms taken orally and was better tolerated.

1. Liuzzi A, *et al.* Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. *N Engl J Med* 1985; 313: 656–9.
2. Tasdemir M, *et al.* Vaginal lisuride for hyperprolactinaemia. *Lancet* 1995; 346: 1362.

Lactation inhibition. Lisuride is used in some countries for the prevention of puerperal lactation (p. 2130.1). However, the routine use of dopaminergics is not recommended for the suppression of physiological lactation.

References.

1. Venturini PL, *et al.* Effects of lisuride and bromocriptine on inhibition of lactation and on serum prolactin levels: comparative double-blind study. *Eur J Obstet Gynecol Reprod Biol* 1981; 11: 395–400.

Mastalgia. In a small placebo-controlled study,[1] lisuride 200 micrograms daily was effective in the treatment of cyclical mastalgia. However, since mastalgia (p. 2265.) can improve spontaneously, treatment should rarely be

considered unless pain has been present for about 6 months.

1. Kaleli S, *et al.* Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study. *Fertil Steril* 2001; 75: 718–23.

Migraine. Although lisuride has been used in some countries for the prophylaxis of migraine (p. 670.3) it is not usually considered to be the drug of choice or even one of the main alternatives.

Parkinsonism. While some neurologists use dopamine agonists such as lisuride early in the treatment of parkinsonism (p. 889.1) in an attempt to delay therapy with levodopa, others reserve them for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. They are sometimes useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations in mobility in the later stages of the disease.

References.

1. Rinne UK. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. *Neurology* 1989; 39: 336–9.
2. Clarke CE, Speller J. Lisuride for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
3. Clarke CE, *et al.* Lisuride versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
4. Allain H, *et al.* Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. *Eur Neurol* 2000; 44: 22–30.

ADMINISTRATION. Lisuride has been of benefit when given by continuous intravenous or subcutaneous infusion in patients having fluctuations in mobility with levodopa therapy[1–4] but severe psychiatric effects have been associated with the use of these routes.[3] Transdermal lisuride has also been investigated for the treatment of Parkinson's disease and restless legs syndrome.[5,6]

1. Obeso JA, *et al.* Intravenous lisuride corrects oscillations of motor performance in Parkinson's disease. *Ann Neurol* 1986; 19: 31–5.
2. Obeso JA, *et al.* Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. *Lancet* 1986; i: 467–70.
3. Critchley P, *et al.* Psychosis and the lisuride pump. *Lancet* 1986; i: 349.
4. Stocchi F, *et al.* Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. *Brain* 2002; 125: 2058–66.
5. Woitalla D, *et al.* Transdermal lisuride delivery in the treatment of Parkinson's disease. *J Neural Transm Suppl* 2004; 68: 89–95.
6. Benes H. Transdermal lisuride: short-term efficacy and tolerability study in patients with severe restless legs syndrome. *Sleep Med* 2006; 7: 31–5.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3. Infusion of lisuride in parkinsonian patients has been associated with severe psychiatric adverse effects.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including lisuride, see under Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including lisuride, see under Adverse Effects of Bromocriptine, p. 897.3.

Interactions

As for Bromocriptine, p. 899.1.

Pharmacokinetics

Plasma concentrations varied widely after a single oral dose of lisuride maleate 300 micrograms in 11 patients with Parkinson's disease.[1] Absorption was rapid and the mean plasma elimination half-life was 2.2 hours. Only a mean of 0.05% of the dose was excreted unchanged in the urine in 24 hours. The mean oral bioavailability of lisuride maleate has been reported[2] to be 10% after a 100-microgram dose and 22% after a 300-microgram dose.

A single dose of lisuride 25 micrograms given by intravenous, intramuscular, or subcutaneous injection reduced plasma-prolactin concentrations by up to 60% in 11 of 12 healthy subjects, the effect lasting for about 10 hours.[3] Plasma-lisuride concentrations after intravenous injection fell in 2 phases with half-lives of 14 minutes and 1.5 hours, respectively. Peak plasma concentrations after subcutaneous and intramuscular injection were obtained after 12 and 15 minutes, respectively.

1. Burns RS, *et al.* Disposition of oral lisuride in Parkinson's disease. *Clin Pharmacol Ther* 1984; 35: 548–56.
2. Kümpel M, *et al.* Radioimmunoassay of plasma lisuride in man following intravenous and oral administration of lisuride hydrogen maleate: effect on plasma prolactin level. *Eur J Clin Pharmacol* 1981; 20: 47–51.
3. Krause W, *et al.* The pharmacokinetics and pharmacodynamics of lisuride in healthy volunteers after intravenous, intramuscular, and subcutaneous injection. *Eur J Clin Pharmacol* 1991; 40: 399–403.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Dopergin; ***Fr.***: Arolac; Dopergine; ***Ger.***: Dopergin; ***Gr.***: Dipergon; ***Ital.***: Dopergin; ***Mex.***: Dopergin; ***NZ***: Dopergin; ***Spain***: Dopergin; ***Turk.***: Dopergin.

Metixene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de metixeno; Methixene Hydrochloride (USAN); Methixene Hydrochloride; Methixene Hydrochloride Monohydrate; Metikseenihydrokloridi; Metikseno hidrochloridas; Métixène, Chlorhydrate de; Metixén-hidroklorid; Metixenhydrochlorid; Metixen-hydrochlorid monohydrát; Metixenhydroklorid; Metixeni Hydrochloridum; Metixeni Hydrochloridum Monohydricum; Metixeno, hidrocloruro de; NSC-78194; SJ-1977; Метиксена Гидрохлорид.

(*RS*)-9-(1-Methyl-3-piperidylmethyl)thioxanthene hydrochloride monohydrate.

$C_{20}H_{23}NS,HCl,H_2O$=363.9

CAS — 4969-02-2 (metixene); 1553-34-0 (anhydrous metixene hydrochloride); 7081-40-5 (metixene hydrochloride monohydrate).

ATC — N04AA03.

ATC Vet — QN04AA03.

UNII — 84L8XK6N1G.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Metixene Hydrochloride). A white or almost white, crystalline or fine crystalline powder. Soluble in water, in alcohol, and in dichloromethane. A 1.8% solution in water has a pH of 4.4 to 5.8. Protect from light.

Profile

Metixene hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p. 1312.1); it also has antihistaminic and direct antispasmodic properties.

It is used for the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. The usual oral dose of metixene hydrochloride is 2.5 mg three to six times daily initially, gradually increased according to response to a total of 20 to 60 mg daily in divided doses.

Metixene hydrochloride has also been used in preparations to relieve gastrointestinal spasms.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metixene 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 30/09/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Tremarit†; ***Hung.***: Tremaril; ***Ital.***: Tremaril.

Multi-ingredient Preparations. ***Philipp.***: Spasmo-Canulase; ***Port.***: Espasmo Canulase†; ***S.Afr.***: Spasmo-Canulase†; ***Switz.***: Spasmo-Canulase.

Orphenadrine Citrate *(BANM, rINNM)*

Citrato de orfenadrina; Mephenamine Citrate; Orfenadriinisitraatti; Orfenadrina, citrato de; Orfenadrincitrat; Orfenadrincitrát; Orfenadrino citratas; Orphenadin Citrate; Orphenadrincitrat; Orphénadrine, Citrate d'; Orphenadrini Citras; Орфенадрина Цитрат.

(*RS*)-Dimethyl[2-(2-methylbenzhydryloxy)ethyl]amine dihydrogen citrate.

$C_{18}H_{23}NO,C_6H_8O_7$=461.5

CAS — 83-98-7 (orphenadrine); 4682-36-4 (orphenadrine citrate).

ATC — M03BC01.

ATC Vet — QM03BC01.

UNII — X0A40N8I4S.

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

Ph. Eur. 8: (Orphenadrine Citrate). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Orphenadrine Citrate). A white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Orphenadrine Hydrochloride *(BANM, rINNM)*

BS-5930; Hidrocloruro de orfenadrina; Mephenamine Hydrochloride; Orfenadriinihydrokloridi; Orfenadrina, hidrocloruro de; Orfenadrin-hidroklorid; Orfenadrin-hydrochlorid; Orfenadrinhydroklorid; Orfenadrino hidrochloridas; Orphenadin Hydrochloride; Orphénadrine, Chlorhydrate d'; Orphenadrinhydrochlorid; Orphenadrini Hydrochloridum; Орфенадрина Гидрохлорид.

(*RS*)-Dimethyl[2-(2-methylbenzhydryloxy)ethyl]amine hydrochloride.

$C_{18}H_{23}NO,HCl$=305.8

CAS — 341-69-5.

ATC — N04AB02.

ATC Vet — QN04AB02.

UNII — UBY910DUXH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Orphenadrine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol. Protect from light.

Uses and Administration

Orphenadrine, which is a congener of diphenhydramine (p. 626.1) without sharing its soporific effect, is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3). It also has weak antihistaminic and local anaesthetic properties. Orphenadrine is used as the hydrochloride and the citrate; doses are expressed in terms of the relevant salt.

Orphenadrine is used as the hydrochloride in the symptomatic treatment of **parkinsonism** (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. The initial oral dose of orphenadrine hydrochloride is 150 mg daily in divided doses gradually increased by 50 mg every 2 or 3 days according to response; the usual maintenance dose is in the range of 150 to 300 mg daily, but some patients may require a total of up to 400 mg daily. Orphenadrine hydrochloride has also been given intramuscularly.

Orphenadrine is also used as the citrate to relieve pain due to **skeletal muscle spasm** (below). It is given orally in a dose of 100 mg twice daily or by intramuscular or slow intravenous injection in a dose of 60 mg which has been repeated every 12 hours.

Combinations of orphenadrine with an NSAID, usually diclofenac, or with paracetamol, have been used in the treatment of musculoskeletal and joint disorders.

Hiccup. Orphenadrine citrate has been used in some countries for the treatment of intractable hiccup. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3.

Muscle and joint disorders. References to the use of orphenadrine in the management of leg cramps and other painful conditions associated with skeletal muscle spasm,[1,2] and with diclofenac in osteoarthritis and other musculoskeletal disorders.[3,4]

1. Latta D, Turner E. An alternative to quinine in nocturnal leg cramps. *Curr Ther Res* 1989; 45: 833–7.
2. Hunskaar S, Donnell D. Clinical and pharmacological review of the efficacy of orphenadrine and its combination with paracetamol in painful conditions. *J Int Med Res* 1991; 19: 71–87.
3. Ulitz E, *et al.* Diclofenac/Orphenadrin-Infusionstherapie bei Patienten mit aktivierten Arthrosen. *Wien Med Wochenschr* 1998; 148: 179–82.
4. Aglas F, *et al.* Ergebnisse einer Anwendungsbeobachtung mit Diclofenac/Orphenadrin-Infusionen bei Patienten mit muskuloskelettalen Krankheiten und Funktionsstörungen. *Acta Med Austriaca* 1998; 25: 86–90.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1. Orphenadrine may cause insomnia.

Abuse. A 23-year-old schizophrenic man, whose treatment included orphenadrine 100 mg three times daily, obtained illicit supplies and increased the dose for euphoric effect.[1] On one occasion he had an epileptic convulsion after a 600-mg dose.

See also under Trihexyphenidyl Hydrochloride, p. 918.1.

1. Sharlatmadari ME. Orphenadrine dependence. *BMJ* 1975; 3: 486.

Overdosage. A report[1] of acute poisoning with orphenadrine after massive overdosage in a schizophrenic patient, who responded to intensive supportive treatment, including large doses of adrenaline, dopamine, and dobutamine to restore blood pressure following asystole. Between 1977

and 1980 twelve deaths due to orphenadrine were recorded by the UK National Poisons Unit.

1. Clarke B, *et al.* Acute poisoning with orphenadrine. *Lancet* 1985; i: 1386.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies orphenadrine 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 30/09/11)

Withdrawal. A suspected withdrawal syndrome was reported in a 56-year-old woman who showed slow neurological postoperative recovery after her orphenadrine treatment had been stopped abruptly;[1] her status improved when the drug was restarted.

1. Esler MD, *et al.* Postoperative orphenadrine withdrawal. *Br J Anaesth* 2000; 85: 497.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3). Orphenadrine is an inhibitor of the cytochrome P450 isoenzyme CYP2B6, which is involved in the metabolism of bupropion to its major metabolite; licensed product information advises that orphenadrine should be used with caution in patients also receiving bupropion.

Chlorpromazine. For the effect of orphenadrine on plasma concentrations of chlorpromazine, see Antiparkinsonian Drugs, p. 1052.3.

Dextropropoxyphene. A suggested interaction between orphenadrine and dextropropoxyphene was open to question.[1,2]

1. Pearson RE, Salter FJ. Drug interaction? — orphenadrine with propoxyphene. *N Engl J Med* 1970; 282: 1215.
2. Puckett WH, Visconti JA. Orphenadrine and propoxyphene (corr.). *N Engl J Med* 1970; 283: 544.

Pharmacokinetics

Orphenadrine is readily absorbed from the gastrointestinal tract and after intramuscular injection. It is almost completely metabolised to at least 8 metabolites. It is mainly excreted in the urine as metabolites and small amounts of unchanged drug. The half-life of orphenadrine has been reported to be 14 hours (but see below).

Half-life. While the mean elimination half-life of orphenadrine in 5 healthy subjects given a single dose of the hydrochloride was found to be 15.5 hours, elimination half-lives of 30.5 and 40 hours were calculated in 2 patients given repeated oral doses.[1]

1. Labout JJM, *et al.* Difference between single and multiple dose pharmacokinetics of orphenadrine hydrochloride in man. *Eur J Clin Pharmacol* 1982; 21: 343–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Norflex; *Canad.*: Norflex; Orfenace; *Chile*: Plenactol†; *Denm.*: Lysantin; *Fin.*: Norflex; *Ger.*: Norflex; *Gr.*: Disipal; Norflex; *India*: Orphipal; *Israel*: Flexin; *Ital.*: Disipal; *Malaysia*: Norflex; *Mex.*: Norflex; *NZ*: Disipal; Norflex; *S.Afr.*: Disipal; Norflex; Phenerine†; *Singapore*: Onadrine; *Swed.*: Norflex; *Thai.*: Norflex; Ofee; Orfenal; Phemax; Sinogesic; *UK*: Biorphen; Disipal; *USA*: Banflex; Flexon; Norflex; *Venez.*: Norflex.

Multi-ingredient Preparations. *Arg.*: Belmalen; Flogodisten; Mio Aldoron; Mio-Virobron; *Austral.*: Norgesic; *Austria*: Neodolpasse; Norgesic; *Braz.*: Ana-Flex; Bioflex; Dalgex†; Doralgex; Dorciflex†; Dorflex; Doricin; Dorzone; Flexalgex; Flexdor; Miorrelax; Nevralgex; Novralflex; Reflex; Relaflex; Rheumafim; Rielex; Royflex; Sedalex; *Chile*: Norgesic†; *Cz.*: Neodolpasse; *Fin.*: Dolan; Norgesic; *Gr.*: Norgesic; *Hong Kong*: Myodrine†; Norgesic; Pormus; *Hung.*: Neodolpasse; *India*: Orphamol; *Israel*: Muscol; Norgesic†; *Malaysia*: Anarex; Cetagesic; Norgesic; Orphenadol; Paragesic; Suniton†; *Mex.*: Norflex Plus; *NZ*: Norgesic; *Philipp.*: Norgesic; *S.Afr.*: Besemax; Besenol; Norflex Co; Uniflex; *Singapore*: Anarex; Camgesic; Cetagesic; Norgesic; Norphen; Orcigesic; Orphenadol; Suniton; *Swed.*: Norgesic; *Thai.*: Cenasic; Corilax; Dorpane; Dysmenic; Fagesic†; GPO Gesic; M-Gesic; Medgesic; Muscol; Muscolic; Muslexac; Myodrine; Myoflex; Myopa; Myopas; Myosic; Myospa; Mypara Plus; Nabesac; Neosec; Noraphen; Norgesic; Norgetex; Norgic; Norphen; Norsica; Nuosic; Nurasic; Orano; Orapa; Orflex; Orgesic; Ornadine; Orpar; Orphengesic; Orphensic; Paradine; Parina; Patargesic; Poli-Relaxane; Polydol; Pormus; Pronadrine; Prospa; Relar; Relaxic; Rena; Rexodrin; Togesic; *UAE*: Muscadol; *USA*: Norgesic†; Orphenadrine Compound; Orphengesic†; *Venez.*: Norgesic.

Pharmacopoeial Preparations

BP 2014: Orphenadrine Hydrochloride Tablets;

USP 36: Orphenadrine Citrate Extended-Release Tablets; Orphenadrine Citrate Injection; Orphenadrine Citrate, Aspirin, and Caffeine Tablets.

Pergolide Mesilate *(BANM, rINNM)*

LY-127809; Mesilato de pergolida; Pergolid Mesilat; Pergolid mesylát; Pergolida, mesilato de; Pergolide, mésilate de; Pergolide Mesylate (USAN); Pergolidi Mesilas; Pergolidimesilaatti; Pergolidmesilat; Pergolid-mezilát; Pergolido mesilatas; Пергонида Мезилат.

8β-Methylthiomethyl-6-propylergoline methanesulphonate; Methyl (8*R*,10*R*)-6-propylergolin-8-ylmethyl sulphide methanesulphonate.

$C_{19}H_{26}N_2S,CH_4O_3S$=410.6

CAS — 66104-22-1 (pergolide); 66104-23-2 (pergolide mesilate).

ATC — N04BC02.

ATC Vet — QN04BC02.

UNII — 55B9HQY616.

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

Ph. Eur. 8: (Pergolide Mesilate). A white or almost white crystalline powder. Slightly soluble in water, in alcohol, and in dichloromethane; very slightly soluble in acetone; sparingly soluble in methyl alcohol. Protect from light.

USP 36: (Pergolide Mesylate). A white to off-white powder. Slightly soluble in water, in dehydrated alcohol, and in chloroform; very slightly soluble in acetone; practically insoluble in ether; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Pergolide mesilate, an ergot derivative, is a dopamine D_2-agonist with actions and uses similar to those of bromocriptine (p. 895.3), but in contrast to bromocriptine (a dopamine D_2-agonist) it also has agonist properties at D_1 and D_3 receptors. Pergolide is used in the management of Parkinson's disease (below) as monotherapy, or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response; in the UK pergolide is restricted to patients who are intolerant of, or who fail to respond to, non-ergot drug treatment. Pergolide is given orally as the mesilate with doses expressed as the base. Pergolide mesilate 65.3 mg is equivalent to about 50 mg pergolide.

For use as *monotherapy* an initial dose equivalent to 50 micrograms of pergolide is given on the first evening of therapy. The dose is thereafter gradually increased: 50 micrograms twice daily is taken on days 2 to 4, then increased by 100 to 250 micrograms every 3 or 4 days, given in 3 divided doses, up to a daily dose of 1.5 mg at day 28. After day 30, the dose should be increased further by a maximum of 250 micrograms twice a week until an optimum response is achieved. Usual maintenance doses are 2.1 to 2.5 mg daily; doses above 3 mg daily are not recommended by the EMEA. The daily dose is usually given in 3 divided doses.

For use as *adjunctive therapy* with levodopa, pergolide should be introduced gradually and during this period patients can have their levodopa dosage decreased gradually until an optimum response is achieved. The initial dose of pergolide is the equivalent of 50 micrograms daily for the first 2 days, increased gradually by 100 or 150 micrograms every third day over the next 12 days of therapy. Further increases of 250 micrograms may then be made every third day until an optimum response is achieved. A usual maintenance dose is 3 mg daily; doses above 3 mg daily are not recommended by the EMEA. The daily dose is usually given in 3 divided doses.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p. 1921.1). While bromocriptine and cabergoline have been the main dopamine agonists used pergolide has also been tried.[1]

1. Kleinberg DL, *et al.* Pergolide for the treatment of pituitary tumors secreting prolactin or growth hormone. *N Engl J Med* 1983; 309: 704–9.

Hyperprolactinaemia and prolactinomas. Dopamine agonists are widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p. 2252.2). Pergolide has been suggested as an alternative to bromocriptine in this condition.

Studies[1-3] of pergolide mesilate in patients with hyperprolactinaemia indicate that single doses reduce serum-prolactin concentrations for more than 24 hours. In most patients, the effective dose was between 50 and 150 micrograms daily. Adverse effects were similar to those seen with bromocriptine, although some patients who could not take bromocriptine were able to tolerate pergolide (and vice versa). Pergolide reportedly lost favour for this indication after reports of an increased incidence of uterine neoplasms in *rodents* receiving high doses. However, licensed product information states that no cases of uterine malignancies have to date been reported in humans receiving pergolide. The long-term outcome of treatment of macroprolactinomas with pergolide has been examined in 23 patients,[4] and efficacy and relative safety of pergolide was shown after an average of 27 months (range: 9 to 64 months) treatment.

1. Franks S, *et al.* Treatment of hyperprolactinaemia with pergolide mesylate: acute effects and preliminary evaluation of long-term treatment. *Lancet* 1981; ii: 659–61.
2. Franks S, *et al.* Effectiveness of pergolide mesylate in long-term treatment of hyperprolactinaemia. *BMJ* 1983; 286: 1177–9.
3. Kleinberg DL, *et al.* Pergolide for the treatment of pituitary tumors secreting prolactin or growth hormone. *N Engl J Med* 1983; 309: 704–9.
4. Preda PU, *et al.* Long-term treatment of prolactin-secreting macroadenomas with pergolide. *J Clin Endocrinol Metab* 2000; 85: 8–13.

Parkinsonism. Dopamine agonists such as pergolide are often used to begin the treatment of parkinsonism (p. 889.1) in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations in mobility in the later stages of the disease. Pergolide has a relatively long duration of action compared with other dopamine agonists commonly used. Although the duration of the clinical antiparkinsonian effect of pergolide remains to be determined, studies suggest it is of the order of 5 to 8 hours. Depending on the dose used the response to other dopamine agonists in late parkinsonism is 1 to 4 hours for levodopa, 2 to 4 hours for lisuride, and 4 to 6 hours for bromocriptine.

References.

1. Anonymous. Pergolide (Celance)—a third dopamine agonist. *Drug Ther Bull* 1991; 29: 79.
2. Markham A, Benfield P. Pergolide: a review of its pharmacology and therapeutic use in Parkinson's disease. *CNS Drugs* 1997; 7: 328–40.
3. Barone P, *et al.* Pergolide monotherapy in the treatment of early PD: a randomized, controlled study. *Neurology* 1999; 53: 573–9.
4. Clarke CE, Speller J. Pergolide for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews, Issue 2. Chichester: John Wiley; 1999 (accessed 16/02/06).
5. Clarke CE, Speller J. Pergolide versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 16/02/06).

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has largely been empirical although dopaminergic therapy has emerged as a common first-line choice. Pergolide has produced some benefit in several studies.[1-6] In a randomised placebo-controlled study,[6] therapeutic effects were seen with mean daily doses of pergolide 400 micrograms after 6 weeks and maintained after 12 months with doses of up to 720 micrograms daily.

1. Silber MH, *et al.* Pergolide in the management of restless legs syndrome: an extended study. *Sleep* 1997; 20: 878–82.
2. Winkelmann J, *et al.* Treatment of restless legs syndrome with pergolide—an open clinical trial. *Mov Disord* 1998; 13: 566–9.
3. Earley CJ, *et al.* Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. *Neurology* 1998; 51: 1599–1602.
4. Wetter TC, *et al.* A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology* 1999; 52: 944–50.
5. Stiasny K, *et al.* Long-term effects of pergolide in the treatment of restless legs syndrome. *Neurology* 2001; 56: 1399–1402.
6. Trenkwalder C, *et al.* Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS study. *Neurology* 2004; 62: 1391–7.

Tourette's syndrome. Pergolide has been studied in the management of Tourette's syndrome (see Tics, p. 1030.1). A preliminary study[1] produced encouraging results, subsequently confirmed by placebo-controlled studies in children and adolescents.[2,3]

1. Lipinski JF, *et al.* Dopamine agonist treatment of Tourette disorder in children: results of an open-label trial of pergolide. *Mov Disord* 1997; 12: 402–7.
2. Gilbert DL, *et al.* Tourette's syndrome improvement with pergolide in a randomized, double-blind, crossover trial. *Neurology* 2000; 54: 1310–15.
3. Gilbert DL, *et al.* Tic reduction with pergolide in a randomized controlled trial in children. *Neurology* 2003; 60: 606–11.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3.

An increased incidence of uterine neoplasms has been reported in *rodents* given high doses of pergolide mesilate.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including pergolide, see under Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

Fibrosis. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including pergolide, see under Adverse Effects of Bromocriptine, p. 897.3.

In Australia,[1] Canada,[2] and Europe[3] regulatory authorities recommended that patients undergo a cardiovascular evaluation before starting treatment with pergolide; periodic clinical monitoring for development of valvular disease or fibrosis is also recommended. Doses of pergolide above 3 mg daily are not recommended by the EMEA.[3] Furthermore, use is restricted to patients who are intolerant of, or who fail to respond to, non-ergot drug treatment and it is contra-indicated in patients with a history of fibrotic disorders or in those with anatomical evidence of cardiac valvulopathy.[4] In 2007, based on further evidence from 2 studies,[5,6] pergolide was withdrawn from the market in the USA[7] and Canada.[8]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Cardiac valvulopathy with pergolide. *Aust Adverse Drug React Bull* 2004; 23: 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0408.pdf (accessed 16/02/06)
2. Shire, Canada. New Safety information regarding Permax and occurrence of cardiac valvulopathy/fibrosis: update on the use of Permax (pergolide mesylate) (issued 12th October, 2004). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/shire_permax_2_hpc-cps-eng.pdf (accessed 12/08/08)
3. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)
4. MHRA. Dopamine agonists for Parkinson's disease (issued 30th March, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/DopamineagonistsforParkinson146sdisease/CON2030729 (accessed 03/06/08)
5. Schade R, *et al.* Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007; 356: 29–38.
6. Zanettini R, *et al.* Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007; 356: 39–46.
7. FDA. FDA public health advisory: pergolide (marketed as Permax) (issued 29th March, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/UCM051285 (accessed 24/08/10)
8. Eli Lilly, Canada. Health Canada-mandated important safety information on Permax (pergolide mesylate) (issued 10th August, 2007). Available at: http://www.lilly.ca/serviets/sfs;jsessionid=9E0E83CA662673A89F439C68DAA3AC4B?t=/documentManager/sfdoc.file.supply&e=UTF-8&i=1233164768976&l=0&s=S62tYOHmUjqiTRlfa&fileID=1251138472378 (accessed 23/08/10)

Interactions

As for Bromocriptine, p. 899.1.

Pharmacokinetics

Pergolide mesilate is absorbed from the gastrointestinal tract. It is reported to be about 90% bound to plasma proteins. It is excreted mainly in the urine in the form of metabolites.

References.
1. Blin O. The pharmacokinetics of pergolide in Parkinson's disease. *Curr Opin Neurol* 2003; 16 (suppl 1): S9–S12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aroltex; Celance; Geranil; ***Austral.***: Permax; ***Austria***: Permax; ***Belg.***: Permax; ***Braz.***: Celance†; ***Cz.***: Permax; ***Fr.***: Celance†; ***Ger.***: Parkotil†; ***Gr.***: Celance†; ***Irl.***: Celance; ***Ital.***: Nopar; ***Mex.***: Permax; ***Neth.***: Permax†; ***NZ***: Permax; ***Port.***: Permax; ***S.Afr.***: Permax†; ***Singapore***: Celance; ***Spain***: Pharken†; ***Switz.***: Permax†; ***Turk.***: Permax; ***UK***: Celance†.

Pharmacopoeial Preparations
USP 36: Pergolide Tablets.

Piribedil *(rINN)*

ET-495; EU-4200; Piribédil; Piribedilum; Пирибедил.
2-(4-Piperonylpiperazin-1-yl)pyrimidine.
$C_{16}H_{18}N_4O_2$=298.3
CAS — 3605-01-4.
ATC — N04BC08.
ATC Vet — QN04BC08.
UNII — DO22K1PRDJ.

Profile

Piribedil is a non-ergot dopamine agonist that has been given orally in the treatment of parkinsonism (below) and in circulatory disorders. Piribedil mesilate has been given by injection for circulatory disorders. Preparations of piribedil are licensed in some countries for the management of impaired memory and cognitive function in the elderly.

Adverse effects reported include nausea and vomiting, dizziness, hallucinations, confusion, drowsiness, hypothermia, dyskinesias, and occasional changes in liver function.

When used as monotherapy in Parkinson's disease a usual daily oral dose of piribedil is 150 to 250 mg in divided doses; a daily dose of 80 to 140 mg may be suitable when used as an adjunct to levodopa.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including piribedil, see under Adverse Effects of Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Adverse Effects of Levodopa, p. 905.2.

Parkinsonism. Piribedil is a dopamine D_2-agonist while its metabolite is reported to act on D_1 receptors. It has been mainly used as an adjunct to levodopa therapy in the treatment of Parkinson's disease (p. 889.1).

References.
1. Montastruc JL, *et al.* Current status of dopamine agonists in Parkinson's disease management. *Drugs* 1993; 46: 384–93.
2. Montastruc JL, *et al.* A randomized, double-blind study of a skin patch of a dopaminergic agonist, piribedil, in Parkinson's disease. *Mov Disord* 1999; 14: 336–41.
3. Ziegler M, Rondot P. Activité du piribédil dans la maladie de Parkinson: étude multicentrique. *Presse Med* 1999; 28: 1414–18.
4. Ziegler M, *et al.* Efficacy of piribedil as early combination to levodopa in patients with stable Parkinson's disease: a 6-month, randomized, placebo-controlled study. *Mov Disord* 2003; 18: 418–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Trastoner; Trivastal; ***Braz.***: Trivastal; ***China***: Trastal (泰舒达); ***Fr.***: Trivastal; ***Ger.***: Clarium; ***Gr.***: Trivastal; ***India***: Trivastal; ***Ital.***: Trivastan; ***Malaysia***: Trivastal; ***Philipp.***: Trivastal; ***Pol.***: Pronoran; ***Port.***: Trivastal; ***Rus.***: Pronoran (Проноран); ***Singapore***: Trivastal; ***Thai.***: Trivastal; ***Turk.***: Trivastal; ***Ukr.***: Pronoran (Проноран); ***Venez.***: Trivastal.

Pramipexole Hydrochloride

(BANM, rINNM)

Hidrocloruro de pramipexol; PNU-98528-E; Pramipexol, hidrocloruro de; Pramipexole, Chlorhydrate de; Pramipexole, dichlorhydrate de; Pramipexole Dihydrochloride (USAN); Pramipexoli dihydrochloridum; Pramipexoli Hydrochloridum; SND-919-CL-2Y (pramipexole hydrochloride); SUD-919Y (pramipexole); Прамипексола Гидрохлорид.
(*S*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate.
$C_{10}H_{17}N_3S,2HCl, H_2O$=302.3
CAS — 104632-26-0 (pramipexole); 104632-25-9 (anhydrous pramipexole hydrochloride); 191217-81-9 (pramipexole hydrochloride monohydrate).
ATC — N04BC05.
ATC Vet — QN04BC05.
UNII — 3D867NP06J.

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

Ph. Eur. 8: (Pramipexole Dihydrochloride Monohydrate). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble to slightly soluble in alcohol; soluble in methyl alcohol; practically insoluble in dichloromethane. pH of a 2% solution in water is 2.8 to 3.4.

USP 36: (Pramipexole Dihydrochloride). A white to almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol; practically insoluble in dichloromethane. Protect from moisture and light.

Uses and Administration

Pramipexole is a non-ergot dopamine agonist with actions similar to those of bromocriptine (p. 895.3). It is used similarly in the management of Parkinson's disease (below), either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response. Pramipexole is also used for the treatment of moderate to severe restless legs syndrome (below). It is given orally as the hydrochloride; doses have been described in terms of the hydrochloride (as below) or of the base. In terms of equivalency:

- pramipexole hydrochloride 125 micrograms is equivalent to about 88 micrograms of pramipexole
- pramipexole hydrochloride 250 micrograms is equivalent to about 180 micrograms of pramipexole
- pramipexole hydrochloride 500 micrograms is equivalent to about 350 micrograms of pramipexole
- pramipexole hydrochloride 1 mg is equivalent to about 700 micrograms of pramipexole

In the treatment of **Parkinson's disease**, the dose of pramipexole should be increased gradually and the dose of levodopa gradually reduced during the dose-titration and maintenance phases until an optimum response is achieved. The initial dose of pramipexole *hydrochloride* is 125 micrograms three times daily increased to 250 micrograms three times daily in the second week and then to 500 micrograms three times daily in the third week according to response. Thereafter the daily dose may be increased if necessary by 750 micrograms at weekly intervals to a maximum of 4.5 mg daily. Modified-release preparations are also available for once-daily use. The dosage should be reduced in patients with renal impairment (see below).

If it is necessary to stop pramipexole therapy, it should be withdrawn gradually. The dose of pramipexole hydrochloride should be tapered off at a rate of 750 micrograms daily until a daily dose of 750 micrograms has been reached; thereafter, the dose should be reduced by 375 micrograms daily.

Pramipexole is also given as a single daily dose, 2 to 3 hours before bedtime, in the treatment of **restless legs syndrome**. The initial dose of pramipexole *hydrochloride* is 125 micrograms daily. This may be increased if necessary after 4 to 7 days to 250 micrograms daily. Subsequent doses may be increased if necessary by 250 micrograms every 4 to 7 days to a maximum of 750 micrograms daily. Response to therapy should be evaluated after 3 months; if treatment is interrupted for more than a few days, it should be restarted at 125 micrograms daily, and then increased, if required, as described above. For this indication, pramipexole may be withdrawn without gradual tapering of the dose.

Administration in renal impairment. The elimination of pramipexole is dependent on renal function and the oral dosage of pramipexole hydrochloride should therefore be reduced in patients with renal impairment.

In the treatment of *Parkinson's disease*, the following dosage schedule has been suggested in UK licensed product information adjusted according to the patient's creatinine clearance (CC):

- CC 20 to 50 mL/minute: initially 125 micrograms twice daily increased, if necessary, to a maximum of 2.25 mg daily
- CC less than 20 mL/minute: initially 125 micrograms once daily increased, if necessary, to a maximum of 1.5 mg daily

Similar reductions are suggested in US licensed information for patients with a CC of 30 to 50 mL/minute and 15 to less than 30 mL/minute, respectively; no recommendation is made for those with a CC of less than 15 mL/minute.

If renal function declines during maintenance therapy it is recommended that the daily dose of pramipexole should be reduced by the same percentage as the decline in CC.

Lower doses are used in the treatment of *restless legs syndrome* and UK licensed information considers dosage reductions unnecessary in patients with CC of more than 20 mL/minute. US licensed information recommends that the interval between titration steps is increased to 14 days in those patients with CC of 20 to 60 mL/minute.

Parkinsonism. Pramipexole is a dopamine agonist used in the treatment of Parkinson's disease (p. 889.1) as an adjunct to levodopa therapy to reduce 'off' periods with levodopa and ameliorate other fluctuations of mobility in the later stages of the disease. It is also used as monotherapy early in the course of the disease in an attempt to delay therapy with levodopa.

References.
1. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson disease: a randomized dose-ranging study. *JAMA* 1997; 278: 125–30.
2. Lieberman A, *et al.* Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology* 1997; 49: 162–8.
3. Shannon KM, *et al.* Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology* 1997; 49: 724–8.
4. Guttman M. International Pramipexole-Bromocriptine Study Group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. *Neurology* 1997; 49: 1060–5.
5. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *JAMA* 2000; 284: 1931–8.
6. Clarke CE, *et al.* Pramipexole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/02/06).
7. Clarke CE, *et al.* Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/02/06).
8. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol* 2004; 61: 1044–53. Correction. *ibid.* 2005; 62: 430.
9. Moller JC, *et al.* Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: results from a European multicenter trial. *Mov Disord* 2005; 20: 602–10.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has largely been empirical, although dopaminergic therapy has emerged as a common first-line choice. Low-dose pramipexole has produced some benefit in several studies[1-8] and is licensed for the treatment of moderate to severe RLS in some countries.

1. Lin S-C, *et al.* Effect of pramipexole in treatment of resistant restless legs syndrome. *Mayo Clin Proc* 1998; 73: 497–500.
2. Montplaisir J, *et al.* Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology* 1999; 52: 938–43.

3. Montplaisir J, *et al.* Pramipexole in the treatment of restless legs syndrome: a follow-up study. *Eur J Neurol* 2000; 7 (suppl 1): 27–31.
4. Saletu M, *et al.* Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. *Eur Arch Psychiatry Clin Neurosci* 2002; 252: 185–94.
5. Silber MH, *et al.* Pramipexole in the management of restless legs syndrome: an extended study. *Sleep* 2003; 26: 819–21.
6. Stiasny-Kolster K, Oertel WH. Low-dose pramipexole in the management of restless legs syndrome: an open label trial. *Neuropsychobiology* 2004; 50: 65–70.
7. Winkelman JW, *et al.* Efficacy and safety of pramipexole in restless legs syndrome. *Neurology* 2006; 67: 1034–9.
8. Oertel WH, *et al.* Pramipexole RLS Study Group. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). *Mov Disord* 2007; 22: 213–19.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3.

Pramipexole should be used with caution in patients with renal impairment and reduced doses are recommended.

Ophthalmological monitoring is recommended at regular intervals or if vision abnormalities occur.

Incidence of adverse effects. References.

1. Etminan M, *et al.* Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. *Drug Safety* 2003; 26: 439–44.

Effects on mental function. Pramipexole has been associated with attacks of sudden onset of sleep, sometimes without any prior feeling of drowsiness, that can occur at any time during treatment. Licensed product information states that the incidence of **daytime somnolence** is increased at daily doses of pramipexole hydrochloride higher than 1.5 mg. A retrospective analysis[1] of data to evaluate the incidence and nature of somnolence in patients receiving pramipexole in clinical studies showed that for patients with moderate or severe somnolence, the onset of worst-reported somnolence occurred at a mean daily dose of around 4 mg (range: 0.75 to 4.5 mg).

For further reports of daytime somnolence occurring in patients receiving dopamine agonists including pramipexole, see under Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, including pramipexole, see under Levodopa, p. 905.2.

1. Hauser RA, *et al.* Pramipexole-induced somnolence and episodes of daytime sleep. *Mov Disord* 2000; 15: 658–63.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pramipexole 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 30/09/11)

Interactions

As for Bromocriptine, p. 899.1. Cimetidine is reported to reduce the renal clearance of pramipexole.

Caution is advised when other sedating drugs or alcohol are used with pramipexole because of possible additive effects and the risk of precipitating sudden onset of sleep (see above).

References.

1. Wright CE, *et al.* Influence of probenecid and cimetidine on pramipexole pharmacokinetics. *Clin Pharmacol Ther* 1996; 59: 183.

Pharmacokinetics

Pramipexole is readily absorbed from the gastrointestinal tract and peak plasma concentrations have occurred within about 2 hours in fasting patients and in about 3 hours when given with food. Oral bioavailability is reported to be about 90%. Pramipexole is widely distributed throughout the body and plasma-protein binding is less than 20%. Metabolism is minimal and more than 90% of a dose is excreted via renal tubular secretion unchanged into the urine. Elimination half-lives of 8 to 12 hours have been reported. On the basis of studies in *rats*, it is thought to be distributed into breast milk.

References.

1. Wright CE, *et al.* Steady-state pharmacokinetic properties of pramipexole in healthy volunteers. *J Clin Pharmacol* 1997; 37: 520–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Maxtenk; Neurosomat; Nixol; Noxopran; Nulipar; Parfeno; Parmital; Parxium†; Portiv; Proats; Sifrol; Treminel; ***Austral.***: Sifrol; ***Austria***: Sifrol; ***Belg.***: Sifrol; ***Braz.***: Livipark; Mirapex; Sifrol; ***Canad.***: Mirapex; ***Chile***: Biopsol; Intaxel; Sifrol; ***China***: Sifrol (森福罗); ***Cz.***: Aperixon; Emwepel; Glepark; Medopexol; Mirapexin; Oprymea; Pexogles; Pexopaul; Pramigen; Pramithan; Pramixil; Ritmorest; Sifrol; ***Denm.***: Derinik; Mirapexin; Nelipraxt; Oprymea; Pramithon; Sifrol; Tifripext; ***Fin.***: Derinik; Glepark; Pramigen; Sifrol; ***Fr.***: Sifrol; ***Ger.***: Oprymea; Pramip; Sifrol; ***Gr.***: Glepark; Mariprax; Medopexol; Miraleton; Miraparkin; Mirapexin; ***Hong Kong***: Mirapex; ***Hung.***: Mirapexin; Oprymea; Pramitenorm; ***Indon.***: Sifrol; ***Irl.***: Glepark; Meroximer; Miramel; Mirapexin; Mirole; Oprymea; Sifrol; ***Israel***: Sifrol; Trimexol; ***Ital.***: Ezaprev; Mariprax; Miparkan; Miraper; Mirapexin; Miviren; Pramigen; Ramixole; ***Jpn***: BI-Sifrol; Mirapex; ***Malaysia***: Sifrol; ***Mex.***: Sifrol; ***Neth.***: Glepark; Mirapexin; Oprymea; Pramipexolane; Pramithon; Sifrol; ***Norw.***: Sifrol; ***NZ***: Sifrol; ***Philipp.***: Sifrol; ***Pol.***: Miparkan; Mirapexin; Neliprax; Oprymea; Pramixil; Ritmorest; Sifrol; ***Port.***: Ezaprev; Mirapexin; Oprymea; Sifrol; ***Rus.***: Mirapex (Мирапекс); ***S.Afr.***: Pexola; ***Singapore***: Sifrol; ***Spain***: Mirapexin; ***Swed.***: Derinik; Oprymea; Sifrol; ***Switz.***: Sifrol; ***Thal.***: Sifrol; ***Turk.***: Parkyn; Parson; Pexola; ***UK***: Mirapexin; ***Ukr.***: Mirapex (Мирапекс); Miraxol (Мираксол); ***USA***: Mirapex; ***Venez.***: Sifrol/Mirapex.

Procyclidine Hydrochloride

(BANM, rINNM)

Hidrocloruro de prociclidina; Prociclidina, hidrocloruro de; Procyclidine, Chlorhydrate de; Procyclidini Hydrochloridum; Прециклидина Гидрохлорид.

1-Cyclohexyl-1-phenyl-3-(pyrrolidin-1-yl)propan-1-ol hydrochloride.

$C_{19}H_{29}NO,HCl$=323.9

CAS — 77-37-2 (procyclidine); 1508-76-5 (procyclidine hydrochloride).

ATC — N04AA04.

ATC Vet — QN04AA04.

UNII — CQC932Z7YW.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Procyclidine Hydrochloride). A white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in acetone and in ether. A 1% solution in water has a pH of 4.5 to 6.5.

USP 36: (Procyclidine Hydrochloride). A white crystalline powder, having a moderate characteristic odour. Soluble 1 in 35 of water, 1 in 9 of alcohol, 1 in 6 of chloroform, and 1 in 11 000 of ether; insoluble in acetone. pH of a 1% solution in water is between 5.0 and 6.5. Store in a dry place in airtight containers. Protect from light.

Uses and Administration

Procyclidine hydrochloride is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3). It is used for the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias (but see under Uses and Administration of Levodopa, p. 903.3); for doses in children, see below.

In **parkinsonism**, the initial oral dose of 2.5 mg three times daily may be increased gradually by 2.5 to 5 mg every 2 or 3 days (or by 2.5 mg daily if used for drug-induced extrapyramidal syndrome) until the optimum maintenance dose, usually 10 to 30 mg daily in 3 (or occasionally 4) divided doses, is reached; daily doses of up to 60 mg have occasionally been required. As a rule, postencephalitic patients tolerate and require the larger doses; elderly and arteriosclerotic patients may require smaller doses.

In an emergency such as **acute dystonias**, 5 to 10 mg may be given by intravenous injection; higher doses have sometimes been used. The intramuscular route has also been employed: 5 to 10 mg may be given as a single injection, repeated if necessary after 20 minutes to a maximum of 20 mg daily. Parenteral doses are usually effective within 5 to 10 minutes but may need 30 minutes to produce relief.

Administration in children. Although procyclidine hydrochloride is not licensed in the UK for management of dystonias (p. 903.3) in children, the *BNFC* suggests that oral doses of 1.25 mg 3 times daily may be given to those aged 7 to 12 years, and 2.5 mg 3 times daily to those aged 12 to 18 years. In an emergency, a single dose may be given by intramuscular or intravenous injection according to age as follows: under 2 years, 0.5 to 2 mg; 2 to 10 years, 2 to 5 mg; 10 to 18 years, 5 to 10 mg or occasionally more. Parenteral doses are usually effective within 5 to 10 minutes but may need 30 minutes to produce relief.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1. Psychotic episodes may be precipitated in patients with mental disorders when procyclidine is used for the treatment of drug-induced extrapyramidal syndrome.

Abuse. Like other antimuscarinics (see also under Trihexyphenidyl Hydrochloride, p. 918.1) procyclidine has been abused for its euphoriant effects.[1,2]

1. McGucken RB, *et al.* Teenage procyclidine abuse. *Lancet* 1985; I: 1514.
2. Dooris B, Reid C. Feigning dystonia to feed an unusual drug addiction. *J Accid Emerg Med* 2000; 17: 311.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Paroxetine increases plasma-procyclidine concentrations and it is recommended that the dose of procyclidine should be reduced if antimuscarinic effects are seen in patients receiving both drugs.

Pharmacokinetics

Procyclidine hydrochloride is absorbed from the gastrointestinal tract and bioavailability has been reported to be 75% after oral doses; it disappears rapidly from the tissues. Procyclidine given intravenously acts within 5 to 20 minutes and has a duration of effect of up to 4 hours. The mean plasma elimination half-life after oral or intravenous doses is about 12 hours. About one-fifth of an oral dose is metabolised in the liver, mainly by the cytochrome P450 isoenzymes, followed by conjugation with glucuronic acid. A small amount of unchanged drug is excreted in the urine.

References.

1. Whiteman PD, *et al.* Pharmacokinetics and pharmacodynamics of procyclidine in man. *Eur J Clin Pharmacol* 1985; 28: 73–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Kemadrin; ***Belg.***: Kemadrin; ***Cz.***: Kemadrin; ***Denm.***: Kemadrin; ***Ger.***: Osnervin; ***Hung.***: Kemadrin; ***India***: Kemadrin; ***Irl.***: Kemadrin; ***Israel***: Kemadrin; ***NZ***: Kemadrin; ***Spain***: Kemadren; ***Switz.***: Kemadrin; ***UK***: Arpicolin; Kemadrin.

Pharmacopoeial Preparations

BP 2014: Procyclidine Injection; Procyclidine Tablets;

USP 36: Procyclidine Hydrochloride Tablets.

Profenamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Profenamina; Ethopropazine Hydrochloride; Hidrocloruro de profenamina; Isothazine Hydrochloride; Profenamina, hidrocloruro de; Profénamine, Chlorhydrate de; Profenamini Hydrochloridum; Prophenamini Chloridum; Профенамина Гидрохлорид.

10-(2-Diethylaminopropyl)phenothiazine hydrochloride.

$C_{19}H_{24}N_2S,HCl$=348.9

CAS — 522-00-9 (profenamine); 1094-08-2 (profenamine hydrochloride).

ATC — N04AA05.

ATC Vet — QN04AA05.

UNII — O007111VRN.

Profile

Profenamine hydrochloride is a phenothiazine derivative with antimuscarinic, adrenergic-blocking, antihistaminic, local anaesthetic, and ganglion-blocking properties. Adverse effects associated with phenothiazines may occur, especially with high doses (see under Chlorpromazine, p. 1047.2). Profenamine has been used in the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as other phenothiazines, but, like other antimuscarinics (see Atropine Sulfate, p. 1310.2), is of no value against tardive dyskinesias. It has been used in a usual initial oral dose of 50 mg three times daily, gradually increased to 500 mg or more daily in divided doses, according to response.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Parsitan.

Rasagiline Mesilate *(rINNM)*

Mesilato de rasagilina; Rasagiline, Mésilate de; Rasagiline Mesylate (USAN); Rasagilini Mesilas; TV-1030 (rasagiline); TVP 1012; Разагилина Мезилат.

(R)-*N*-2-Propynyl-1-indanamine methanesulfonate.

$C_{12}H_{13}N,CH_4O_3S$=267.3

CAS — 136236-51-6 (rasagiline); 161735-79-1 (rasagiline mesilate).

ATC — N04BD02.

ATC Vet — QN04BD02.

UNII — LH8C2JI290.

Uses and Administration

Rasagiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease (p. 889.1), either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' fluctuations in response. Rasagiline is given orally as the mesilate and doses are expressed in terms of the base; rasagiline mesilate 1.56 mg is equivalent to about 1 mg of rasagiline. The usual dose is the equivalent of rasagiline 1 mg once daily. In the USA, an initial daily dose of 500 micrograms is recommended for adjunctive therapy.

The dose of rasagiline may need to be reduced when given with drugs that inhibit the cytochrome P450 isoenzyme CYP1A2 (see Interactions, below for details) and in patients with hepatic impairment (see below).

References.
1. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol* 2002; **59**: 1937–43.
2. Stern MB, *et al.* Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Mov Disord* 2004; **19**: 916–23.
3. Thebault JJ, *et al.* Tolerability, safety, pharmacodynamics, and pharmacokinetics of rasagiline: a potent, selective, and irreversible monoamine oxidase type B inhibitor. *Pharmacotherapy* 2004; **24**: 1295–1305.
4. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol* 2004; **61**: 561–6.
5. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* 2005; **62**: 241–8.
6. Rascol O, *et al.* Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet* 2005; **365**: 947–54.
7. Rascol O. Rasagiline in the pharmacotherapy of Parkinson's disease: a review. *Expert Opin Pharmacother* 2005; **6**: 2061–75.
8. Chen JJ, *et al.* Clinical pharmacology of rasagiline: a novel, second-generation propargylamine for the treatment of Parkinson disease. *J Clin Pharmacol* 2005; **45**: 878–94.
9. Siderowf A, Stern M. Clinical trials with rasagiline: evidence for short-term and long-term effects. *Neurology* 2006; **66** (suppl 4): S80–S88.
10. Goetz CG, *et al.* Parkinson Study Group TEMPO and PRESTO Investigators. Safety of rasagiline in elderly patients with Parkinson disease. *Neurology* 2006; **66**: 1427–9.
11. Oldfield V, *et al.* Rasagiline: a review of its use in the management of Parkinson's disease. *Drugs* 2007; **67**: 1725–47.
12. Olanow CW, *et al.* ADAGIO Study Investigators. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009; **361**: 1268–78.
13. Ahlskog JE. Uitti RJ. Rasagiline, Parkinson neuroprotection, and delayed-start trials: still no satisfaction? *Neurology* 2010; **74**: 1143–8.

Administration in hepatic impairment. UK licensed product information for rasagiline advises caution when used in patients with mild hepatic impairment whereas US licensed information recommends that the oral dose be reduced to 500 micrograms daily. Rasagiline should not be used in those with moderate or severe impairment.

Adverse Effects and Precautions

Common adverse effects reported with rasagiline monotherapy include headache, flu-like syndrome, malaise, neck pain, angina pectoris, dyspepsia, anorexia, leucopenia, arthralgia, arthritis, depression, vertigo, rhinitis, conjunctivitis, skin rashes, melanoma, and urinary urgency. Cerebrovascular accidents and myocardial infarction have been reported rarely. Other adverse effects include orthostatic hypotension and hallucinations.

Rasagiline should not be used in patients with severe hepatic impairment; use in moderate impairment should also be avoided. It should be used with caution in patients with mild hepatic impairment and therapy should be stopped in those who progress to moderate impairment.

Interactions

As for Selegiline Hydrochloride, p. 916.1. Unlike the non-selective MAOIs, such as phenelzine, rasagiline can be used safely without dietary tyramine restrictions, although these have been recommended in some countries.

Rasagiline should not be given with other MAOIs because of the risk of non-selective MAO inhibition that may lead to hypertensive reactions.

It is metabolised by the cytochrome P450 isoenzyme CYP1A2 and potent inhibitors of this enzyme such as ciprofloxacin may increase the plasma levels of rasagiline. UK licensed product information for rasagiline advises caution when such drugs are used with rasagiline whereas US licensed product information recommends that the dose of rasagiline be reduced to 500 micrograms daily when given with CYP1A2 inhibitors. Tobacco smoking induces hepatic metabolic enzymes and may decrease the plasma levels of rasagiline.

Entacapone has been reported to increase the clearance of oral rasagiline by 28% when used together.

Pharmacokinetics

Rasagiline is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur in about 30 minutes to 1 hour. Bioavailability is reported to be about 36%. Rasagiline is about 60 to 70% bound to plasma proteins.

It is extensively metabolised in the liver by *N*-dealkylation and hydroxylation, via the cytochrome P450 isoenzyme CYP1A2, and conjugation. 1-Aminoindan is a major metabolite and is stated to be active although it is not a monoamine oxidase B inhibitor. Metabolites are excreted mainly in the urine and partly in the faeces; less than 1% of a dose is excreted as unchanged drug in the urine. The terminal half-life is 0.6 to 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Elbrus; Rasax; *Austria*: Azilect; *Belg.*: Azilect; *Canad.*: Azilect; *Cz.*: Azilect; *Denm.*: Azilect; *Fin.*: Azilect; *Fr.*: Azilect; *Ger.*: Azilect; *Gr.*: Azilect; *Hung.*: Azilect; *Irl.*: Azilect; *Israel*: Azilect; *Ital.*: Azilect; *Mex.*: Azilect; *Neth.*: Azilect; *Norw.*: Azilect; *Pol.*: Azilect; *Port.*: Azilect; *Rus.*: Azilect (Азилект); *S.Afr.*: Azilect; *Spain*: Azilect; *Swed.*: Azilect; *Switz.*: Azilect; *Thai.*: Azilect; *Turk.*: Azilect; *UK*: Azilect; *USA*: Azilect.

Ropinirole Hydrochloride

(BANM, USAN, pINNM)

Hidrocloruro de ropinirol; Ropinirol, hidroclaruro de; Ropinirole, Chlorhydrate de; Ropiniroli Hydrochloridum; SKF-101468 (ropinirole); SKF-0101468-A (ropinirole hydrochloride); Ропинирола Гидрохлорид.

4-[2-(Dipropylamino)ethyl]-2-indolinone hydrochloride.

$C_{16}H_{24}N_2O,HCl=296.8$

CAS — 91374-21-9 (ropinirole); 91374-20-8 (ropinirole hydrochloride).

ATC — N04BC04.

ATC Vet — QN04BC04.

UNII — D7ZD41RZI9.

Pharmacopoeias. In *US*.

USP 36: (Ropinirole Hydrochloride). A pale cream to yellow powder. Soluble in water.

Uses and Administration

Ropinirole is a non-ergot dopamine D_2-agonist with similar actions to those of bromocriptine (p. 895.3), but in contrast to bromocriptine it also has agonist properties at D_3 receptors. It is used similarly in the management of Parkinson's disease (below), either alone or as an adjunct to reduce 'on-off' fluctuations in levodopa response. Ropinirole is also used for the treatment of moderate to severe idiopathic restless legs syndrome (below). It is given orally as the hydrochloride; doses are expressed in terms of the base. Ropinirole hydrochloride 1.14 mg is equivalent to about 1 mg of ropinirole.

In the treatment of **Parkinson's disease**, ropinirole should be introduced gradually and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved; the concurrent dose of levodopa may be reduced by about 20 to 30%. The daily dosage of ropinirole should be given in three divided doses, preferably with food. The initial daily dose of ropinirole is 750 micrograms increased at weekly intervals in steps of 750 micrograms for the first 4 weeks. After week 4, the weekly increments may be made in steps of 1.5 mg up to a dose of 9 mg daily according to response; subsequent weekly increments may be made in steps of up to 3 mg. The daily dosage should not exceed 24 mg. Optimal response is usually achieved within the range of 3 to 9 mg daily; higher doses may be required if used with levodopa. If it is necessary to stop ropinirole therapy, it should be withdrawn gradually by reducing the number of daily doses over a period of 1 week. Once adequate symptomatic control has been established, ropinirole may be given as once-daily modified-release tablets.

Ropinirole is also given as a single daily dose, 1 to 3 hours before bedtime, in the treatment of **restless legs syndrome**. The initial dose of ropinirole is 250 micrograms daily for 2 days; if tolerated, the dose is then increased to 500 micrograms daily for the rest of the first week. Dosage is then increased as necessary up to a maximum of 4 mg daily. Increases are made weekly in steps of 500 micrograms up to a dose of 3 mg daily; a final increase after one further week of 1 mg to a dose of 4 mg daily can then be made. In the UK, it has been recommended that treatment should be reassessed 3 months after starting therapy. For this indication, ropinirole may be withdrawn without gradual tapering of the dose.

If treatment with ropinirole is interrupted for more than a few days it should be restarted at the low initial dose and increased gradually as required.

Reviews.
1. Tulloch IF. Pharmacologic profile of ropinirole: a nonergoline dopamine agonist. *Neurology* 1997; **49** (suppl 1): S58–S62.

Parkinsonism. Dopamine agonists such as ropinirole may be used to begin treatment of parkinsonism (p. 889.1) in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease.

References.
1. Rascol O, *et al.* A placebo-controlled study of ropinirole a new D_2 agonist, in the treatment of motor fluctuations of L-DOPA-treated parkinsonian patients. *Adv Neurol* 1996; **69**: 531–4.
2. Adler CH, *et al.* The Ropinirole Study Group. Ropinirole for the treatment of early Parkinson's disease. *Neurology* 1997; **49**: 393–9.
3. Rascol O, *et al.* Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. *Mov Disord* 1998; **13**: 39–45.
4. Korczyn AD, *et al.* A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. *Neurology* 1999; **53**: 364–70.
5. Matheson AJ, Spencer CM. Ropinirole: a review of its use in the management of Parkinson's disease. *Drugs* 2000; **60**: 115–37.
6. Clarke CE, Deane K. Ropinirole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
7. Clarke CE, Deane K. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
8. Whone AL, *et al.* Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol* 2003; **54**: 93–101.
9. Pahwa R, *et al.* Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology* 2007; **68**: 1108–15.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p. 1034.2) is obscure and treatment has largely been empirical although dopaminergic therapy has emerged as a common first-line choice. Ropinirole is licensed for the treatment of moderate to severe RLS in some countries.

References.
1. Trenkwalder C, *et al.* Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry* 2004; **75**: 92–7.
2. Cheer SM, *et al.* Ropinirole: for the treatment of restless legs syndrome. *CNS Drugs* 2004; **18**: 747–54.
3. Walters AS, *et al.* Ropinirole is effective in the treatment of restless legs syndrome—TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord* 2004; **19**: 1414–23.
4. Bogan RK, *et al.* TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81**: 17–27.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3. Hypersensitivity reactions including angioedema, pruritus, rash, and urticaria have been reported with ropinirole therapy. Licensed product information states that the pharmacokinetics of ropinirole have not been studied in patients with hepatic or severe renal impairment and therefore it should be used with caution, if at all, in such patients. No pharmacokinetic changes were noted in those with mild to moderate renal impairment.

In the treatment of restless legs syndrome, earlier onset of symptoms in the afternoon or evening (augmentation) and recurrence of symptoms in the early morning hours (rebound) have been reported with ropinirole.

Incidence of adverse effects. References.

1. Etminan M, *et al.* Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. *Drug Safety* 2003; **26**: 439–44.
2. Kullisevsky J, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of Parkinson's disease: meta-analysis of randomized controlled trials. *Drug Safety* 2010; **33**: 147–61.

Effects on mental function. For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including ropinirole, see under Levodopa, p. 905.2.

For reference to **disturbed behaviour** including **excessive gambling** reported in patients with Parkinson's disease receiving dopamine agonists, see under Levodopa, p. 905.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ropinirole 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 30/09/11)

Interactions

Since it is a dopamine agonist, ropinirole may share some of the pharmacological interactions of bromocriptine, p. 899.1. In addition, high doses of oestrogens can increase plasma concentrations of ropinirole and dosage adjustments may be necessary if oestrogen therapy is started or withdrawn during treatment with ropinirole. Ropinirole is metabolised by the cytochrome P450 isoenzyme CYP1A2 and there is therefore the potential for interactions between ropinirole and other drugs that are metabolised similarly or more particularly with inducers or inhibitors of this enzyme. Dosage adjustments may be necessary if therapy with such drugs is started or withdrawn during treatment with ropinirole.

Pharmacokinetics

Ropinirole is rapidly absorbed from the gastrointestinal tract and mean peak plasma concentrations have occurred 1.5 hours after oral doses; the rate of absorption, but not the extent, may be reduced if taken with food. Bioavailability is reported to be about 50%. It is widely distributed throughout the body and plasma protein binding is low (10 to 40%).

Ropinirole is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP1A2, and excreted in the urine as inactive metabolites; less than 10% of an oral dose is excreted as unchanged drug. A mean elimination half-life of about 6 hours has been reported for ropinirole. It is thought to be distributed into breast milk on the basis of studies in *rats*.

References.
1. Brefel C, *et al.* Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients. *Br J Clin Pharmacol* 1998; 45: 412–15.
2. Hubble J, *et al.* Linear pharmacokinetic behavior of ropinirole during multiple dosing in patients with Parkinson's disease. *J Clin Pharmacol* 2000; 40: 641–6.
3. Kaye CM, Nicholls B. Clinical pharmacokinetics of ropinirole. *Clin Pharmacokinet* 2000; 39: 243–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Requip; ***Austral.***: Appese; Repreve; ***Austria***: Requip; ***Belg.***: Requip; ***Canad.***: Requip; ***Chile***: Requip; ***Cz.***: Adartrel; Aropilo; Aropix; Lironat†; Requip; Rolpryna; Ropinstad; Ropison; ***Denm.***: Adartrel; Requip; Ropinict; ***Fin.***: Adartrel†; Requip; ***Fr.***: Adartrel; Requip; ***Ger.***: Adartrel; Ralnea; Requip; Ropinal; ***Gr.***: Adartrel; Requip; ***Hong Kong***: Requip; ***Hung.***: Aropilo; Ralnea; Requip; Romyl; Ropidopin; ***Irl.***: Adartrel†; Eironil†; Requip; Rolpryna; Roni†; Ropirade; ***Israel***: Requip; ***Ital.***: Adartrel†; Requip; Roprima; ***Jpn***: ReQuip; ***Malaysia***: Requip; ***Mex.***: Requip; ***Neth.***: Adartrel; Requip; Ropison; Soniro†; ***Norw.***: Adartrel; Requip; ***NZ***: Requip; Ropaccord; Ropin; ***Philipp.***: Requip; ***Pol.***: Adartrel; Aropilo; Aropix; Contexine; Parnirol; Requip; ***Port.***: Adartrel; Requip; Ropimed; Zyatrol†; ***Rus.***: Requip (Реквип); ***S.Afr.***: Requip; Resure; ***Singapore***: Requip; ***Spain***: Adartrel; Niromylan†; Requip; Rolpryna; Ropigen†; ***Swed.***: Adartrel; Requip; ***Switz.***: Adartrel; Requip; ***Thai.***: Requip; ***Turk.***: Requip; ***UK***: Adartrel; Aimpart; Ralnea; Raponer; Repinex; Requip; ***USA***: Requip.

Pharmacopoeial Preparations
USP 36: Ropinirole Tablets.

Rotigotine *(BAN, USAN, rINN)*

N-0923; Rotigotina; Rotigotinum; SPM-962; Ротиготин.
(-)-(*S*)-5,6,7,8-Tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol.
$C_{19}H_{25}NOS$=315.5
CAS — 99755-59-6 (rotigotine); 125572-93-2 (rotigotine hydrochloride).
ATC — N04BC09.
ATC Vet — QN04BC09.
UNII — 87T4T88O2E.

Uses and Administration

Rotigotine is a non-ergot dopamine D_2-agonist with similar actions to those of bromocriptine (p. 895.3), but in contrast to bromocriptine (a dopamine D_2-agonist) it also has agonist properties at D_1 and D_3 receptors. It is used as monotherapy in the management of Parkinson's disease (p. 889.1), mainly in the early stage. It may also be used as an adjunct to levodopa therapy. Rotigotine is also used for the treatment of moderate to severe idiopathic restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2). Rotigotine is given as transdermal patches delivering amounts ranging from 1 to 8 mg per 24 hours.

In the treatment of **Parkinson's disease**, when given as *monotherapy*, the initial dose is 2 mg daily, increased in weekly steps of 2 mg if necessary, to a maximum of 8 mg daily. Rotigotine may also be used as *adjunctive therapy* with levodopa in an initial dose of 4 mg daily, increased in weekly steps of 2 mg if necessary, to a maximum of 16 mg daily. Treatment with rotigotine should be withdrawn gradually; the daily dose should be reduced in steps of 2 mg every other day until complete withdrawal is achieved.

In the treatment of **restless legs syndrome**, the initial dose is 1 mg daily, increased in weekly steps of 1 mg according to response, to a maximum of 3 mg daily. The need for treatment continuation should be assessed every 6 months. If stopping treatment, the daily dose should be reduced in steps of 1 mg every other day until complete withdrawal is achieved.

Patches are applied once daily and should be replaced every 24 hours with the new patch being applied to a different site.

References.
1. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol* 2003; 60: 1721–8.
2. Stiasny-Kolster K, *et al.* Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. *Mov Disord* 2004; 19: 1432–8.
3. Poewe W, Leussi F. Clinical studies with transdermal rotigotine in early Parkinson's disease. *Neurology* 2005; 65 (suppl 1): S11–S14. Correction. *ibid.*: 1328.
4. Watts RL, *et al.* Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology* 2007; 68: 272–6. Correction. *ibid.*: 69: 617.
5. Splinter MY. Rotigotine: transdermal dopamine agonist treatment of Parkinson's disease and restless legs syndrome. *Ann Pharmacother* 2007; 41: 285–95.
6. LeWitt PA, *et al.* Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. *Neurology* 2007; 68: 1262–7.
7. Trenkwalder C, *et al.* Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord* 2008; 23: 2267–2302.
8. Reading P. Treating restless legs syndrome with rotigotine. *Br J Hosp Med* 2010; 71: 216–19.

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3. Reactions may occur at the site of application and are usually mild or moderate in intensity. The site should be rotated on a daily basis and the same site should not be used within 14 days.

Licensed product information recommends that rotigotine should be used with caution in patients with severe hepatic impairment and reduced doses may be necessary in cases of worsening impairment; however, this is based on a lack of evidence in such patients.

Interactions

Since it is a dopamine agonist, rotigotine may share some of the pharmacological interactions of bromocriptine, p. 899.1.

Caution is advised when other sedating drugs or alcohol are used with rotigotine because of possible additive effects.

Pharmacokinetics

Rotigotine has poor oral bioavailability as it undergoes extensive first-pass metabolism via glucuronidation in the gut wall and liver. Peak plasma concentrations occur 24 hours after transdermal application. Steady-state concentrations are reached after 24 to 48 hours of continuous daily application. It undergoes *N*-dealkylation and conjugation to form inactive metabolites. Rotigotine is excreted mainly in the urine and about 23% appears in the faeces. The elimination half-life is 5 to 7 hours. It is distributed into milk of *rats*.

References.
1. Cawello W, *et al.* Transdermal administration of radiolabelled [^{14}C] rotigotine by a patch formulation: a mass balance trial. *Clin Pharmacokinet* 2007; 46: 851–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Neupro; ***Austria***: Neupro; ***Belg.***: Neupro; ***Cz.***: Neupro; ***Denm.***: Neupro; ***Fr.***: Neupro; ***Ger.***: Leganto; Neupro; ***Gr.***: Neupro; ***Hong Kong***: Neupro; ***Hung.***: Neupro; ***Irl.***: Leganto; Neupro; ***Israel***: Neupro; ***Ital.***: Neupro; ***Jpn***: Neupro; ***Neth.***: Neupro; ***Norw.***: Neupro; ***Pol.***: Neupro; ***Port.***: Neupro; ***Spain***: Neupro; ***Swed.***: Neupro; ***Switz.***: Neupro; ***Thai.***: Neupro; ***UK***: Neupro; ***Ukr.***: Neupro (Неупро); ***USA***: Neupro.

Selegiline Hydrochloride

(BANM, USAN, rINNM) ⊗

Deprenilo; Deprenyl; L-Deprenyl; Hidrocloruro de selegilina; Selegiliinihydrokloridi; Selegilin Hidroklorür; Selegilin hydrochlorid; Selegilina, hidrocloruro de; Sélégiline, Chlorhydrate de; Selegilinhydrochlorid; Selegilinhydroklorid; Selegilini Hydrochloridum; Selegilino hidrochloridas; Szelegilin-hidroklorid; Селегилина Гидрохлорид.
(-)-(*R*)-*N*,α-Dimethyl-*N*-(prop-2-ynyl)phenethylamine hydrochloride; (*R*)-Methyl(α-methylphenethyl)prop-2-ynylamine hydrochloride.
$C_{13}H_{17}N,HCl$=223.7
CAS — 14611-51-9 (selegiline); 2079-54-1 (selegiline hydrochloride); 14611-52-0 (selegiline hydrochloride).
ATC — N04BD01.
ATC Vet — QN04BD01.
UNII — 6W731X367Q ((-)-selegiline hydorchloride); 63G7R4955A ((±)-selegiline hydrochloride).

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

Ph. Eur. 8: (Selegiline Hydrochloride). A white or almost white, crystalline powder. M.p. about 143 degrees. Freely soluble in water and in methyl alcohol; slightly soluble in acetone and in ethyl acetate. A 2% solution in water has a pH of 3.5 to 4.5. Protect from light.

USP 36: (Selegiline Hydrochloride). A white, odourless crystalline powder. Freely soluble in water, in chloroform, and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Selegiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease mainly as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response, but see Parkinsonism, p. 915.1. Addition of selegiline to levodopa therapy may enable the dosage of levodopa to be reduced by about 10 to 30%. Selegiline may be given alone in early Parkinson's disease in an attempt to delay the need for levodopa therapy. It is also used in the treatment of depression (p. 915.1).

In the treatment of **Parkinson's disease**, selegiline hydrochloride is given orally as conventional preparations such as capsules, tablets, or liquid, or as lyophilisate tablets. The dose of the conventional preparations is 10 mg daily, either as a single dose in the morning or in 2 divided doses of 5 mg at breakfast and lunchtime. The initial dose of the oral lyophilisate tablets is 1.25 mg daily at least 5 minutes before breakfast; patients already receiving 10 mg of conventional preparations can be transferred to 1.25 mg of the oral lyophilisate. US product information states that the initial oral lyophilisate dose of 1.25 mg daily may be increased, after at least 6 weeks, to 2.5 mg given once daily, if necessary.

In the USA, transdermal patches delivering 6, 9, or 12 mg of selegiline over 24 hours are available for the treatment of **depression**. The initial dose is 6 mg daily, increased in steps of 3 mg every 2 weeks if necessary, to a maximum of 12 mg daily. Patches are applied once daily and should be replaced every 24 hours with the new patch being applied to a different site. Dose increases should be made with caution in the elderly and patients should be closely observed for postural changes in blood pressure during treatment. Dietary restrictions are necessary at doses of 9 mg daily and above, see Interactions, p. 916.1.

Other conditions in which selegiline has been tried include dementia.

Some references to the actions of selegiline.

1. Youdim MBH, Finberg JPM. Pharmacological actions of l-deprenyl (selegiline) and other selective monoamine oxidase B inhibitors. *C in Pharmacol Ther* 1994; 56: 725–33.
2. Lange KW, *et al.* Biochemical actions of l-deprenyl (selegiline). *C in Pharmacol Ther* 1994; 56: 734–41.

Cocaine dependence. Cocaine use may affect the dopaminergic modulation of CNS function; selegiline is one of several drugs that interact with dopaminergic systems and have been tried in treatment of cocaine abuse and dependence (p. 1990.1).

References.
1. Houtsmuller EJ, *et al.* Transdermal selegiline and intravenous cocaine: safety and interactions. *Psychopharmacology (Berl)* 2004; 172: 31–40.

Dementia. The hypothesis that neurodegeneration in Alzheimer's disease (p. 388.1) might be due to free radical formation has led to drugs such as selegiline being tried as antoxidant therapy.

Early double-blind studies[1,2] indicated that oral selegiline 10 mg daily might produce beneficial effects in patients with Alzheimer's disease but it was suggested that improvements in mood and cognitive function may have been due to a reduction in tension and depression.[3] A 15-month study in Alzheimers's patients with mild cognitive impairment showed oral selegiline 10 mg daily to have little effect,[4] although the authors pointed out that those with more severe dementia have shown more response in other studies. The conclusion of a later study[5] that oral selegiline 10 mg daily slowed progression in patients with moderate disease has been criticised[6] on the grounds that any effect was only evident after statistical adjustment to the original analysis. In addition a systematic review[7] examining the effects of selegiline concluded that there was no meaningful evidence of a beneficial effect of oral selegiline in patients with Alzheimer's disease. They also considered that there

was no longer any justification for its use in patients with Alzheimer's disease.

1. Piccinin GL, *et al.* Neuropsychological effects of L-deprenyl in Alzheimer's type dementia. *Clin Neuropharmacol* 1990; 13: 147–63.
2. Mangoni A, *et al.* Effects of a MAO-B inhibitor in the treatment of Alzheimer disease. *Eur Neurol* 1991; 31: 100–107.
3. Anonymous. Drugs for Alzheimer's disease. *Drug Ther Bull* 1990; 28: 42–4.
4. Burke WJ, *et al.* L-Deprenyl in the treatment of mild dementia of the Alzheimer type: results of a 15-month trial. *J Am Geriatr Soc* 1993; 41: 1219–25.
5. Sano M, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997; 336: 1216–22.
6. Pincus MM. Alpha-tocopherol and Alzheimer's disease. *N Engl J Med* 1997; 337: 572.
7. Birks J, Flicker L. Selegiline for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/02/06).

Depression. Selegiline is a selective inhibitor of monoamine oxidase type B and there are reports[1-3] of it producing improvement in depression (p. 398.1). However, at the doses usually required to produce an antidepressant effect the specificity of oral selegiline is reported to be lost and it has been suggested that the efficacy of selegiline as an antidepressant might depend on inhibition of monoamine oxidase A rather than inhibition of monoamine oxidase B alone. Such a loss of specificity would mean that patients taking selegiline for depression would need to observe the dietary restrictions applicable to non-selective MAOIs.

To overcome the problems associated with the oral route, transdermal selegiline has also been tried and may be more effective than placebo in the treatment of depression.[4] The use of the transdermal route allows sustained blood levels of selegiline to be delivered without extensive inhibition of peripheral monoamine oxidase A. Transdermal patches of selegiline are licensed for the treatment of depression in the USA.

1. Mendlewicz J, Youdim MBH. L-Deprenil, a selective monoamine oxidase type B inhibitor, in the treatment of depression: a double-blind evaluation. *Br J Psychiatry* 1983; 142: 508–11.
2. Mann JJ, *et al.* A controlled study of the antidepressant efficacy and side-effects of (-)-deprenyl. *Arch Gen Psychiatry* 1989; 46: 45–50.
3. Sunderland T, *et al.* High-dose selegiline in treatment-resistant older depressive patients. *Arch Gen Psychiatry* 1994; 51: 607–15.
4. Prampton JE, Plosker GL. Selegiline transdermal system: in the treatment of major depressive disorder. *Drugs* 2007; 67: 257–65.

Narcoleptic syndrome. Small controlled studies[1,2] have suggested that oral selegiline 20 to 40 mg daily has a beneficial effect on symptoms of narcolepsy and cataplexy (p. 2314.3); at such a dosage a low-tyramine diet is considered necessary.

1. Hublin C, *et al.* Selegiline in the treatment of narcolepsy. *Neurology* 1994; 44: 2095–2101.
2. Mayer G, *et al.* Selegeline [sic] hydrochloride treatment in narcolepsy: a double-blind, placebo-controlled study. *Clin Neuropharmacol* 1995; 18: 306–19.

Parkinsonism. As a selective monoamine oxidase type B inhibitor, selegiline reduces the metabolism of dopamine and thereby enhances its actions. It reduces levodopa's 'end-of-dose' effect and has a dose-sparing effect. Some have used it as **monotherapy** in an attempt to delay the need for levodopa. If progression of Parkinson's disease (p. 889.1) were due to a cytotoxic effect of free radicals, generated during the metabolism of dopamine, on dopaminergic neurones in the substantia nigra, selegiline might slow the process by reducing their formation. In a large early study,[1] the DATATOP study, selegiline monotherapy delayed the need to start levodopa in patients with early Parkinson's disease. These findings were corroborated by other smaller studies.[2,3] There has been much debate over whether the benefit was due to a neuroprotective or symptomatic effect. Re-analysis of the DATATOP data by independent workers[4,5] and findings of other studies[6] supported a symptomatic effect. Subsequent studies involving DATATOP patients were also consistent with a symptomatic effect; any benefit produced by selegiline appeared to be less pronounced as the duration of treatment increased[7] and was lost completely long term.[8,9] However, a later study[10] designed to minimise any symptomatic effect cast doubt on whether the delay in progression of the signs and symptoms of Parkinson's disease obtained with selegiline was entirely due to a symptomatic effect.

Studies of the use of selegiline as an **adjunct** to levodopa therapy[6,11,12] indicate that selegiline permits a modest reduction in the dosage requirements of levodopa. An interim analysis of a study of the early addition of selegiline to levodopa has also suggested that selegiline might stabilise the long-term daily levodopa dosage.[13] As with monotherapy, combined therapy has been reported to slow symptom progression.[14]

The use of selegiline in Parkinson's disease has been questioned after a UK study[11] found an unexpected increase in mortality in patients taking levodopa with selegiline compared with those taking levodopa alone. No difference in mortality had been detected at the 3-year follow-up[15] but after an average follow-up time of 5.6 years[11] mortality was 60% higher in the group also receiving selegiline. The study has been criticised on many grounds including the fact that mortality was very high in both arms of the study[16] and has been the subject of much debate.[17,18] The authors of the study[11] had stated that they would advise the study patients to withdraw selegiline therapy. Analysis of follow-up data[19] until the selegiline arm of the study was terminated (average 6.8 years) found an excess mortality of about 35%, a figure calculated[20] to be no longer significant. However, because of the premature termination of the study such results were considered[21] to be biased. Whether any excess in mortality is causally related to selegiline is still unclear. Some consider that changes in prescribing practice based on this study are not warranted.[17] Others[21] have made a cautious recommendation not to start combination treatment in patients with newly diagnosed Parkinson's disease but consider that there is little evidence to advise patients who have been using selegiline with levodopa for years without problem to change their treatment. An evaluation of mortality among patients taking antiparkinsonian drugs (using the UK General Practice Research Database) provided evidence against there being substantial excess mortality associated with the use of selegiline.[22] These results are supported by systematic reviews[23,24] and meta-analyses[25,26] of randomised, double-blind studies which found no increase in mortality associated with selegiline treatment regardless of concurrent levodopa. Furthermore, increased mortality was not seen in patients in the original DATATOP study[1] after an average follow-up time of 8.2 years. However, it was noted that the delay of disability seen in the early phase of selegiline therapy[1,7] was not associated with longer life during follow-up.[27] A later systematic review[23] has also found no convincing evidence that selective monoamine oxidase type B inhibitors (selegiline and lazabemide) significantly delay disease progression in early Parkinson's disease and routine use is not recommended. Similarly, another recent systematic review[24] found insufficient evidence to recommend the routine use of selegiline over the use of levodopa and dopamine agonists (bromocriptine and lisuride) in early disease.

1. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989; 321: 1364–71.
2. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science* 1989; 245: 519–22.
3. Allain H, *et al.* Selegiline in de novo parkinsonian patients: the French selegiline multicenter trial (FSMT). *Acta Neurol Scand* 1991; 84 (suppl 136): 73–8.
4. Schulzer M, *et al.* The antiparkinson efficacy of deprenyl derives from transient improvement that is likely to be symptomatic. *Ann Neurol* 1992; 32: 795–8.
5. Ward CD. Does selegiline delay progression of Parkinson's disease? A critical re-evaluation of the DATATOP study. *J Neurol Neurosurg Psychiatry* 1994; 57: 217–20.
6. Brannan T, Yahr MD. Comparative study of selegiline plus L-dopa–carbidopa versus L-dopa–carbidopa alone in the treatment of Parkinson's disease. *Ann Neurol* 1995; 37: 95–8.
7. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; 328: 176–83.
8. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. *Ann Neurol* 1996; 39: 29–36.
9. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* 1996; 39: 37–45.
10. Olanow CW, *et al.* The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1996; 38: 771–7.
11. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; 311: 1602–7.
12. Myllylä VV, *et al.* Early selegiline therapy reduces levodopa dose requirement in Parkinson's disease. *Acta Neurol Scand* 1995; 91: 177–82.
13. Larsen JP, Boas J. Norwegian-Danish Study Group. The effects of early selegiline therapy on long-term treatment and parkinsonian disability: an interim analysis of a Norwegian-Danish 5-year study. *Mov Disord* 1997; 12: 175–82.
14. Pålhagen S, *et al.* Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology* 2006; 66: 1200–6.
15. Parkinson's Disease Research Group in the United Kingdom. Comparisons of the therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993; 307: 467–72.
16. Olanow CW, *et al.* Patients taking selegiline may have received more levodopa than necessary. *BMJ* 1996; 312: 702–3.
17. Ahlskog JE. Treatment of early Parkinson's disease: are complicated strategies justified? *Mayo Clin Proc* 1996; 71: 659–70.
18. Mizuno Y, Kondo T. Mortality associated with selegiline in Parkinson's disease: what do the available data mean? *Drug Safety* 1997; 16: 289–94.
19. Ben-Shlomo Y, *et al.* Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry. *BMJ* 1998; 316: 1191–6.
20. Abrams KR. Monitoring randomised controlled trials. *BMJ* 1998; 316: 1183–4.
21. Breteler MMB. Selegiline, or the problem of early termination of clinical trials. *BMJ* 1998; 316: 1182–3.
22. Thorogood M, *et al.* Mortality in people taking selegiline: observational study. *BMJ* 1998; 317: 252–4.
23. Macleod A, *et al.* Monoamine oxidase B inhibitors for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 16/02/06).
24. Caslake R, *et al.* Monoamine oxidase B inhibitors versus other dopaminergic agents in early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/05/10).
25. Olanow CW, *et al.* Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. *Neurology* 1998; 51: 825–30.
26. Ives NJ, *et al.* Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients. *BMJ* 2004; 329: 593–6.
27. The Parkinson Study Group. Mortality in DATATOP: a multicenter trial in early Parkinson's disease. *Ann Neurol* 1998; 43: 318–25.

Smoking cessation. Selegiline has been investigated as an aid to smoking cessation (p. 2570.2).

References.
1. George TP, *et al.* A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biol Psychiatry* 2003; 53: 136–43.
2. Biberman R, *et al.* A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation. *Addiction* 2003; 98: 1403–7.

Adverse Effects

Selegiline is often given as an adjunct to levodopa therapy and many of the adverse effects reported may be attributed to enhanced levodopa activity; dosage of levodopa may have to be reduced. However, most reported adverse effects, with the possible exception of increased dyskinesias and cardiac arrhythmias, have also been seen with selegiline monotherapy. Adverse effects have included orthostatic hypotension, chest pain, nausea, vomiting, constipation, diarrhoea, confusion, headache, tremor, vertigo, dizziness, psychosis, depression, hallucinations, agitation, dry mouth, sore throat, difficulty in micturition, skin reactions, back pain, muscle cramps, joint pain, and myopathy. The amfetamine metabolites of selegiline may cause insomnia and abnormal dreams; evening doses should be avoided. Transient increases in liver enzymes have been reported. Mouth ulcers and stomatitis may occur with the oral lyophilisate.

Since the selectivity of selegiline is lost at higher doses, signs and symptoms of overdosage may resemble those of non-selective MAOIs such as phenelzine (see p. 442.2).

Effects on carbohydrate metabolism. Profound hypoglycaemia developed in a 70-year-old man after selegiline was added to his existing medication for Parkinson's disease.[1] Hypoglycaemia was accompanied by hyperinsulinaemia and resolved 1 week after stopping selegiline.

1. Rowland MJ, *et al.* Hypoglycemia caused by selegiline, an antiparkinsonian drug: can such side effects be predicted? *J Clin Pharmacol* 1994; 34: 80–5.

Effects on mortality. For reference to a study that found an increased mortality rate in patients with Parkinson's disease taking selegiline and levodopa compared with those taking levodopa alone, see Parkinsonism, under Uses and Administration, above.

Precautions

Selegiline should be used with caution in patients with a history of peptic ulceration and avoided in those with active ulceration. It should also be used with caution in uncontrolled hypertension, arrhythmias, angina, severe liver or kidney dysfunction, or psychosis.

When selegiline is used in the management of 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.

Cardiovascular disorders. An investigation[1] of the autonomic effects of selegiline as a potential cause of the unexpected mortality seen in a study[2] in patients with Parkinson's disease receiving selegiline and levodopa (see Parkinsonism, above) suggested that the risk of orthostatic hypotension with this combination may have been underestimated. It was considered prudent to withdraw selegiline from those with symptomatic orthostatic hypotension or cardiovascular or cerebrovascular disease. For those without symptomatic morbidity, but a greater than 20 mmHg fall in blood pressure on standing for 2 minutes, gradual withdrawal of selegiline with adjustment of levodopa dosage should be considered.

1. Churchyard A, *et al.* Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; 63: 228–34.
2. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; 311: 1602–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies selegiline 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 30/09/11)

Interactions

Selegiline is less likely than non-selective MAOIs, such as phenelzine, to interact with tyramine in food; such hypertensive reactions have been reported rarely at usual doses but UK licensed product information for oral formulations states that its selectivity is lost at higher doses and it must be assumed that selegiline can usually only be used safely without dietary restrictions at doses of up to 10 mg daily. US licensed information for the transdermal preparation states that dietary restrictions are necessary at doses of 9 mg daily and above: patients should be warned not to eat any tyramine-rich foods while being treated with, and for at least 14 days after discontinuation of, these doses or after dose reduction to 6 mg daily. For further details on dietary restrictions applicable to patients taking MAOIs, see p. 444.3.

Even when given in therapeutic doses life-threatening interactions can occur between selegiline and pethidine. Serious reactions, sometimes fatal, have also been reported when selegiline was used with tricyclic antidepressants or serotonin reuptake inhibitors including the SSRIs and venlafaxine. Licensed product information states that 14 days should elapse between stopping selegiline and starting treatment with tricyclic or serotonergic antidepressants. Conversely, selegiline should not be given to patients who have recently received these antidepressants; at least 5 weeks should elapse between stopping fluoxetine and starting treatment with selegiline. Use of selegiline with non-selective MAOIs may cause severe hypotension and such use is not recommended.

Antidepressants. Although there have been studies in which patients with parkinsonism have received selegiline with *SSRIs* such as fluoxetine[1] or paroxetine[2] (apparently without any problems) there have been reports of reactions[3-5] such as shivering and sweating, hypertension, hyperactivity, and ataxia occurring when selegiline and fluoxetine have been used together. The FDA noted[6] that reactions similar to those between SSRIs and non-selective MAOIs had also been reported in patients taking selegiline with paroxetine or sertraline.

Severe reactions, sometimes fatal, have also occurred in patients taking selegiline and *tricyclic antidepressants*.[6] For a report of serotonin syndrome developing when *venlafaxine* was given after selegiline (despite a drug-free period), see p. 457.1.

There has been a report[7] of a patient receiving the non-selective MAOI *iproniazid* who had severe orthostatic hypotension when given selegiline. Selegiline given with the reversible MAOI *moclobemide* to healthy subjects markedly increased the pressor response to tyramine compared with the effects of each drug used alone.[8] The authors concluded that dietary restriction of tyramine-containing foods would be necessary if these drugs were to be used together.

One UK manufacturer (*Cephalon, UK*) states that oral selegiline should not be given with any type of antidepressant, while another (*Orion, UK*) advises that use with SSRIs or venlafaxine be avoided and recommends caution when used with the tricyclics. The US manufacturer of transdermal selegiline (*Bristol-Myers Squibb, USA*), used for depression, states that use with other antidepressants such as *bupropion, mirtazapine,* serotonin reuptake inhibitors, *St John's wort,* and tricyclics is contra-indicated.

1. Waters CH. Fluoxetine and selegiline—lack of significant interaction. *Can J Neurol Sci* 1994; 21: 259–61.
2. Toyama SC, Iacono RP. Is it safe to combine a selective serotonin reuptake inhibitor with selegiline? *Ann Pharmacother* 1994; 28: 405–6.
3. Suchowersky O, de Vries JD. Interaction of fluoxetine and selegiline. *Can J Psychiatry* 1990; 35: 571–2.
4. Jermain DM, *et al.* Potential fluoxetine-selegiline interaction. *Ann Pharmacother* 1992; 26: 1300.
5. Montastruc JL, *et al.* Pseudophaeochromocytoma in parkinsonian patient treated with fluoxetine plus selegiline. *Lancet* 1993; 341: 555.
6. Anonymous. Eldepryl and antidepressant interaction. *FDA Med Bull* 1995; 25 (Feb.): 6.
7. Pare CMB, *et al.* Attempts to attenuate the 'cheese effect': combined drug therapy in depressive illness. *J Affect Disord* 1985; 9: 137–41.
8. Korn A, *et al.* Tyramine pressor sensitivity in healthy subjects during combined treatment with moclobemide and selegiline. *Eur J Clin Pharmacol* 1996; 49: 273–8.

Antimigraine drugs. Some serotonin agonists including *rizatriptan, sumatriptan,* and *zolmitriptan* are metabolised via monoamine oxidase type A and therefore it is considered unlikely that selegiline, a monoamine oxidase type B inhibitor, would interact with these drugs. Nevertheless, one manufacturer (*Cephalon, UK*) of oral selegiline contra-indicates its use in patients also receiving serotonin agonists; it is also recommended that at least 24 hours should elapse between stopping selegiline and starting treatment with these drugs.

Opioid analgesics. Selegiline can produce life-threatening reactions when given with *pethidine*.[1]

Some manufacturers contra-indicate use of selegiline with pethidine and other opioid analgesics such as *dextropropoxyphene, methadone,* and *tramadol*.

1. Zornberg GL, *et al.* Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; 337: 246. Correction. *Ibid.*; 440.

Oral contraceptives. The total area under the concentration-time curve for selegiline given in single doses of 5 to 40 mg was raised ten- to twentyfold in 4 women who were using oral hormonal contraceptives when compared with 4 women receiving no other medication.[1] It was suggested that use of selegiline and oral hormonal contraceptives should be avoided or the dosage of selegiline reduced.

1. Laine K, *et al.* Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids. *Br J Clin Pharmacol* 1999; 47: 249–54.

Sympathomimetics. Licensed information for a US product (*Eldepryl; Somerset, USA*) states that there has been a report of hypertensive crisis in a patient taking recommended doses of selegiline and *ephedrine*. A hypertensive reaction after low-dose *dopamine* infusion has been reported[1] in a 75-year-old patient taking selegiline 10 mg daily for Parkinson's disease. The authors suggest that this may indicate a non-specific action of selegiline at usual doses on peripheral monoamine oxidase type-A. UK licensed product information states that dopamine should be used with caution in patients taking selegiline.

1. Rose LM, *et al.* A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* 2000; 34: 1020–4.

Pharmacokinetics

Selegiline is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur in 30 minutes after oral doses of conventional preparations. Although subject to large interindividual variation, bioavailability is about 10% and is increased when given with food. Selegiline is rapidly distributed throughout the body and crosses the blood-brain barrier. It undergoes extensive first-pass metabolism in the liver to produce at least 5 metabolites, including *l*-(-)-desmethylselegiline (norselegiline), *l*- (-)-*N*-methylamfetamine, and *l*- (-)-amfetamine. Plasma concentrations of selegiline metabolites are greatly reduced after doses of the oral lyophilisate preparation, the majority of which undergoes absorption through the buccal mucosa. Topical use also avoids first-pass metabolism and about 25 to 30% of the stated content is available systemically. Selegiline is excreted as metabolites mainly in the urine and about 15% appears in the faeces. At steady state the elimination half-life is reported to be 10 hours.

References.

1. Heinonen EH, *et al.* Pharmacokinetic aspects of l-deprenyl (selegiline) and its metabolites. *Clin Pharmacol Ther* 1994; 56: 742–9.
2. Mahmood I, *et al.* Clinical pharmacokinetics and pharmacodynamics of selegiline: an update. *Clin Pharmacokinet* 1997; 33: 91–102.
3. Anttila M, *et al.* Marked effect of liver and kidney function on the pharmacokinetics of selegiline. *Clin Pharmacol Ther* 2005; 77: 54–62.
4. Azzaro AJ, *et al.* Pharmacokinetics and absolute bioavailability of selegiline following treatment of healthy subjects with the selegiline transdermal system (6 mg/24 h): a comparison with oral selegiline capsules. *J Clin Pharmacol* 2007; 47: 1256–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Brintenal; Jumex; Zelapar; *Austral.*: Eldepryl; Selgene; *Austria*: Amboneural; Cognitiv; Jumex; Xilopar; *Belg.*: Eldepryl; *Braz.*: Deprilan; Elepril; Jumexil; Niar; Parkexin; *Chile*: Selgina; *China*: Eldepryl (咪多吐); Fu An (辅安); Jin Si Ping (金思平); *Cz.*: Apo-Seleg; Cognitiv; Jumex; Niar†; *Denm.*: Eldepryl; *Fin.*: Eldepryl; *Fr.*: Deprenyl; Otrasel; *Ger.*: Antiparkin; Jutagilin†; Movergan; Seleparkt; Selgimed†; Xilopar; *Gr.*: Calaquin; Cosmopril; Ermolax; Feliselin; Krautin; Legil; Procythol; Resostyl; *Hong Kong*: Julab†; Jumex; Sefmex; Selegos; *Hung.*: Cognitiv†; Jumex; *India*: Eldepryl; Elegelin; Jumax; Jumex; Selerin; Selgin; *Indon.*: Jumex; *Irl.*: Eldepryl; *Israel*: Selgin; *Ital.*: Egibren; Jumex; Selecom; Seledat; Xilopar; *Jpn*: FP Tab; *Malaysia*: Jumex; Sefmex; *Mex.*: Niar; *Neth.*: Eldepryl; *Norw.*: Eldepryl; *NZ*: Eldepryl; *Philipp.*: Jumex; *Pol.*: Apo-Selin; Jumex; Segan; Selerin; Selgin†; Selgres; *Port.*: Jumex; Niponeurin†; Xilopar; *Rus.*: Cognitiv (Когнитив); Jumex (Юмекс); Segan (Сеган)†; Selegos (Селегос)†; *S.Afr.*: Eldepryl; Parkilyne; *Singapore*: Jumex; Selegos; *Spain*: Plurimen; *Swed.*: Eldepryl; *Switz.*: Jumexal†; *Thai.*: Julab; Jumex; Sefmex; *Turk.*: Moverdin; Seldepar; *UK*: Eldepryl; Zelapar; *Ukr.*: Eldepryl (Эльдеприл); Segan (Сеган); *USA*: Atapryl; Carbex†; Eldepryl; Emsam; Zelapar; *Venez.*: Jumex.

Pharmacopoeial Preparations

BP 2014: Selegiline Oral Solution; Selegiline Tablets;
USP 36: Selegiline Hydrochloride Tablets.

Talipexole Hydrochloride *(rINNM)*

Alefexole Hydrochloride; B-HT-920; Hidrocloruro de talipexol; Talipexol, hidrocloruro de; Talipexole, Chlorhydrate de; Talipexoli Hydrochloridum; Талипексола Гидрохлорид.

6-Allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*d*]azepine dihydrochloride.

$C_{10}H_{15}N_3S.2HCl=282.2$

CAS — 101626-70-4 (talipexole); 36085-73-1 (talipexole hydrochloride).

UNII — 9R6E1D8H1O.

Profile

Talipexole hydrochloride is a dopamine D_2-agonist that is used in the management of parkinsonism (p. 889.1); it is given orally in usual maintenance doses of 1.2 to 3.6 mg daily, in divided doses. It has also been investigated in the treatment of schizophrenia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Domin.

Terguride *(rINN)*

Tergurida; Terguridum; Теругид.

1,1-Diethyl-3-(6-methylergolin-8α-yl) urea.

$C_{20}H_{28}N_4O=340.5$

CAS — 37686-84-3.

ATC — G02CB06.

ATC Vet — QG02CB06.

UNII — 21OJT43Q88.

Profile

Terguride, an ergot derivative, is a partial dopamine agonist with general properties similar to those of bromocriptine (p. 895.3). It is used in the treatment of disorders related to hyperprolactinaemia (p. 2252.2) in a usual oral dose of 500 micrograms twice daily. It is also being investigated in the management of parkinsonism and pulmonary hypertension.

References.

1. Krause W, *et al.* Pharmacokinetics and endocrine effects of terguride in healthy subjects. *Eur J Clin Pharmacol* 1990; 38: 609–15.
2. Baronti F, *et al.* Partial dopamine agonist therapy of levodopa-induced dyskinesias. *Neurology* 1992; 42: 1241–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Teluron.

Tolcapone *(BAN, USAN, rINN)*

Ro-40-7592; Tolcapona; Tolcaponum; Tolkapon; Tolkapone; Толкапон.

3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone; 3,4-Dihydroxy-5-nitrophenyl(4-methylphenyl)methanone.

$C_{14}H_{11}NO_5=273.2$

CAS — 134308-13-7.

ATC — N04BX01.

ATC Vet — QN04BX01.

UNII — CIF6334OLY.

Pharmacopoeias. In *US*.

USP 36: (Tolcapone). A yellow, fine powder or fine powder with lumps. Insoluble in water and in *n*-hexane; Freely soluble in acetone and in tetrahydrofuran; sparingly soluble in chloroform and in dichloromethane; soluble in methanol alcohol and in ethyl acetate. Store in airtight containers at a temperature between 20 degrees and 25 degrees. Protect from light.

Uses and Administration

Tolcapone is a peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of dopamine and levodopa. It is used as an adjunct to levodopa and dopa-decarboxylase inhibitor combinations in the management of Parkinson's disease (p. 917.1) for patients who cannot be stabilised on these levodopa combinations or for those who have 'end-of-dose' deterioration. Because of the risk of serious hepatotoxicity (see Effects on the Liver, p. 917.1) the FDA in the USA restricted its use to when other adjunctive therapy was ineffective or contra-indicated. In the EU, tolcapone was withdrawn from the market in November 1998 and subsequently returned in 2004, its use being similarly restricted to patients who fail to respond to, or are intolerant of, other COMT inhibitors.

The usual recommended dosage of tolcapone is 100 mg given orally three times daily; up to a maximum of 200 mg three times daily may be considered if the clinical benefit justifies the increased risk of hepatotoxicity. The first dose of the day should be taken at the same time as the combined levodopa preparation. Most patients already taking more

than 600 mg of levodopa daily will require a reduction in their dosage of levodopa; patients on lower levodopa doses may also require a dose reduction.

Tolcapone should be withdrawn if a substantial clinical benefit is not obtained within the first 3 weeks of treatment. An adjustment in the levodopa dose may be necessary following tolcapone withdrawal.

Parkinsonism. Tolcapone is a reversible peripheral inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme involved in the metabolism of levodopa and dopamine.[1] It appears to differ from entacapone (p. 901.2) by being a more potent COMT inhibitor in the periphery and by penetrating into the brain (although the significance of any central effects of COMT inhibition are not known).[1] When given to patients with Parkinson's disease (p. 889.1) and levodopa-related fluctuations in disability or 'end-of-dose' effects, it has prolonged the clinical benefit obtained with levodopa and allowed the total daily dosage of levodopa to be reduced.[2,3] Benefit has also been reported[4] when added to levodopa therapy in patients with stable Parkinson's disease. However, a systematic review[5] concluded that there were insufficient data to show any significant difference in efficacy between tolcapone and bromocriptine or pergolide in the adjunctive treatment of levodopa-induced motor complications.

The use of tolcapone is restricted in some countries because of the risk of serious hepatotoxicity (see Effects on the Liver, below).

1. Nutt JG. Catechol-O-methyltransferase inhibitors for treatment of Parkinson's disease. *Lancet* 1998; 351: 1221–2.
2. Kurth MC, *et al.* Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. *Neurology* 1997; 48: 81–7.
3. Rajput AH, *et al.* Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind placebo-controlled, multicenter trial. *Neurology* 1997; 49: 1066–71.
4. Waters CH, *et al.* Tolcapone Stable Study Group. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. *Neurology* 1997; 49: 665–71.
5. Deane K, *et al.* Catechol-O-methyltransferase inhibitors versus active comparators for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 16/02/06).

Adverse Effects

The most common adverse effects associated with tolcapone are diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth, anorexia, dyskinesia, dystonia, dizziness, orthostatic hypotension, hallucinations, confusion, excessive dreaming, somnolence, headache, increased sweating, and sleep disorders. Diarrhoea may be severe enough for treatment to be stopped. Behavioural disturbances including intense urges to gamble and increased sexual urges have also been reported (see Effects on Mental Function, in Levodopa, p. 905.2). Increases in liver enzyme values have occurred and hepatitis and hepatic failure, sometimes fatal, have been reported. Isolated cases of neuroleptic malignant syndrome have also been reported after dose reduction or stopping tolcapone; rhabdomyolysis may develop as a complication of the syndrome. Tolcapone and its metabolites can produce a yellow intensification in the colour of urine.

Effects on the liver. The UK CSM had noted[1] that, after a report[2] in September 1998 of fatal acute hepatic failure associated with tolcapone, the European Committee for Proprietary Medicinal Products (CPMP) had reviewed all reports of hepatic injury with tolcapone. There had been 10 reports of serious hepatic adverse reactions since tolcapone was marketed in October 1997, which included 7 reports of hepatitis, 3 of which had a fatal outcome. Serious hepatic reactions occurred unpredictably and their development was not always predicted by liver function monitoring. Consequently, in the EU, the marketing authorisation for tolcapone was suspended in November 1998. This suspension was lifted in April 2004 by the CPMP after further review.

In some countries such as the USA, tolcapone has always remained available albeit with restricted indications and strict monitoring requirements (see Precautions, below). Up to 2003, there had been no further reports of fatal hepatic failure after the introduction of these measures although the number of patients eligible to receive the drug has been reduced.[3]

1. CSM/MCA. Withdrawal of tolcapone (Tasmar). *Current Problems* 1999; 25: 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 11/08/08)
2. Assal F, *et al.* Tolcapone and fulminant hepatitis. *Lancet* 1998; 352: 958.
3. Borges N. Tolcapone-related liver dysfunction: implications for use in Parkinson's disease therapy. *Drug Safety* 2003; 26: 743–7.

Effects on the skin. For reference to the development of vitiligo in a patient following addition of tolcapone to levodopa/carbidopa treatment, see under Levodopa, p. 906.1.

Precautions

Tolcapone should not be given to patients with hepatic impairment or raised liver enzyme values. Liver enzymes should be monitored:

- when starting treatment with tolcapone or on increasing the dose to 200 mg three times daily
- every 2 weeks during the first year of therapy
- every 4 weeks for a further 6 months
- every 8 weeks thereafter

Tolcapone should be stopped if liver enzyme levels exceed the upper limit of normal or if signs or symptoms suggestive of the onset of hepatic failure occur. Patients who have developed evidence of hepatic injury while receiving tolcapone should not be given the drug again.

Tolcapone should be used with caution in patients with severe renal impairment.

It is contra-indicated in patients with severe dyskinesia or with a history of neuroleptic malignant syndrome (NMS). It is also contra-indicated in patients with a history of nontraumatic rhabdomyolysis or symptoms of hyperpyrexia and confusion possibly related to NMS. Patients with phaeochromocytoma should not be given tolcapone.

Use with levodopa may cause dizziness and orthostatic hypotension; if affected patients should not drive or operate machinery. Excessive daytime sleepiness and sudden onset of sleep may also occur with combination use (see Effects on Mental Function, under Adverse Effects of Levodopa, p. 905.2) and again, caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring.

Abrupt withdrawal or dose reduction of tolcapone should be monitored carefully because of the risk of developing symptoms resembling NMS.

The elderly. Confusion occurred in 3 elderly patients with severe Parkinson's disease after the addition of tolcapone to their antiparkinsonian therapy.[1] It was suggested that a starting dose of tolcapone 100 mg daily might be more suitable in frail patients with severe disease. It was noted[2] that a reduction in levodopa dosage is generally recommended when tolcapone is given to patients such as these, who were receiving 500 to 600 mg of levodopa daily.

1. Henry C, Wilson JA. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; 351: 1965–6.
2. Harper J, Vieira B. Catechol-O-methyltransferase inhibitors in Parkinson's disease. *Lancet* 1998; 352: 578.

Genetic polymorphism. Two patients who developed elevated liver enzyme values while receiving tolcapone, one of whom also had hepatic dysfunction while receiving entacapone, were found to be poor metabolisers with regard to UDP-glucuronosyltransferase activity.[1] Such patients may be predisposed to COMT-inhibitor induced hepatotoxicity.

1. Martignoni E, *et al.* Two patients with COMT inhibitor-induced hepatic dysfunction and UGT1A9 genetic polymorphism. *Neurology* 2005; 65: 1820–2.

Interactions

Tolcapone may influence the pharmacokinetics of drugs metabolised by catechol-*O*-methyltransferase; a dose reduction of such drugs should be considered when given with tolcapone. Increased concentrations of benserazide and its active metabolite have been reported when given with tolcapone. Licensed product information advises that non-selective MAOIs should not be used with tolcapone.

Pharmacokinetics

Tolcapone is rapidly absorbed from the gastrointestinal tract and maximum plasma concentrations have occurred within 2 hours of an oral dose; food delays and decreases the absorption. Absolute bioavailability is reported to be about 65%. Tolcapone is more than 99% bound to plasma proteins (mainly albumin) and is not widely distributed into body tissues. It is extensively metabolised, mainly by conjugation to the inactive glucuronide, but methylation by catechol-*O*-methyltransferase to 3-*O*-methyltolcapone and metabolism by cytochrome P450 isoenzymes CYP3A4 and CYP2A6 also occurs. About 60% of a dose is excreted in the urine with the remainder appearing in the faeces. The elimination half-life has been reported to be about 2 to 3 hours. The clearance of unbound tolcapone may be reduced by 50% in patients with moderate cirrhotic liver disorders.

References.

1. Dingemanse J, *et al.* Integrated pharmacokinetics and pharmacodynamics of the novel catechol-O-methyltransferase inhibitor tolcapone during first administration to humans. *Clin Pharmacol Ther* 1995; 57: 508–17.
2. Jorga KM, *et al.* Effect of liver impairment on the pharmacokinetics of tolcapone and its metabolites. *Clin Pharmacol Ther* 1998; 63: 646–54.
3. Jorga K, *et al.* Metabolism and excretion of tolcapone, a novel inhibitor of catechol-O-methyltransferase. *Br J Clin Pharmacol* 1999; 48: 513–20.
4. Jorga K, *et al.* Population pharmacokinetics of tolcapone in parkinsonian patients in dose finding studies. *Br J Clin Pharmacol* 2000; 49: 39–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tasmar†; *Austria*: Tasmar; *Belg.*: Tasmar; *Braz.*: Tasmar; *Chile*: Tasmar; *China*: Sen De Ning (森得宁); Tasmar (答是美); *Cz.*: Tasmar; *Denm.*: Tasmar; *Fr.*: Tasmar; *Ger.*: Tasmar; *Gr.*: Tasmar; *Hung.*: Tasmar; *Irl.*: Tasmar; *Ital.*: Tasmar; *Mex.*: Tasmar; *Neth.*: Tasmar; *Norw.*: Tasmar; *NZ*: Tasmar; *Philipp.*: Tasmar; *Pol.*: Tasmar; *Port.*: Tasmar; *Rus.*: Tasmar (Тасмар); *S.Afr.*: Tasmar†; *Spain*: Tasmar; *Swed.*: Tasmar; *Switz.*: Tasmar; *UK*: Tasmar; *USA*: Tasmar.

Pharmacopoeial Preparations
USP 36: Tolcapone Tablets.

Trihexyphenidyl Hydrochloride

(BANM, rINNM)

Benzhexol Hydrochloride; Cloridrato de Triexilfenidila; Cyclodolum; Hidrocloruro de trihexifenidilo; Triheksifenidilio hidrochloridas; Triheksyfenidylu chlorowodorek; Triheksyfenidyylihydrokloridi; Trihexifenidilhidroklorid; Trihexifenidilo, hidrocloruro de; Trihexyfenidyl-hydroklorid; Trihexyfenidyl-hydroklorid; Trihexyphénidyle, chlorhydrate de; Trihexyphenidylhydrochlorid; Trihexyphenidyli Hydrochloridum; Trihexyphenidylium Chloratum; Тригексифенидила Гидрохлорид.

1-Cyclohexyl-1-phenyl-3-piperidinopropan-1-ol hydrochloride.

$C_{20}H_{31}NO,HCl=337.9$

CAS — 144-11-6 (trihexyphenidyl); 52-49-3 (trihexyphenidyl hydrochloride).

ATC — N04AA01.

ATC Vet — QN04AA01.

UNII — AO61G82577.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of trihexyphenidyl:

Artanes.

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

Ph. Eur. 8: (Trihexyphenidyl Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 5.2 to 6.2.

USP 36: (Trihexyphenidyl Hydrochloride). A white or slightly off-white, crystalline powder, having not more than a very faint odour. Slightly soluble in water; soluble in alcohol and in chloroform. Store in airtight containers.

Uses and Administration

Trihexyphenidyl hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine (p. 1310.3). It also has a direct antispasmodic action on smooth muscle.

Trihexyphenidyl hydrochloride is given orally in the symptomatic treatment of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias in adults and children, but see p. 918.1. Trihexyphenidyl hydrochloride is given in 3 or 4 divided doses daily before or with food.

In **Parkinson's disease** the usual initial dose of 1 mg daily is gradually increased at intervals of 3 to 5 days by increments of 2 mg to 6 to 10 mg daily, according to response; for advanced cases, 12 to 15 mg daily or even more (up to 20 mg daily) may be needed. As a rule, postencephalitic patients tolerate and require the larger doses.

Usual doses for **drug-induced extrapyramidal symptoms** lie within the range of 5 to 15 mg daily, although as little as 1 mg daily may be sufficient in some cases.

Since the elderly and arteriosclerotic patients are more susceptible to the adverse effects of antimuscarinics a dose at the lower end of the range is usually recommended.

Antimuscarinic treatment of parkinsonism should never be terminated suddenly and it is usual when changing from one drug to another to withdraw one in small amounts while gradually increasing the dose of the other.

Trihexyphenidyl hydrochloride may be given with other drugs used for the relief of parkinsonism, such as levodopa, but the dose of each drug may need to be reduced. Trihexyphenidyl hydrochloride 3 to 6 mg daily is usually adequate.

Administration in children. Although unlicensed, trihexyphenidyl hydrochloride has been used for the management of dystonias in children; for suggested doses, see p. 918.1.

Dystonias. Antimuscarinics such as trihexyphenidyl are used in the management of dystonias (p. 903.3) although only about half of all children and adolescents, and fewer adults (who tolerate antimuscarinics less well) show any response. Adverse effects may be limited by starting with a low dose: one suggested regimen[1] starts with trihexyphenidyl 1 mg daily and rises up to 12 mg daily over the next 4 to 6 weeks; some patients may require up to 60 to 100 mg daily. The *BNFC* suggests that children aged 3 months to 18 years may be given oral doses of 1 to 2 mg daily as a single dose or in 2 divided doses; if necessary, the dose can be increased every 3 to 7 days by 1 mg daily to a maximum of 2 mg/kg daily.

1. Jankovic J. Dystonia: medical therapy and botulinum toxin. *Adv Neurol* 2004; 94: 275–86.

Adverse Effects, Treatment and Precautions

As for Atropine Sulfate, p. 1312.1. In some patients, such as those with arteriosclerosis or a history of drug idiosyncrasy, trihexyphenidyl may produce mental disturbances, excitement, or nausea and vomiting; such patients should be allowed to develop a tolerance by starting with a small initial dose and gradually increasing it until an effective level is reached. If a severe reaction occurs, trihexyphenidyl should be stopped for a few days and resumed at a lower dose. Trihexyphenidyl may provoke or exacerbate tardive dyskinesia.

Abuse. Trihexyphenidyl hydrochloride has been abused for its euphoric effect[1,2] especially by psychiatric patients.[3] Its abuse potential in schizophrenic patients has been questioned[4] and its unpleasant antimuscarinic effects tend to limit its repeated use,[5] but a small survey among psychiatric patients found that trihexyphenidyl was reported to be the antimuscarinic most frequently abused;[6] procyclidine, benzatropine, and orphenadrine (in decreasing order of frequency) were also misused. A later analysis of health insurance data from one region of France[7] examined prescriptions for trihexyphenidyl in 3028 subjects, most of whom were also receiving antipsychotics, and concluded that there was evidence of an abnormal pattern of use in about 2%. Patients in this subgroup were mostly young, male, and also receiving benzodiazepines or high doses of buprenorphine.

1. Crawshaw JA, Mullen PE. A study of benzhexol abuse. *Br J Psychiatry* 1984; 145: 300–3.
2. Nappo SA, *et al.* Trihexyphenidyl (Artane): a Brazilian study of its abuse. *Subst Use Misuse* 2005; 40: 473–82.
3. Pullen GP, *et al.* Anticholinergic drug abuse: a common problem? *BMJ* 1984; 289: 612–13.
4. Goff DC, *et al.* A placebo-controlled trial of trihexyphenidyl in unmedicated patients with schizophrenia. *Am J Psychiatry* 1994; 151: 429–31.
5. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995.
6. Buhrich N, *et al.* Misuse of anticholinergic drugs by people with serious mental illness. *Psychiatr Serv* 2000; 51: 928–9.
7. Prauger E, *et al.* Détournement d'usage du trihexyphénidyle (Artane, Parkinane): tendances récentes. *Therapie* 2003; 58: 541–7.

Effects on the heart. Paradoxical sinus bradycardia developed in a schizophrenic patient after receiving trihexyphenidyl for extrapyramidal effects due to antipsychotic medication.[1] Normal sinus rhythm was restored after trihexyphenidyl was stopped. The patient had previously received trihexyphenidyl and suffered bradycardia which at the time was attributed to haloperidol.

1. Blumensohn R, *et al.* Bradycardia due to trihexyphenidyl hydrochloride. *Drug Intell Clin Pharm* 1986; 20: 786–7.

Effects on mental function. Oral trihexyphenidyl 2 mg significantly impaired memory function compared with placebo in a study in 13 elderly patients.[1] Impairment of memory has also been noted in patients with Parkinson's disease given antimuscarinics such as trihexyphenidyl.[2] However, impairment may be reversible on stopping the antimuscarinic (see Atropine, p. 1312.2).

1. Potamianos G, Kellett JM. Anti-cholinergic drugs and memory: the effects of benzhexol on memory in a group of geriatric patients. *Br J Psychiatry* 1982; 140: 470–2.
2. Sadeh M, *et al.* Effects of anticholinergic drugs on memory in Parkinson's disease. *Arch Neurol* 1982; 39: 666–7.

Overdosage. A 34-year-old woman developed a toxic reaction with widely dilated pupils, dry skin, and visual hallucinations within 24 hours of taking about 300 mg of trihexyphenidyl hydrochloride with suicidal intent.[1] After 3 to 4 days the hallucinations were replaced by illusions; complete recovery occurred after a week, with no special treatment. Death associated with moderate blood concentrations of trihexyphenidyl (0.12 micrograms/mL) has been reported[2] in a schizophrenic patient recovering from a respiratory infection. It was thought possible that he had increased his dose to counteract developing tardive dyskinesia, and that the toxic effects had been exacerbated by respiratory inflammation; there was no evidence of suicidal intent.

1. Ananth JV, *et al.* Toxic psychosis induced by benzhexol hydrochloride. *Can Med Assoc J* 1970; 103: 771.
2. Gall JAM, *et al.* Death due to benzhexol toxicity. *Forensic Sci Int* 1995; 71: 9–14.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trihexyphenidyl 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 30/09/11)

Withdrawal. A 61-year-old woman who had taken trihexyphenidyl 6 mg daily for a year for Parkinson's disease developed encephalopathy and miosis on two occasions when treatment was abruptly withdrawn.[1] Slowly tapered withdrawal avoided these effects.

1. Johkura K, *et al.* Trihexyphenidyl withdrawal encephalopathy. *Ann Neurol* 1997; 41: 133–4.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Chlorpromazine. For the effect of trihexyphenidyl on plasma concentrations of chlorpromazine, see Antiparkinsonian Drugs, p. 1052.3.

Pharmacokinetics

Trihexyphenidyl hydrochloride is well absorbed from the gastrointestinal tract and has been stated to exert an effect within 1 hour of an oral dose.

Half-life. The reported half-life of trihexyphenidyl has varied according to the assay method used. Values reported when using radioreceptor and chromatographic techniques have ranged from about 1 to more than 24 hours[1] and from 10 to 29 hours,[2] respectively, but the sensitivity and specificity of these methods have been criticised.[3] With a more recently developed radio immunoassay it was found that after oral doses there was an initial elimination phase with an estimated half-life of 5.33 hours followed by a terminal elimination phase with an estimated half-life of 32.7 hours.

1. Burke RE, Fahn S. Pharmacokinetics of trihexyphenidyl after short-term and long-term administration to dystonic patients. *Ann Neurol* 1985; 18: 35–40.
2. Garbarg S, *et al.* Comparison pharmacoclinique de deux formes galéniques de trihexyphénidyle. *Encephale* 1983; IX: 167–74.
3. He H, *et al.* Development and application of a specific and sensitive radioimmunoassay for trihexyphenidyl to a pharmacokinetic study in humans. *J Pharm Sci* 1995; 84: 561–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Artane; *Austral.*: Artane; *Belg.*: Artane; *Braz.*: Artane; Triexidyl; *Canad.*: Apo-Trihex; *Chile*: Tenvatil; Tonaril; *Fr.*: Artane; Parkinane; Trihexy; *Ger.*: Artane; Parkopan; *Gr.*: Artane; *Hong Kong*: Adtendyl†; *India*: Barohexy; Bexol; Dyskinil; Dystonil; Lahexy; Manohexy; Pacitane; Parales; Parnon; *Indon.*: Arkine; Artane†; Hexymer; *Israel*: Partane; Rodenal; *Ital.*: Artane; *Malaysia*: Aca; Apo-Trihex; *Mex.*: Hipokinon; Kexidil; *Neth.*: Artane; *Pol.*: Parkopan†; *Port.*: Artane; *Rus.*: Cyclodol (Циклодол); *S.Afr.*: Artane†; *Singapore*: Apo-Trihex; B-Hex; Beahexol; *Spain*: Artane; *Swed.*: Pargitan; *Thai.*: Aca; Acamed; Artane; Pozhexol; Tridyl; *UK*: Broflex†; *Ukr.*: Parkopan (Паркопан)†; *USA*: Trihexy.

Multi-ingredient Preparations. *India*: Benzyzine; Chlorectil Plus; Cinris Forte; Cizoren Plus; Clozine Forte; Clozine Plus; Combidol; Don Forte; Don Plus; Don-LS; Emetil DS; Emetil Plus; Etores-TR; F Plus; Gencalm Plus; Genrest Plus; Genrest-LS; Halotex; Hexidol Forte; Hexidol Kit; Hexidol Plus; Kaytrix-C; Lacalm Plus; Lacalm; Manocalm Forte; Manocalm Plus; Manodol; Mindol Forte; Mindol Plus; Neocalm Forte; Neocalm Plus; Sycot; Trinicalm Forte; Trinicalm Plus.

Pharmacopoeial Preparations

BP 2014: Trihexyphenidyl Tablets;

USP 36: Trihexyphenidyl Hydrochloride Elixir; Trihexyphenidyl Hydrochloride Extended-release Capsules; Trihexyphenidyl Hydrochloride Tablets.

Tropatepine Hydrochloride *(rINNM)*

Hidrocloruro de tropatepina; SD-1248-17; Tropatepin, hidrocloruro de; Tropatépine, Chlorhydrate de; Tropatepinii Hydrochloridum; Тропатепина Гидрохлорид.

3-(Dibenzo[*b*,*e*]thiepin-11(6*H*)-ylidene)tropane hydrochloride.

$C_{22}H_{23}NS,HCl$=370.0.

CAS — 27574-24-9 (tropatepine); 27574-25-0 (tropatepine hydrochloride).

ATC — N04AA12.

ATC Vet — QN04AA12.

UNII — 17N1U39U3Z.

Profile

Tropatepine hydrochloride is an antimuscarinic with actions and uses similar to those of trihexyphenidyl (p. 917.3). It is used in the management of parkinsonism (p. 889.1), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value in tardive dyskinesia. Tropatepine hydrochloride is given orally in usual doses of 10 to 30 mg daily; it is also given intramuscularly or by slow intravenous injection in doses of 10 to 20 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Lepticur.

Antiprotozoals

Amoebic infections, p. 919
Amoebiasis, p. 919
Acanthamoeba keratitis, p. 919
Disseminated amoebic infections, p. 920
Primary amoebic meningoencephalitis, p. 920
Babesiosis, p. 920
Balantidiasis, p. 920
Blastocystis hominis infection, p. 920
Coccidiosis, p. 921
Cryptosporidiosis, p. 921
Cyclosporiasis, p. 921
Gastro-enteritis, p. 921
Giardiasis, p. 921
Infections in immunocompromised patients, p. 921
Isosporiasis, p. 921
Leishmaniasis, p. 922
Malaria, p. 924
Microsporidiosis, p. 924
Pneumocystis pneumonia, p. 924
Toxoplasmosis, p. 924
Trichomoniasis, p. 925
African trypanosomiasis, p. 925
American trypanosomiasis, p. 925

The drugs described in this chapter are those used mainly in the treatment of parasitic protozoal infections. In addition to their use as antiprotozoals, metronidazole and related nitroimidazole derivatives are also important in the treatment of anaerobic bacterial infections. Some veterinary antiprotozoal drugs are included. Drugs used in the treatment of malaria are described in the Antimalarials chapter; some of these are also used in other protozoal infections.

The principal antiprotozoal drugs are listed in Table 1, below.

Choice of Antiprotozoal

Protozoal infections occur throughout the world and are a major cause of morbidity and mortality in some regions. The choice of treatment for the principal protozoal diseases in humans is discussed below.

Amoebic infections

The most common amoebic infection of man is **amoebiasis** caused by infection with the protozoan parasite *Entamoeba histolytica* and related species. Free-living amoebae occur worldwide and are distributed in soil and water. They can also cause disease in man, though these infections are rare. Diseases include:

- **amoebic keratitis** caused by *Acanthamoeba* spp.
- **disseminated amoebic infections** including granulomatous amoebic encephalitis and cutaneous, pulmonary, and nasopharyngeal infections caused by *Acanthamoeba* spp., *Balamuthia mandrillaris* (previously referred to as leptomyxid amoebae), and very rarely by *Sappinia diploidea*
- **primary amoebic meningoencephalitis** caused by *Naegleria fowleri*

Amoebiasis. Amoebiasis[1-3] is a parasitic infection caused mainly by the protozoan *Entamoeba histolytica*. Although about 10% of the world's population is infected with *Entamoeba* spp., most individuals are infected with *E. dispar*, one of 2 non-pathogenic species recognised in humans (the other being *E. moshkovskii*). Transmission of *E. histolytica* is usually by the faeco-oral route and infection results from the ingestion of cysts, usually in contaminated food and water. Amoebiasis occurs throughout the world, but the incidence is higher in developing countries and is closely related to sanitation and socio-economic status.

Colonisation of the bowel lumen with *E. histolytica* usually results in asymptomatic infection, although infected people chronically pass cysts in stools. In about 10% of cases symptomatic (invasive) disease may occur days to years after the initial infection; factors increasing susceptibility to tissue invasion include malnutrition, immunosuppression, and pregnancy. Symptomatic (invasive) amoebiasis may be classified as intestinal or extra-intestinal amoebiasis.

- *Intestinal amoebiasis* comprises two main states, amoebic dysentery and non-dysenteric amoebic colitis; amoeboma, a localised form of intestinal amoebiasis, and amoebic appendicitis may also occur. A few patients may develop fulminant or necrotising amoebic colitis which is associated with a mortality rate of more than 40%.
- The most common form of *extra-intestinal amoebic disease* is hepatic amoebiasis, which may present as acute non-suppurative disease or as amoebic liver abscess. Amoebic infection is a less common cause of liver abscess than bacterial infection. Amoebiasis may also involve the skin, genito-urinary tract, or organs such as the lungs and brain.

Drugs used in the **treatment** of amoebiasis may be classified according to their site of action as follows:

- *luminal amoebicides* acting mainly in the bowel lumen. Diloxanide furoate is widely used as the luminal amoebicide of choice, although clefamide, etofamide, and teclozan are also effective. Paromomycin and diiodohydroxyquinoline have also been used[1,2] although most oral preparations of halogenated hydroxyquinolines have been withdrawn because of the association between clioquinol and subacute myelo-opticoneuropathy
- *tissue* or *systemic amoebicides* acting mainly in the intestinal wall and liver. These have included the alkaloid emetine, its synthetic derivative dehydroemetine, and the antimalarial chloroquine which acts mainly in the liver
- *mixed amoebicides* acting at all sites of infection, that is within the intestinal lumen and in the intestinal wall and other tissues. These have included metronidazole and other 5-nitroimidazole derivatives (such as ornidazole, secnidazole, and tinidazole). However, because of their rapid absorption from the gastrointestinal tract, the nitroimidazoles are less effective against parasites in the lumen

Patients with proven *E. histolytica* **asymptomatic** amoebiasis should be treated with a luminal amoebicide to prevent transmission of cysts to others and because of the small but definite risk of potentially severe invasive disease.[2,3] The choice of drug is influenced by availability; diloxanide furoate is generally used in the UK while diiodohydroxyquinoline or paromomycin are also used in the USA.[4] Infection with *E. dispar* and probably infection with *E. moshkovskii* do not need treatment.[3] Those with symptomatic intestinal or extraintestinal **invasive** disease should be treated with a 5-nitroimidazole derivative (usually metronidazole), followed by a luminal amoebicide to eradicate any surviving organisms from the lumen of the large intestine and prevent relapse.[1-3] However, a systematic review[5] to evaluate antiamoebic drugs for the treatment of amoebic colitis found that tinidazole was more effective than metronidazole in reducing clinical failure and better tolerated. Uncomplicated cases usually respond to a 5-day treatment course with metronidazole, while more severe infections are treated for 10 days.[3] In cases of **fulminant** or necrotising amoebic colitis and for severely ill patients, broad-spectrum antibacterials are given with a systemic amoebicide to decrease the risk of superinfection with bowel flora and peritonitis.[1-3] Nitazoxanide has been used in mild to moderate intestinal disease.[4] Standard treatment for amoebic **liver abscess** is metronidazole followed by a luminal amoebicide. The majority of patients with amoebic liver abscess defervesce after 3 to 4 days of treatment with metronidazole.[2,3]

In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2.

Table 1. Classification of principal antiprotozoals.

Antimony compounds	*Nitrofurans*
Meglumine antimonate	Furazolidone
Sodium stibogluconate	Nifuratel
	Nifurtimox
Aromatic diamidines	
Pentamidine	*5-Nitroimidazoles*
	Metronidazole
Arsenicals, pentavalent	Nimorazole
Acetarsol	Ornidazole
Tryparsamide	Secnidazole
	Tinidazole
Arsenicals, trivalent	
Melarsoprol	*Miscellaneous*
	Atovaquone
Dichloroacetamides	Benznidazole
Diloxanide	Dehydroemetine
	Eflornithine
Halogenated hydroxyquinolines	Mepacrine
Diiodohydroxyquinoline	Nitazoxanide
	Paromomycin
	Suramin

The symbol † denotes a preparation no longer actively marketed

1. Stanley SL. Amoebiasis. *Lancet* 2003; 361: 1025–34.
2. Haque R, *et al.* Amebiasis. *N Engl J Med* 2003; 348: 1565–73.
3. Pritt BS, Clark CG. Amebiasis. *Mayo Clin Proc* 2008; 83: 1154–9.
4. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
5. Gonzales MLM, *et al.* Antiamoebic drugs for treating amoebic colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 17/06/09).

Acanthamoeba keratitis. *Acanthamoeba* keratitis may result from corneal trauma or exposure to contaminated water, but is most commonly associated with the wearing of soft contact lenses as well as the use of home-made sodium chloride solutions for cleaning them. Infection usually occurs in otherwise healthy persons. Rare cases have been associated with laser-assisted *in-situ* keratomileusis. Keratitis is a local infection that typically begins with a foreign-body sensation followed by pain, tearing, photophobia, and blurred vision. The infection may progress to involve the sclera and loss of vision may follow.

If the disease is recognised early it usually responds well to topical **antiamoebic treatment**; severe infection and late-presenting cases may require penetrating keratoplasty.[1,2] A combination of antiamoebic drugs is generally used because the cyst form is highly resistant to therapy and may persist for years. Two weeks may be required before a response is seen, and the total duration of therapy is a minimum of 3 to 4 weeks; some recommend treating for 3 to 4 months,[3] or even longer. Infection can recur after treatment due to persistence of the cystic form.

The first drug used with some success was 0.1% propamidine isetionate applied topically.[1,4] It was used with an aminoglycoside such as neomycin or a neomycin-polymyxin-gramicidin preparation and a cure was achieved in about 50% of cases. However, most cysts are resistant to neomycin and due to surface toxicity and poor *in-vitro* sensitivity,[1,5] neomycin is no longer recommended.[1,6] Since then the biguanide cationic antiseptics, chlorhexidine and polihexanide have also been shown to be effective in a 0.02% concentration against trophozoites and cysts and have become the drugs of choice.[2,3,5,7] Propamidine has been tried with these agents, however, poor cysticidal activity, chronic conjunctival infection, and resistance to some strains of *Acanthamoeba* to propamidine has prompted the suggestion that it should be replaced by another diamidine such as hexamidine.[1] Biguanides may also be used alone,[6] and are particularly effective in early infection.

Other drugs that have been tried include the topical imidazoles; when applied in a 1% solution they may be effective against trophozoites but probably not against cysts.[1,5] They should never be used as monotherapy. Voriconazole 1% eye drops have, however, been effective for salvage therapy.[8] Oral ketoconazole and, to a lesser extent, itraconazole penetrate into the cornea and have been used as adjunctive therapy to polihexanide and chlorhexidine, but the levels obtained in the cornea are probably too low to be trophozoiticidal.[2] Possible new therapies include antineoplastic and antimalarial drugs; the biguanide antidiabetic drugs metformin and phenformin, and the antibacterial ofloxacin have been shown to have activity against trophozoites *in vitro*, but not against cysts.[1]

Topical cycloplegic therapy and oral NSAIDs may be given for **symptomatic management** of pain, although opioid analgesics are often necessary.[2] Some authorities suggest the use of topical NSAIDs.[1] The use of topical corticosteroids to control inflammation remains controversial because they suppress macrophage activity, which is essential in scavenging and destroying the amoeba.[1] It is recommended that the use of corticosteroids should be delayed and limited as much as possible. They may be considered with antiamoebic agents in those patients with severe pain, scleritis, or severe anterior-chamber inflammation.[2,9,10] A retrospective study[9] found that the use of topical corticosteroids was not associated with treatment failure, but was associated with a prolonged course of antiamoebic therapy. In patients with severe scleral involvement, systemic immunosuppressants such as oral corticosteroids, ciclosporin, and azathioprine may be needed.[11]

Acanthamoeba keratitis in contact lens wearers should be **preventable** by good lens hygiene (see Contact Lens Care, p. 1731.2).

1. Seal DV. Acanthamoeba keratitis update—incidence, molecular epidemiology and new drugs for treatment. *Eye* 2003; 17: 893–905.
2. Hammersmith KM. Diagnosis and management of Acanthamoeba keratitis. *Curr Opin Ophthalmol* 2006; 17: 327–31.
3. Schuster FL, Visvesvara GS. Opportunistic amoebae: challenges in prophylaxis and treatment. *Drug Resist Updat* 2004; 7: 41–51.
4. Murdoch D, *et al.* Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. *Aust N Z J Ophthalmol* 1998; 26: 231–6.
5. Lindquist TD. Treatment of Acanthamoeba keratitis. *Cornea* 1998; 17: 11–16.
6. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
7. Illingworth CD, *et al.* Acanthamoeba keratitis: risk factors and outcome. *Br J Ophthalmol* 1995; 79: 1078–82.
8. Bang S, *et al.* Treatment with voriconazole in 3 eyes with resistant Acanthamoeba keratitis. *Am J Ophthalmol* 2010; 149: 66–9.
9. Park DH, *et al.* The role of topical corticosteroids in the management of Acanthamoeba keratitis. *Cornea* 1997; 16: 277–83.
10. O'Day DM, Head WS. Advances in the management of keratomycosis and Acanthamoeba keratitis. *Cornea* 2000; 19: 681–7.
11. Lee GA, *et al.* Acanthamoeba sclerokeratitis: treatment with systemic immunosuppression. *Ophthalmology* 2002; 109: 1178–82.

Disseminated amoebic infections. Granulomatous amoebic encephalitis (GAE) and disseminated granulomatous amoebic disease (involving the skin, lungs, and sinuses) are caused by infection with free-living amoebae, usually *Acanthamoeba* spp. or sometimes *Balamuthia mandrillaris* (previously referred to as leptomyxid amoebae). They are opportunistic infections occurring mainly in debilitated or immunocompromised individuals. In GAE the protozoa spread haematogenously to the CNS from the sinuses, lungs, or skin lesions and produce focal neurological deficits that progress over days or weeks to a diffuse meningoencephalitis. The infection is usually fatal and most cases have been diagnosed postmortem so little is known about effective treatments, although many drugs have been tried.

Drugs that have been used in combinations to treat disseminated and CNS infections caused by *Acanthamoeba* spp. include co-trimoxazole, pentamidine, sulfadiazine, flucytosine, rifampicin, and azoles such as ketoconazole, itraconazole, or fluconazole;[1,2] susceptibilities of species and strains appear to vary widely, and susceptibility testing is advisable.

Successful treatment has been reported in 2 apparently immunocompetent children with chronic meningitis caused by *Acanthamoeba* after prolonged treatment with oral co-trimoxazole, rifampicin, and ketoconazole.[3] Successful treatment has also been reported with topical and oral miltefosine in an immunocompromised patient with disseminated acanthamoebiasis, amoebic encephalitis, and underlying miliary tuberculosis and tuberculous meningitis; the patient initially failed treatment with parenteral co-trimoxazole (later changed to oral sulfadiazine), fluconazole, liposomal amphotericin B, and flucytosine.[4]

Similar drugs have been used to treat CNS infections caused by *B. mandrillaris* and 2 patients have been successfully treated with pentamidine, sulfadiazine, flucytosine, fluconazole, a macrolide (such as azithromycin or clarithromycin), and a phenothiazine (such as thioridazine or trifluoperazine).[5]

Clinical responses to chemotherapy have also been reported in a few patients[6-9] with disseminated infection but no evidence of CNS involvement. Disseminated *Acanthamoeba* infection in an immunocompromised patient was successfully treated with intravenous pentamidine followed by maintenance therapy with oral itraconazole.[6] Skin lesions were treated topically with chlorhexidine and ketoconazole.[1] Clinical improvement of disseminated acanthamoebiasis in a patient with AIDS followed treatment with intravenous pentamidine and oral flucytosine; an infant with HIV infection was treated with fluconazole, flucytosine, and sulfadiazine.[7] A lung transplant patient with disseminated acanthamoebiasis was also successfully treated with pentamidine, flucytosine, and azithromycin, plus topical chlorhexidine and ketoconazole.[8] A case of granulomatous dermatitis secondary to *Acanthamoeba* infection in a lung transplant recipient has been successfully treated with a prolonged course of amphotericin B lipid complex and voriconazole.[9]

The use of RNA interference aimed at *Acanthamoeba* genes, using a combination of short-strand interfering RNAs (siRNAs), has been proposed following promising results *in vitro*.[10]

1. Schuster FL, Visvesvara GS. Opportunistic amoebae: challenges in prophylaxis and treatment. *Drug Resist Updat* 2004; 7: 41–51.
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Singhal T, *et al.* Successful treatment of Acanthamoeba meningitis with combination oral antimicrobials. *Pediatr Infect Dis J* 2001; 20: 623–7.
4. Alchelburg AC, *et al.* Successful treatment of disseminated Acanthamoeba sp. infection with miltefosine. *Emerg Infect Dis* 2008; 14: 1743–6.
5. Deetz TR, *et al.* Successful treatment of Balamuthia amoebic encephalitis: presentation of 2 cases. *Clin Infect Dis* 2003; 37: 1304–12.
6. Slater CA, *et al.* Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; 331: 85–7.
7. 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.
8. Oliva S, *et al.* Successful treatment of widely disseminated acanthamoebiasis. *South Med J* 1999; 92: 55–7.
9. Walia R, *et al.* A case of successful treatment of cutaneous Acanthamoeba infection in a lung transplant recipient. *Transpl Infect Dis* 2007; 9: 51–4.
10. Lorenzo-Morales J, *et al.* Therapeutic potential of a combination of two gene-specific small interfering RNAs against clinical strains of Acanthamoeba. *Antimicrob Agents Chemother* 2010; 54: 5151–5.

Primary amoebic meningoencephalitis. Primary amoebic meningoencephalitis is a rare infection usually caused by the free-living amoeba *Naegleria fowleri*. It occurs mainly in healthy children and young adults and is usually associated with swimming in warm fresh water. The protozoa invade the CNS directly through the nasal mucosa to produce a meningoencephalitis that is usually rapidly fatal (7 to 10 days).

A few cases of successful treatment have been reported, and have generally involved intravenous[1-5] and usually intrathecal[1-3] amphotericin B; some patients were also given oral rifampicin,[2-5] intravenous and intrathecal miconazole,[2] intravenous chloramphenicol,[5] or ornidazole.[4]

1. Anderson K, Jamieson A. Primary amoebic meningoencephalitis. *Lancet* 1972; I: 902–3.
2. Seidel JS, *et al.* Successful treatment of primary amebic meningoencephalitis. *N Engl J Med* 1982; 306: 346–8.
3. Brown RL. Successful treatment of primary amebic meningoencephalitis. *Arch Intern Med* 1991; 151: 1201–2.
4. Jain R, *et al.* Naegleria meningitis: a rare survival. *Neurol India* 2002; 50: 470–2.
5. Rai R, *et al.* Primary amebic meningoencephalitis. *Indian Pediatr* 2008; 45: 1004–5.

Babesiosis

Babesiosis (piroplasmosis) is an infection caused by intraerythrocytic protozoa of the *Babesia* genus, which are transmitted to man by the bite of infected *Ixodes* ticks. Transmission by blood transfusion has also been reported. *Ixodes scapularis*, one of the ticks that may cause babesiosis, may also be infected with, and transmit, *Anaplasma phagocytophilum* and/or *Borrelia burgdorferi* and therefore the bite from this tick may lead to babesiosis, human granulocytic anaplasmosis (see Ehrlichiosis, p. 179.1), or Lyme disease (p. 190.1) as a single infection or as a co-infection.[1] Babesiosis occurs worldwide in animals. In the US, human infection is most commonly due to *B. microti*; the disease is much rarer in Europe where it is usually caused by *B. divergens* or *B. bovis*.[1-3] Infection with the babesia-like piroplasms WA-1 and MO-1 has also been reported in the USA.[1,2]

Clinical features of babesiosis acquired in the USA differ from that acquired in Europe. Infection in the USA is often asymptomatic and self-limiting, but may produce prolonged severe viral-like illness with fever and haemolytic anaemia, particularly in patients who are asplenic, elderly, debilitated, or immunocompromised (including those infected with HIV). Symptoms include chills, sweating, myalgia, arthralgia, weakness, fatigue, anorexia, nausea, vomiting, jaundice, and headache. The most common complications are heart failure, disseminated intravascular coagulation, acute respiratory distress syndrome, and renal failure.[1-3] Co-infection with *B. microti* and *Borrelia burgdorferi* has resulted in more severe symptoms. In Europe, infections have mostly been described in asplenic persons, in many of whom the infection was rapidly fatal. Clinical features include severe haemolytic anaemia, jaundice, pulmonary oedema, and renal failure.

There is no established specific **treatment** for babesiosis. Treatment is not recommended for asymptomatic patients although all symptomatic patients should be treated with antibacterials to prevent the development of complications.[1] For serious infections, supportive therapies include red blood cell exchange transfusions to reduce parasitaemia. *Clindamycin with quinine* was the first regimen used[4] for the treatment of *B. microti* infections, but has been associated with significant toxicity. A prospective randomised study[5] in 58 patients found *azithromycin with atovaquone* to be as effective as clindamycin and quinine and associated with less toxicity. *Azithromycin with quinine* has been reported to be effective in 2 patients who had not responded to quinine plus clindamycin.[6,7] *Pentamidine* has also been reported to produce clinical improvement in patients with *B. microti* infection,[8] but the efficacy and safety of pentamidine has been questioned.[9] *Other drugs* that have been tried with variable results include chloroquine, primaquine, pyrimethamine, sulfadiazine, and tetracycline.[2,3]

The Infectious Diseases Society of America[1] recommends a combination of either clindamycin plus quinine or atovaquone plus azithromycin, both orally for 7 to 10 days; the combination of intravenous clindamycin plus oral quinine should be used in severe babesiosis. In immunocompromised patients higher doses of azithromycin may be used; they are prone to relapsing disease, and treatment should be given for 6 weeks or more, including 2 weeks after parasites are no longer detectable in blood smears.[10] Partial or complete exchange transfusion may also be given. Patients with persistent infection should be re-treated.

Patients *co-infected* or suspected to be co-infected with *Anaplasma phagocytophilum* and/or *Borrelia burgdorferi* should also be given doxycycline for 10 days.[1,3] For information on the treatment of co-infected patients see Lyme Disease, p. 190.1. In *B. divergens* infections, treatment is complicated by the rapid progression of the disease. Antiprotozoal and antimalarial drugs have been tried with limited success, although pentamidine with co-trimoxazole was successful in a patient,[11] and a marked reduction in parasite load was seen in a patient treated with pentamidine plus exchange transfusions.[12] The combination of clindamycin plus quinine with exchange transfusion has also been suggested.[2]

Preventive measures against babesiosis include the use of tick repellents, physical protection, and prompt removal of attached ticks.[1]

1. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 43: 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 17/07/08)
2. Homer MJ, *et al.* Babesiosis. *Clin Microbiol Rev* 2000; 13: 451–69.
3. Mylonakis E. When to suspect and how to monitor babesiosis. *Am Fam Physician* 2001; 63: 1969–74.
4. Wittner M, *et al.* Successful chemotherapy of transfusion babesiosis. *Ann Intern Med* 1982; 96: 601–4.
5. Krause PJ, *et al.* Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; 343: 1454–8.
6. Shaio MF, Yang KD. Response of babesiosis to a combined regimen of quinine and azithromycin. *Trans R Soc Trop Med Hyg* 1997; 91: 214–15.
7. Shih C-M, Wang C-C. Ability of azithromycin in combination with quinine for the elimination of babesial infection in humans. *Am J Trop Med Hyg* 1998; 59: 509–12.
8. Francioli PB, *et al.* Response of babesiosis to pentamidine therapy. *Ann Intern Med* 1981; 94: 326–30.
9. Teutsch SM, Juranek DD. Babesiosis. *Ann Intern Med* 1981; 95: 241.
10. Krause PJ, *et al.* Persistent and relapsing babesiosis in immunocompromised patients. *Clin Infect Dis* 2008; 46: 370–6.
11. Raoult D, *et al.* Babesiosis, pentamidine, and cotrimoxazole. *Ann Intern Med* 1987; 107: 944.
12. Clarke CS, *et al.* Babesiosis: under-reporting or case-clustering? *Postgrad Med J* 1989; 65: 591–3.

Balantidiasis

Balantidiasis is an uncommon infectious disease of the large intestine caused by a ciliated protozoan, *Balantidium coli*, that frequently infects pigs. Humans and usually resistant but may become infected by eating food or drinking water that has been contaminated by human or animal faeces containing *B. coli* cysts, or by handling infected animals. Those with poor nutrition and achlorhydria appear more vulnerable to infection.

Most cases of balantidiasis are asymptomatic and the organism lives in the large intestine as a luminal commensal, however, asymptomatic people can transmit the disease. Those with symptomatic infections may develop a chronic illness characterised by intermittent diarrhoea, abdominal cramps, and weight loss; colitis with mucus and bloody stools occurs less commonly. Colonic ulceration resulting in a syndrome resembling amoebic dysentery may occur in some individuals, while others may develop a fulminating form of balantidiasis. Untreated cases have proved fatal.

Oral tetracycline for 10 days is the **treatment** of choice; metronidazole, diiodohydroxyquinoline,[1] paromomycin, or nitazoxanide are alternatives. Treatment courses of up to 20 days may be required in immunosuppressed patients, including those who are infected with HIV.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Blastocystis hominis infection

There is controversy over whether the protozoan parasite *Blastocystis hominis* is a pathogen or a harmless commensal of the intestinal tract. It has been reported both in immunocompetent and immunocompromised subjects,[1,2] with transmission probably by the faeco-oral route. Diarrhoea and other gastrointestinal symptoms have been ascribed to the organism.

Treatment with standard antiprotozoals, especially metronidazole, has had variable success; metronidazole resistance may occur.[3,4] Co-trimoxazole was reported to have eliminated *B. hominis* from the stools of all but one of 47 otherwise healthy subjects with diarrhoea in one study,[1] and similarly in 36 of 38 children, and 14 of 15 adults, in another.[6] In patients heavily infected with *B. hominis*, only 4 of 12 treated with metronidazole and 2 of 9 given co-trimoxazole achieved eradication of the organism.[1] Diiodohydroxyquinoline,[5] nitazoxanide,[4,5] or paromomycin[4] may be effective in some cases.

1. Kaya S, *et al.* Pathogenicity of Blastocystis hominis, a clinical reevaluation. *Turkiye Parazitol Derg* 2007; 31: 184–7.
2. Kuo H-Y, *et al.* Clinical significance of Blastocystis hominis: experience from a medical center in northern Taiwan. *J Microbiol Immunol Infect* 2008; 41: 222–6.
3. Haresh K, *et al.* Isolate resistance of Blastocystis hominis to metronidazole. *Trop Med Int Health* 1999; 4: 274–7.

4. Stensvold CR, *et al.* Eradication of *Blastocystis* carriage with antimicrobials: reality or delusion? *J Clin Gastroenterol* 2010; 44: 85–90.
5. Schwartz E, Houston R. Effect of co-trimoxazole on stool recovery of Blastocystis hominis. *Lancet* 1992; 339: 428–9.
6. Ok UZ, *et al.* Effect of trimethoprim-sulfamethaxazole [sic] in Blastocystis hominis infection. *Am J Gastroenterol* 1999; 94: 3245–7.
7. Moghaddam DD, *et al.* Blastocystis hominis and the evaluation of efficacy of metronidazole and trimethoprim/sulfamethoxazole. *Parasitol Res* 2005; 96: 273–5.
8. Stenzel DJ, Boreham PFL. Blastocystis hominis revisited. *Clin Microbiol Rev* 1996; 9: 563–84.
9. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Coccidiosis

Coccidiosis is a term sometimes applied to infections with protozoa of the order *Eucoccidiorida*. The predominant coccidian infections in man are caused by *Cryptosporidium* (below), *Cyclospora cayetanensis* (below), *Isaspora* (below), *Plasmodium* (see Malaria, p. 644.1), and *Toxoplasma* (p. 924.2). Coccidian protozoa, mainly *Eimeria*, cause economically important infections in domesticated animals.

Cryptosporidiosis

Cryptosporidiosis[1] is a gastrointestinal infection caused by species of the coccidian protozoan parasite *Cryptosporidium*. It has a worldwide distribution and occurs in many animal species as well as in man. Infection is acquired through ingestion, and perhaps inhalation, of oocysts. Infection in immunocompetent individuals usually causes a self-limiting watery, non-bloody diarrhoea lasting up to 2 weeks. In immunocompromised patients and particularly AIDS patients with a CD4+ count below 100 cells/microlitre, there may be profuse and persistent diarrhoea (for 2 months or longer), profound weight loss, and severe abdominal pain, and the infection may be life-threatening. Other sites of infection include the respiratory and biliary tracts.

There is currently no consistently effective specific treatment[2,3] and priority should be given to maintaining hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Beneficial responses to octreotide have been reported in a few cases,[4–6] but US guidelines for the prevention and treatment of opportunistic infection in HIV-infected patients[7] consider that octreotide is no more effective than oral antidiarrhoeals and its use is not recommended. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2. In patients with AIDS the severity of the infection may be controlled if the immune function is improved with HAART,[2,3,7,8] but where this is not possible, therapy with an antimicrobial and an antidiarrhoeal drug continues to be standard.[2] Several drugs have been studied in small clinical studies; for nitazoxanide, paromomycin,[7,8] spiramycin,[7] and azithromycin,[9,10] benefits were at best moderate,[2] although evidence is perhaps best for nitazoxanide,[11] particularly in patients not infected with HIV.[3] Other treatments reported to have produced benefit in a few patients include hyperimmune bovine colostrum,[12–16] eflornithine,[17] rifabutin or rifaximin,[3] or normal immunoglobulin with high cryptosporidium antibody titres.[18]

Guidelines for the treatment of opportunistic infection in HIV-infected patients in the USA suggest that, in addition to optimising the HAART regimen, the addition of nitazoxanide[7,8] or alternatively paromomycin[7] therapy may be considered; azithromycin[8] is not recommended.

Clarithromycin and rifabutin may be useful for disease prophylaxis,[19] although the efficacy of clarithromycin has been questioned.[20] Guidelines for the prevention and treatment of opportunistic infection in HIV-infected patients in the USA[7,8] consider that the data on these drugs are insufficient to recommend their use for chemoprophylaxis.

1. Davies AP, Chalmers RM. Cryptosporidiosis. *BMJ* 2009; 339: 963–7. Also available at: http://www.bmj.com/cgi/section_pdf/339/oct19_1/b4168.pdf (accessed 06/07/10)
2. Chen X-M, *et al.* Cryptosporidiosis. *N Engl J Med* 2002; 346: 1723–31.
3. Cabada MM, White AC. Treatment of cryptosporidiosis: do we know what we think we know? *Curr Opin Infect Dis* 2010; 23: 494–9.
4. Cook DJ, *et al.* Somatostatin treatment for cryptosporidial diarrhea in a patient with the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988; 108: 708–9.
5. Clotet B, *et al.* Efficacy of the somatostatin analogue (SMS-201-995), Sandostatin, for cryptosporidial diarrhoea in patients with AIDS. *AIDS* 1989; 3: 857–8.
6. Cello JP, *et al.* Effect of octreotide on refractory AIDS-associated diarrhea: a prospective, multicenter clinical trial. *Ann Intern Med* 1991; 115: 705–10.
7. 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)
8. CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR* 2009; 58 (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 05/08/10)
9. Vargas SL, *et al.* Azithromycin for treatment of severe Cryptosporidium diarrhea in two children with cancer. *J Pediatr* 1993; 123: 154–6.
10. Bessette RE, Amsden GW. Treatment of non-HIV cryptosporidial diarrhea with azithromycin. *Ann Pharmacother* 1995; 29: 991–3.
11. Abubakar II, *et al.* Prevention and treatment of cryptosporidiosis in immunocompromised patients. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley, 2007 (accessed 09/07/08)
12. Tzipori S, *et al.* Remission of diarrhoea due to cryptosporidiosis in an immunodeficient child treated with hyperimmune bovine colostrum. *BMJ* 1986; 293: 1276–7.
13. Tzipori S, *et al.* Chronic cryptosporidial diarrhoea and hyperimmune cow colostrum. *Lancet* 1987; ii: 344–5.
14. Nord J, *et al.* Treatment with bovine hyperimmune colostrum of cryptosporidial diarrhea in AIDS patients. *AIDS* 1990; 4: 581–4.
15. Shield J, *et al.* Bovine colostrum immunoglobulin concentrate for cryptosporidiosis in AIDS. *Arch Dis Child* 1993; 69: 451–3.
16. Greenberg PD, Cello JP. Treatment of severe diarrhea caused by Cryptosporidium parvum with oral bovine immunoglobulin concentrate in patients with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996; 13: 348–54.
17. Rolston KVI, *et al.* Intestinal cryptosporidiosis treated with eflornithine: a prospective study among patients with AIDS. *J Acquir Immune Defic Syndr* 1989; 2: 426–30.
18. Borowitz SM, Saulsbury FT. Treatment of chronic cryptosporidial infection with orally administered human serum immune globulin. *J Pediatr* 1991; 119: 593–5.
19. Holmberg SD, *et al.* Possible effectiveness of clarithromycin and rifabutin for cryptosporidiosis chemoprophylaxis in HIV disease. *JAMA* 1998; 279: 384–6.
20. Fichtenbaum CJ, *et al.* Rifabutin but not clarithromycin prevents cryptosporidiosis in persons with advanced HIV infection. *AIDS* 2000; 14: 2889–93.

Cyclosporiasis

An organism originally described as cyanobacterium-like or coccidian-like bodies, but now identified as the coccidian protozoan *Cyclospora cayetanensis*, has been reported to be a cause of diarrhoea in both immunocompromised and immunocompetent patients. Infection results from ingestion of spores or oocysts in contaminated food or water and can result in diarrhoea, nausea, vomiting, abdominal cramps, loss of appetite, and flu-like symptoms. In immunocompetent patients, infection may be asymptomatic or self-limiting while immunocompromised patients may develop severe or persistent symptoms. Prolonged *C. cayetanensis* infection has been associated with various extraintestinal complications including biliary disease, acalculous cholecystitis, Guillain-Barré syndrome, and reactive arthritis.

Successful treatment of cyclosporiasis has been reported with oral co-trimoxazole;[1–4] treatment is usually given for 7 to 10 days, but HIV-infected patients can relapse after treatment and higher doses[4] or long-term suppressive treatment may be required. Alternative treatments have not yet been found for those allergic to sulfonamides.[1,3] However, a small, randomised study[2] comparing co-trimoxazole and ciprofloxacin for treatment of and secondary prophylaxis for *Cyclospora* infection in HIV infected patients found ciprofloxacin to be moderately effective, but less active than co-trimoxazole. Successful use of nitazoxanide has also been reported.[5]

1. Hoge CW, *et al.* Placebo-controlled trial of co-trimoxazole for cyclospora infections among travellers and foreign residents in Nepal. *Lancet* 1995; 345: 691–3. Correction. *Ibid.*: 1060.
2. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; 132: 885–8.
3. Yazar S, *et al.* Human cyclosporiosis in Turkey. *World J Gastroenterol* 2004; 10: 1844–7.
4. Karanja RM, *et al.* Cyclosporiasis: an emerging public health concern around the world and in Africa. *Afr Health Sci* 2007; 7: 62–7.
5. Zimmer SM, *et al.* Efficacy of nitazoxanide for cyclosporiasis in patients with sulfa allergy. *Clin Infect Dis* 2007; 44: 466–7.

Gastro-enteritis

Although bacteria and viruses are responsible for many cases of infective diarrhoea, protozoal infections are also a cause of diarrhoea,[1,2] which can be severe (especially in immunocompromised patients, including those with AIDS). Patients with diarrhoea lasting for more than 7 days should be tested for protozoal parasites.[3] In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly.[3] Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2. Specific therapy with antiprotozoals may also be necessary to control enteric protozoal infections.

For the management of the protozoal infections that are generally associated with diarrhoea, see under Amoebiasis (p. 919.1), Balantidiasis (p. 920.3), *Blastocystis hominis* infections (p. 920.3), Cryptosporidiosis (above), Cyclosporiasis (above), Giardiasis (below), Isosporiasis (below), and Microsporidiosis (p. 924.1).

1. Goodgame RW. Diagnosis and treatment of gastrointestinal protozoal infections. *Curr Opin Infect Dis* 1996; 9: 346–52.
2. Okhuysen PC. Traveler's diarrhea due to intestinal protozoa. *Clin Infect Dis* 2001; 33: 110–14.
3. Thielman NM, Guerrant RL. Clinical practice. Acute infectious diarrhea. *N Engl J Med* 2004; 350: 38–47.

Giardiasis

Infection with *Giardia intestinalis* (*G. duodenalis*, *G. lamblia*; *Lamblia intestinalis*) is one of the commonest intestinal protozoal infections throughout the world, especially in areas with poor sanitation and unsafe water. Infection is acquired by oral ingestion of *Giardia* cysts, either from direct contact with infected animals or humans, or by ingestion of water and foodstuffs contaminated by the faeces of infected animals or humans.

Many infected people are asymptomatic and most infections are self-limited. However, asymptomatic people may still act as carriers. Symptomatic giardiasis is usually characterised by diarrhoea, fatigue, abdominal cramps, bloating, nausea, and weight loss. Symptoms usually improve in 2 to 6 weeks but some people have chronic symptoms. Malabsorption of fat, lactose, and vitamins A and B_{12}, and failure of children to thrive have been reported in those with chronic giardiasis.

Priority in the management of acute diarrhoea of any aetiology is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2.

One of the most effective antiprotozoal treatments is metronidazole or another nitroimidazole derivative such as tinidazole,[1–3] ornidazole, and secnidazole.[1] Nitazoxanide is also effective[4–6] and some consider it a drug of choice.[3] Other alternatives include furazolidone, and mepacrine.[1,3] Paromomycin has been suggested;[3] although it is less effective than other drugs, it is not absorbed systemically and may be a useful alternative in resistant infection and during pregnancy.[1] The benzimidazoles (albendazole and mebendazole) have been tried with mixed results, but they might be useful in the developing world where their broad antiparasitic effect would be an advantage,[1] and some suggest[7] that albendazole is comparable in efficacy to metronidazole. Treatment may sometimes need to be repeated, possibly due to resistance or relapse,[1] and drug combinations such as a nitroimidazole with mepacrine[1,8] have been reported to be of value in such cases.

1. Gardner TB, Hill DR. Treatment of giardiasis. *Clin Microbiol Rev* 2001; 14: 114–28.
2. Chandy E, McCarthy J. Evidence behind the WHO Guidelines, hospital care for children: what is the most appropriate treatment for giardiasis? *J Trop Pediatr* 2009; 55: 5–7.
3. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
4. Rossignol J-F, *et al.* Treatment of diarrhea caused by Giardia intestinalis and Entamoeba histolytica or E. dispar: a randomized, double-blind, placebo-controlled study of nitazoxanide. *J Infect Dis* 2001; 184: 381–4.
5. Abboud P, *et al.* Successful treatment of metronidazole- and albendazole-resistant giardiasis with nitazoxanide in a patient with acquired immunodeficiency syndrome. *Clin Infect Dis* 2001; 32: 1792–4.
6. Ortiz JJ, *et al.* Randomized clinical study of nitazoxanide compared to metronidazole in the treatment of symptomatic giardiasis in children from Northern Peru. *Aliment Pharmacol Ther* 2001; 15: 1409–15.
7. Solaymani-Mohammadi S, *et al.* A meta-analysis of the effectiveness of albendazole compared with metronidazole as treatments for infections with *Giardia duodenalis*. *PLoS Negl Trop Dis* 2010; 4: e682.
8. Nash TE, *et al.* Treatment of patients with refractory giardiasis. *Clin Infect Dis* 2001; 33: 22–8.

Infections in immunocompromised patients

Patients with a defective immune system are at particular risk of infection. Primary immune deficiency is rare, whereas secondary deficiency is more common: immunosuppressive therapy, cancer and its treatment, HIV infection, and splenectomy may all cause neutropenia and impaired humoral and cellular immunity in varying degrees. The risk of infection is linked to the duration and severity of neutropenia. Most protozoal infections present in a more severe form in immunocompromised patients than in immunocompetent patients. Those of particular concern in patients with HIV infection include Cryptosporidiosis (above), Isosporiasis (below), Leishmaniasis (p. 922.1), Microsporidiosis (p. 924.1), and Toxoplasmosis (p. 924.2).

Detailed guidelines for the treatment and prevention of opportunistic infections (including some protozoal infections) among HIV-infected adults, adolescents, and children have been developed in the USA.[1,2]

1. 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)
2. CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR* 2009; 58 (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 05/08/10)

Isosporiasis

Isosporiasis is a coccidian protozoal infection of the gastrointestinal tract caused by *Cystoisospora belli*, formerly

called *Isospora belli*. It has a worldwide distribution but occurs more frequently in tropical and subtropical regions. Oocysts are excreted in faeces and infection is acquired when sporulated oocysts are ingested.

In immunocompetent individuals the infection is usually mild and self-limiting but in immunocompromised patients, including those with AIDS, the infection can vary from a chronic and intermittent illness to a severe, life-threatening diarrhoeal disease.

Treatment is usually with co-trimoxazole for 10 days.[1-3] Immunocompromised patients may need higher doses and treatment for up to 3 to 4 weeks.[2,3] Ciprofloxacin may be an alternative in those unable to tolerate co-trimoxazole, although it is somewhat less effective.[1,2] Pyrimethamine has been used successfully in individual patients with sulfonamide sensitivity.[2] In acute diarrhoea of any aetiology the priority is to maintain hydration by prevention or treatment of fluid and electrolyte depletion, especially in infants and the elderly. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2.

HIV-infected patients with a CD4+ count below 200 cells/microlitre should receive long-term suppressive therapy (secondary **prophylaxis**) with co-trimoxazole. Pyrimethamine may be used in patients allergic to sulfonamides; ciprofloxacin may be given as an alternative.[2] Secondary prophylaxis may be stopped in those patients taking effective antiretroviral therapy who have a CD4+ count above 200 cells/microlitre for at least 6 months.[2]

1. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; 132: 885–8.
2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://aidsinfo.nih.gov/contentfiles/adult_oi.pdf (accessed 23/08/13)
3. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Leishmaniasis

Leishmaniasis[1,2] is caused by parasitic protozoa of the genus *Leishmania*; the species involved depends on the geographical distribution. It occurs throughout Africa, the Middle East, Central Asia, and the Mediterranean (Old World leishmaniasis), and throughout Central and South America (New World leishmaniasis). In endemic areas there is generally a reservoir of disease in a mammalian host, often dogs or rodents. The usual vectors are sandflies of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World. Some species of *Leishmania* may also be transmitted by blood transfusions or contaminated needles; congenital transmission has been reported.

Leishmaniasis ranges from self-limiting, localised, cutaneous ulcers to widely disseminated progressive disease with involvement of the reticuloendothelial system, and can be categorised as:

- cutaneous (below)
- mucocutaneous (mucosal) (p. 923.1)

or

- visceral (p. 923.1)

Incubation periods can be prolonged, with clinical features not appearing until several months or even years after the primary infection.

Leishmaniasis has also emerged as an opportunistic infection in immunocompromised patients (including HIV and AIDS), in whom it is particularly difficult to treat. For further information see also p. 923.3. The most common clinical presentation of leishmaniasis in persons with AIDS is visceral disease, but the distribution varies geographically; in Europe visceral disease has been reported in 95% of cases, while in Brazil, mucocutaneous (43%) and cutaneous (20%) are common. Clinical manifestations in patients with AIDS may be atypical and severe, and relapse after treatment is common. Since the introduction of HAART the incidence of leishmaniasis has decreased substantially in developed countries, but co-infection is a growing problem in Asia and Africa.

In endemic areas an integrated approach to controlling leishmaniasis involves case detection and treatment of patients, vector and animal reservoir control, environmental management to reduce suitable vector habitats, and personal protection against sandfly bites including the use of insect repellents and bednets. Strategies aimed at controlling malaria are believed to have reduced leishmaniasis transmission dramatically.

1. Murray HW, *et al.* Advances in leishmaniasis. *Lancet* 2005; 366: 1561–77.
2. Roberts MTM. Current understandings on the immunology of leishmaniasis and recent developments in prevention and treatment. *Br Med Bull* 2005; 75-76: 115–30.

Cutaneous leishmaniasis. Cutaneous leishmaniasis is caused by various species of *Leishmania*. Old World disease is normally caused by *L. tropica*, *L. major*, or *L. aethiopica*, although cutaneous lesions due to *L. infantum* and *L. donovani* have been reported. New World cutaneous leishmaniasis (American cutaneous leishmaniasis) is caused by many species and subspecies of *Leishmania* including *L. braziliensis*, *L. mexicana*, *L. panamensis*, and *L. peruviana*. Worldwide, about 90% of cases occur in Algeria, Pakistan, Saudi Arabia, Syria, Afghanistan, Brazil, and Peru. In general, New World forms tend to be more severe and longer lasting than Old World forms.

Cutaneous leishmaniasis has been categorised into different clinical forms:

- *localised* disease is confined to the skin and lesions are mainly on exposed parts of the body. The disease ranges from single, self-healing lesions which are troublesome and unsightly but not a threat to life, to multiple, deep, and destructive ulcers which cause considerable disfigurement and disability. A 'classical' lesion starts as a nodule at the site of inoculation. A crust develops centrally which may fall away exposing an ulcer which heals gradually. Satellite nodules at the edge of the lesion are common
- *diffuse* cutaneous leishmaniasis occurs occasionally after infection with *L. aethiopica* or members of the *L. mexicana* complex and involves dissemination of the disease from the original site of infection to distant skin sites, typically the face and exterior surfaces of the limbs. The lesions resemble lepromatous leprosy, do not heal spontaneously, and are resistant to treatment
- *leishmaniasis recidivans* is a lupoid or tuberculoid form caused by infection with *L. tropica*. This chronic disease often occurs as slowly progressive, destructive and disfiguring lesions on the face which are very resistant to most forms of therapy

There is no consensus on the optimum **treatment** for cutaneous leishmaniasis[1] and a systematic review[2] on the treatment of Old World cutaneous leishmaniasis found 49 randomised controlled studies covering at least 19 different treatments. Current methods include physical interventions, topical ointments, local injection, and systemic anti-protozoals;[3] vaccines containing *Leishmania* spp. are under investigation, see p. 2397.2. The decision to treat depends upon the site and extent of the lesions and the likelihood of dissemination. Small lesions, particularly in Old World cutaneous leishmaniasis, may be left untreated if they are not troublesome to the patient; most lesions heal spontaneously within 2 to 15 months depending on the infecting species. The aim of treatment is to accelerate cure, reduce scarring, and prevent parasitic dissemination or relapse. Treatment is usually given to those patients with persistent lesions (6 months or more), lesions located over joints or on the face, or multiple or large lesions. Systemic therapy should be given to those with large and disfiguring lesions and those caused by *L. braziliensis* or other New World *Leishmania* species associated with mucocutaneous disease. Healing occurs slowly and may be incomplete at the end of a treatment course; patients who fail to respond after the initial course may be given a second or third treatment course of the same drug or treatment with an alternative drug. Drugs mainly used for the treatment of cutaneous leishmaniasis include:[1,2,4]

- intralesional, intramuscular, or intravenous pentavalent antimonials (meglumine antimonate, sodium stibogluconate)
- oral azoles
- topical paromomycin
- oral miltefosine
- intramuscular pentamidine

Old World cutaneous leishmaniasis. The pentavalent antimonials have been widely used and are the current mainstays of systemic treatment. Lesions at exposed sites that are small and few in number have been successfully treated with intralesional pentavalent antimonials.[3,5,6] Oral azole antifungals have been investigated for potential use in cutaneous leishmaniasis. Ketoconazole given for 4 to 6 weeks has been reported to be effective in about 70% of patients with *L. major* infections, but is not effective against infections caused by *L. tropica* and *L. aethiopica*.[7,8] Itraconazole has been found to be effective[9,10] and a systematic review[2] reported that for *L. tropica* infections there was reasonable evidence that a 6-week itraconazole regimen was more effective than placebo. Similarly a 6-week course of fluconazole was more effective than placebo for infections caused by *L. major*.[11] Conventional amphotericin B is an effective alternative, but has been associated with substantial toxicity and there is little experience with liposomal amphotericin B. The use of oral miltefosine is being investigated[1] and there is a case report of successful treatment in a patient with infection caused by *L. major*.[12] A small study[13] in Iran found oral miltefosine to be at least as good as intramuscular meglumine antimonate for the treatment of infections caused by *L. major*; another retrospective, observational study[14] also reported successful treatment with oral miltefosine of *L. major* infection acquired in northern Afghanistan. Topical paromomycin has been studied with variable results;[3,15-18] the vehicle may affect benefit. A systematic review[2] reported that for *L. major* infections there was reasonable evidence that topical paromomycin (15%) with methylbenzethonium (12%) twice daily for 28 days was more effective than placebo. Oral nitazoxanide has also been tried.[19] Local cryotherapy or, alternatively, application of heat to bring the temperature of the lesion to about 40 degrees which may aid healing have been tried for both Old World[20] and New World leishmaniasis.[3] Some suggest a step-wise approach to treatment of Old World cutaneous leishmaniasis.[21] They propose that patients with single, small lesions of short duration (less than 6 months) may be treated with cryotherapy, while those with multiple, atypical, large or extensive lesions, recidivans-type lesions, and relapsed cases should be treated with a combination of systemic and topical treatments. Combination therapies found to be effective are topical imiquimod (5%) with either oral dapsone or oral itraconazole, and cryotherapy with oral itraconazole.[21]

New World cutaneous leishmaniasis. Disease caused by *L. mexicana* may be treated with a parenteral pentavalent antimonial for 10 days, while disease caused by other species is treated for 20 days.[1] (However, a systematic review,[22] while noting the poor quality of the evidence, failed to find a significant difference in cure rates of *L. braziliensis* or *L. panamensis* infections when treated for 10 versus 20 days with parenteral antimonials.) In regions where the risk for mucosal disease is very low, topical treatment with paromomycin sulfate 15% plus methylbenzethonium chloride 12% has produced promising responses;[23,24] but in Columbia, the addition of topical paromomycin did not augment the clinical response to a short course of treatment with parenteral meglumine antimonate.[25] The addition of topical imiquimod to a standard treatment regimen with parenteral meglumine antimonate accelerated healing of lesions and decreased scar prominence in patients who had failed an initial course of antimony therapy[26] and in those with newly diagnosed disease.[27] Patients treated only with imiquimod cream all relapsed after treatment was stopped.[27] Results for the use of oral miltefosine have varied. A placebo-controlled study[28] found oral miltefosine to be effective (91%) in Columbia but much less effective in Guatemala (53%). Another study[29] in Bolivia reported that cure rates with miltefosine (88%) were similar to those with an intramuscular pentavalent antimonial (94%) in the treatment of infection caused by *L. braziliensis*. The authors concluded that oral miltefosine was more effective for *L. braziliensis* in Bolivia than for *L. braziliensis* in Guatemala. A small study[30] in Venezuela reported good initial cure rates with oral miltefosine given daily for between 75 and 218 days in patients with diffuse cutaneous leishmaniasis; however, most patients developed new lesions after treatment was stopped. Another small study[31] in Brazil reported that high-dose oral fluconazole, given daily for a median duration of 6 weeks, was effective for infections caused by *L. braziliensis*. There is limited and sometimes inconsistent evidence of benefit from the use of oral allopurinol or oral pentoxifylline as an adjuvant to parenteral antimonial therapy.[22]

Among the **non-specific therapies** tried in cutaneous leishmaniasis, topical application of the nitric oxide donor *S*-nitroso-*N*-acetylpenicillamine (SNAP)[32] and intralesional injection of hypertonic sodium chloride solution[33] have produced beneficial responses. Immunomodulation using leishmania antigens mixed with BCG,[34] or interferon gamma,[35] has produced encouraging results.

1. Murray HW, *et al.* Advances in leishmaniasis. *Lancet* 2005; 366: 1561–77.
2. González U, *et al.* Interventions for Old World cutaneous leishmaniasis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 31/03/09).
3. Weina PJ, *et al.* Old world leishmaniasis: an emerging infection among deployed US military and civilian workers. *Clin Infect Dis* 2004; 39: 1674–80.
4. Roberts MTM. Current understandings on the immunology of leishmaniasis and recent developments in prevention and treatment. *Br Med Bull* 2005; 75-76: 115–30.
5. Alkhawajah AM, *et al.* Treatment of cutaneous leishmaniasis with antimony: intramuscular versus intralesional administration. *Ann Trop Med Parasitol* 1997; 91: 899–905.
6. Aste N, *et al.* Intralesional treatment of cutaneous leishmaniasis with meglumine antimoniate. *Br J Dermatol* 1998; 138: 370–1.
7. Ozgoztasi O, Baydar I. A randomized clinical trial of topical paromomycin versus oral ketoconazole for treating cutaneous leishmaniasis in Turkey. *Int J Dermatol* 1997; 36: 61–3.
8. Weinrauch L, *et al.* Ketoconazole in cutaneous leishmaniasis. *Br J Dermatol* 1987; 117: 666–7.
9. Albanese G, *et al.* Cutaneous leishmaniasis: treatment with itraconazole. *Arch Dermatol* 1989; 125: 1540–2.
10. Dogra J, Saxena VN. Itraconazole and leishmaniasis: a randomised double-blind trial in cutaneous disease. *Int J Parasitol* 1996; 26: 1413–15.
11. Alrajhi AA, *et al.* Fluconazole for the treatment of cutaneous leishmaniasis caused by Leishmania major. *N Engl J Med* 2002; 346: 891–5.
12. Stojkovic M, *et al.* First case of typical Old World cutaneous leishmaniasis treated with miltefosine. *Int J Dermatol* 2007; 46: 385–7.
13. Mohebali M, *et al.* Comparison of miltefosine and meglumine antimoniate for the treatment of zoonotic cutaneous leishmaniasis (ZCL) by a randomized clinical trial in Iran. *Acta Trop* 2007; 103: 33–40.
14. van Thiel PP, *et al.* Miltefosine treatment of Leishmania major infection: an observational study involving Dutch military personnel returning from northern Afghanistan. *Clin Infect Dis* 2010; 50: 80–3.

15. 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.
16. 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.
17. 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.
18. 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.
19. Gurgen J, *et al.* Nitazoxanide in the treatment of chronic cutaneous leishmaniasis resistant to traditional sodium stibogluconate. *J Am Acad Dermatol* 2011; 64: 202–3.
20. Navin TR, *et al.* Placebo-controlled clinical trial of meglumine antimonate (Glucantime) vs localized controlled heat in the treatment of cutaneous leishmaniasis in Guatemala. *Am J Trop Med Hyg* 1990; 42: 43–50.
21. Al-Mutairi N, *et al.* Treatment of Old World cutaneous leishmaniasis with dapsone, itraconazole, cryotherapy, and imiquimod, alone and in combination. *Int J Dermatol* 2009; 48: 862–9.
22. González U, *et al.* Interventions for American cutaneous and mucocutaneous leishmaniasis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 01/07/09).
23. 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.
24. 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.
25. 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.
26. 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: 1395–403.
27. 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.
28. Soto J, *et al.* Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis* 2004; 38: 1266–72.
29. Soto J, *et al.* Efficacy of miltefosine for Bolivian cutaneous leishmaniasis. *Am J Trop Med Hyg* 2008; 78: 210–1.
30. Zerpa O, *et al.* Diffuse cutaneous leishmaniasis responds to miltefosine but then relapses. *Br J Dermatol* 2007; 156: 1328–35.
31. Sousa AQ, *et al.* High-dose oral fluconazole therapy effective for cutaneous leishmaniasis due to Leishmania (Vianna) braziliensis. *Clin Infect Dis* 2011; 53: 693–5.
32. López-Jaramillo P, *et al.* Treatment of cutaneous leishmaniasis with nitric-oxide donor. *Lancet* 1998; 351: 1176–7.
33. Sharquie KE. A new intralesional therapy of cutaneous leishmaniasis with hypertonic sodium chloride solution. *J Dermatol* 1995; 22: 732–7.
34. Sharifi I, *et al.* Randomised vaccine trial of single dose of killed Leishmania major plus BCG against anthroponotic cutaneous leishmaniasis in Bam, Iran. *Lancet* 1998; 351: 1540–3.
35. 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.

Mucocutaneous leishmaniasis. Mucocutaneous leishmaniasis of the New World (espundia) is most commonly caused by *L. braziliensis* with about 90% of cases occurring in Brazil, Bolivia, and Peru. In mucocutaneous leishmaniasis the primary lesions do not heal spontaneously. Metastatic spread to the mucosa may occur during the presence of the primary lesion or up to 30 years later. The nasal mucosa is always affected. Ulceration and erosion progressively destroy the soft tissue and cartilage of the oronasal/pharyngeal cavity. Mutilation is severe and secondary bacterial infection is frequent and can be fatal.

The most commonly used drugs for the treatment of mucocutaneous leishmaniasis are:[1-3]

- intramuscular or intravenous pentavalent antimonials (meglumine antimonate, sodium stibogluconate)
- intravenous amphotericin B (conventional and liposomal)

Mucocutaneous leishmaniasis responds poorly to treatment and relapses are common. Initial treatment with pentavalent antimony for 28 days usually results in a cure in 75% of mild cases.[1] Failure to respond is an indication to use amphotericin B[1] or pentamidine, but toxicity limits the use of the latter. A non-randomised study[4] in 72 Bolivian patients given oral miltefosine daily for 28 days reported a cure rate of 83% in those who had mild disease (affecting nasal skin and nasal mucosa) and 58% in those with more extensive disease (involving the palate, pharynx, and larynx); treatment was at least as effective as a course of parenteral amphotericin B. Mucosal disease in Old World leishmaniasis is much less common than visceral or cutaneous forms, but treatment with antimony compounds or ketoconazole has been described.[5]

1. Murray HW, *et al.* Advances in leishmaniasis. *Lancet* 2005; 366: 1561–77.
2. Roberts MTM. Current understandings on the immunology of leishmaniasis and recent developments in prevention and treatment. *Br Med Bull* 2005; 75–76: 115–30.
3. Amato VS, *et al.* Treatment of mucosal leishmaniasis in Latin America: systematic review. *Am J Trop Med Hyg* 2007; 77: 266–74.
4. Soto J, *et al.* Treatment of Bolivian mucosal leishmaniasis with miltefosine. *Clin Infect Dis* 2007; 44: 350–6.
5. El-Hassan AM, Zijlstra EE. Leishmaniasis in Sudan 2: Mucosal leishmaniasis. *Trans R Soc Trop Med Hyg* 2001; 95 (suppl 1): S19–S26.

Visceral leishmaniasis. Visceral leishmaniasis[1-4] is caused by *L. donovani* in the Indian subcontinent, Asia, and Africa and by *L. infantum* or *L. chagasi* elsewhere in the New and Old World. The majority of cases occur in Bangladesh, Brazil, Ethiopia, India, Nepal, and Sudan. The incubation period typically varies from 3 to 8 months, and many infections result in sub-clinical or self-limiting disease. Fever, malaise, shivering or chills, weight loss, anorexia, and discomfort in the left hypochondrium are common; there is often non-tender splenomegaly with or without hepatomegaly, wasting, pallor of mucous membranes, anaemia, leucopenia, and lymphadenopathy. Continued deterioration can lead to potentially fatal secondary infection. Darkening of the skin of the face, hands, feet, and abdomen (kala-azar = black sickness) is uncommon and has only been described in patients from the Indian subcontinent. Rare complications can include severe acute haemolytic anaemia, acute renal damage, and severe mucosal haemorrhage.

A small percentage of patients in India and about 50% of those in the Sudan develop post-kala-azar dermal leishmaniasis after recovery from visceral leishmaniasis caused by *L. donovani* and such patients represent a human reservoir for the disease. Longer treatment courses are needed in Indian post-kala-azar dermal leishmaniasis.

The most commonly used drugs for the treatment of visceral leishmaniasis are:[1-3]

- intramuscular or intravenous pentavalent antimonials (meglumine antimonate, sodium stibogluconate)
- intravenous amphotericin B (conventional, liposomal and lipid complex formulations)
- intramuscular paromomycin
- oral miltefosine
- intramuscular or intravenous pentamidine

The pentavalent antimonials, given daily for 28 days, are the traditional first-line drugs for the treatment of visceral leishmaniasis.[1-4] Patients relapsing after the initial course of treatment may be given a further course, or treated with an alternative drug. There is growing evidence that responsiveness to the antimonials is declining and they are no longer effective in some parts of India.[5]

The use of pentavalent antimonials has also declined in Europe, the USA, and other developed countries where treatment with liposomal amphotericin B is preferred.[1,2,4] The conventional formulation of amphotericin B is also highly effective,[6] but lipid formulations of amphotericin B are better tolerated than conventional amphotericin B, and are likely to be preferred when the toxicity and duration of therapy with conventional forms would compromise patient compliance.

Intramuscular paromomycin has been used alone[7-9] or with a pentavalent antimonial[3,10] and could be an effective alternative for pentavalent antimonials or amphotericin B. Combination treatment with a single dose of liposomal amphotericin B followed by 10 days of paromomycin was found to have a cure rate of 97.5% in patients treated in Bihar, India, where visceral leishmaniasis is more difficult to treat. The combination of paromomycin for 10 days plus oral miltefosine (see below) for 10 days was found to have a cure rate of 98.7%.[11]

Miltefosine is the first oral preparation shown to be effective against Indian visceral leishmaniasis,[12-14] including infections in children[15,16] and those previously treated with pentavalent antimonials.[14] Combination treatment with a single dose of liposomal amphotericin B followed by 7 to 14 days of miltefosine was found to be effective in more than 95% of patients treated in Bihar.[11,17] Longer treatment courses with miltefosine have also been successfully used in the treatment of post-kala-azar dermal leishmaniasis in Bihar.[18]

Pentamidine has been used as a second-line drug but its usefulness as alternative first-line therapy is doubtful[19] given its toxicity, increasing failure rates, and slow disease response. It has been suggested as an alternative for long-term secondary prophylaxis in patients with HIV infection.[20]

Sitamaquine is an orally active 8-aminoquinoline analogue that is under investigation.[3,4] Oral azoles (ketoconazole, itraconazole, and fluconazole) and allopurinol have weak activity against *Leishmania* but have not been found to be effective when used as single-drug therapy.[3] Another line of investigation has been to boost the immune response to the parasite by adding interferon gamma to conventional treatment, although results have been variable.[21-24]

1. Murray HW, *et al.* Advances in leishmaniasis. *Lancet* 2005; 366: 1561–77.
2. Roberts MTM. Current understandings on the immunology of leishmaniasis and recent developments in prevention and treatment. *Br Med Bull* 2005; 75–76: 115–30.
3. Guerin PJ, *et al.* Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. *Lancet Infect Dis* 2002; 2: 494–501.
4. Chappuis F, *et al.* Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? *Nat Rev Microbiol* 2007; 5: 873–82.
5. Sundar S, *et al.* Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. *Clin Infect Dis* 2000; 31: 1104–7.
6. Sundar S, *et al.* Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. *Clin Infect Dis* 2004; 38: 377–83.
7. 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.
8. Thakur CP, *et al.* Treatment of visceral leishmaniasis with injectable paromomycin (aminosidine): an open-label randomized phase-II clinical study. *Trans R Soc Trop Med Hyg* 2000; 94: 432–3.
9. Sundar S, *et al.* Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med* 2007; 356: 2571–81.
10. 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.
11. Sundar S, *et al.* Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011; 377: 477–86.
12. Jha TK, *et al.* Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Engl J Med* 1999; 341: 1795–1800.
13. Sundar S, *et al.* Short-course of oral miltefosine for treatment of visceral leishmaniasis. *Clin Infect Dis* 2001; 31: 1110–13.
14. Sundar S, *et al.* Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med* 2002; 347: 1739–46.
15. Bhattacharya SK, *et al.* Efficacy and tolerability of miltefosine for childhood visceral leishmaniasis in India. *Clin Infect Dis* 2004; 38: 217–21.
16. Paiumbo E. Oral miltefosine treatment in children with visceral leishmaniasis: a brief review. *Braz J Infect Dis* 2008; 12: 2–4.
17. Sundar S, *et al.* New treatment approach in Indian visceral leishmaniasis: single-dose liposomal amphotericin B followed by short-course oral miltefosine. *Clin Infect Dis* 2008; 47: 1000–6.
18. Ramesh V, *et al.* Miltefosine as an effective choice in the treatment of post-kala-azar dermal leishmaniasis. *Br J Dermatol* 2011; 165: 411–14.
19. Sundar S. Drug resistance in Indian visceral leishmaniasis. *Trop Med Int Health* 2001; 6: 849–54.
20. 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)
21. Badaro R, *et al.* Treatment of visceral leishmaniasis with pentavalent antimony and interferon gamma. *N Engl J Med* 1990; 322: 16–21.
22. Sundar S, *et al.* Successful treatment of refractory visceral leishmaniasis in India using antimony plus interferon- γ. *J Infect Dis* 1994; 170: 659–62.
23. Sundar S, *et al.* Immunochemotherapy for a systemic intracellular infection: accelerated response using interferon-γ in visceral leishmaniasis. *J Infect Dis* 1995; 171: 992–6.
24. Sundar S, *et al.* Response to interferon- γ plus pentavalent antimony in Indian visceral leishmaniasis. *J Infect Dis* 1997; 176: 1117–19.

Treatment of leishmaniasis in HIV co-infected patients. For HIV-infected patients with *visceral leishmaniasis*, the efficacy of conventional, liposomal, and lipid complex formulations of amphotericin B appears to be similar to that of the pentavalent antimonials, however, liposomal amphotericin B is regarded by many as the drug of choice.[1] Alternative treatments include miltefosine and paromomycin.[1] A study[2] in Ethiopia found miltefosine to be safer but less effective than sodium stibogluconate in HIV co-infected patients. Oral miltefosine was given to 39 patients with both leishmaniasis and HIV who were resistant to, or had repeatedly relapsed after, treatment with other drugs (usually amphotericin B). Initial parasitological cure was achieved in 16 patients (41%), and 9 patients (23%) had initial improvement in both parasitological and clinical status. A similar cure and improvement rate was achieved in patients who were re-treated with additional courses of miltefosine.[3] For HIV-infected patients with *cutaneous, mucocutaneous, disseminated cutaneous leishmaniasis*, and localised cutaneous disease caused by *L. braziliensis*, US guidelines[1] recommend first-line parenteral treatment with liposomal amphotericin B or a pentavalent antimonial. Alternative drugs for cutaneous leishmaniasis are miltefosine, topical paromomycin, intralesional pentavalent antimonials, and local heat therapy.[1] Patients who fail to respond to initial therapy or have a relapse after initial treatment may be given a repeat course of the initial regimen, or one of the recommended alternatives for initial therapy.[1]

Relapse after treatment is common, therefore US guidelines[1] recommend secondary prophylaxis with an effective antileishmanial drug (given at least every 2 to 4 weeks), particularly for patients with visceral leishmaniasis and CD4+ count less than 200 cells/microlitre. US guidelines note that there are insufficient data to provide a recommendation as to when secondary prophylaxis can be stopped, but that it might be considered after a sustained (more than 3 to 6 months) increase in the CD4+ count to levels more than 200 to 350 cells/microlitre after starting treatment with HAART.[1]

1. 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)
2. Ritmeijer K, *et al.* A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis* 2006; 43: 357–64.
3. Sindermann H, *et al.* Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis* 2004; 39: 1520–3.

Malaria

For a discussion of malaria, its prophylaxis and treatment, see p. 644.1.

Microsporidiosis

Microsporidia are obligate intracellular spore-forming protozoal parasites. They were mainly regarded as a cause of disease in nonhuman species but some genera, including *Brachiola, Encephalitozoon, Enterocytozoon, Microsporidium, Nosema, Pleistophora, Trachipleistophora,* and *Vittaforma* spp., are now recognised as human pathogens. Transmission is believed to be mainly faeco-oral although inhalation and direct inoculation also occur. Infections usually occur only in immunocompromised patients and in particular those with AIDS and a CD4+ T lymphocyte count of less than 100 cells/microlitre. However, infections have also been reported in non-HIV-infected individuals including children, the elderly, and organ transplant recipients. Small bowel infection with *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* have been reported in AIDS patients as causes of chronic diarrhoea and weight loss. Other manifestations of microsporidiosis in AIDS include keratoconjunctivitis, respiratory-tract infections, renal and urinary-tract infections, encephalitis, peritonitis, cholangitis, granulomatous hepatitis, and disseminated myositis.

There is no established treatment[1-3] and supportive care should be given to maintain hydration and correct electrolyte loss. Oral rehydration therapy is discussed under Diarrhoea on p. 1808.2. In patients with AIDS the best treatment is improvement of immune function with HAART.[2,3] Beneficial responses have been reported with albendazole[4-8] and US guidelines for the treatment of opportunistic infections in HIV-infected patients recommend it for treatment of intestinal and disseminated infections caused by microsporidia other than *E. bieneusi* and *Vittaforma corneae*.[2,3] Itraconazole plus albendazole may be useful for disseminated disease.[2] There have also been reports of successful treatment of *E. bieneusi* with nitazoxanide[9] and fumagillin[10,11] (and its synthetic analogue TNP-470).[2]

Topical treatment of keratoconjunctivitis has been disappointing, although there are reports of individual patients responding to topical propamidine isetionate,[12] topical fumagillin,[13,14] oral albendazole,[15] oral albendazole plus topical fumagillin,[16] or oral itraconazole plus topical antibacterials.[17] US guidelines[2,3] recommend the use of topical fumagillin plus oral albendazole for eye infections. Treatment for these should be continued indefinitely in those with a CD4 + T lymphocyte count of less than 200 cells/microlitre, because of the risk of recurrence or relapse if treatment is stopped; treatment may be stopped in those with a relatively competent immune system (CD4+ T lymphocyte count greater than 200 cells/microlitre) once the eye infection has resolved.[2]

1. Conteas CN, *et al.* Therapy for human gastrointestinal microsporidiosis. *Am J Trop Med Hyg* 2000; 63: 121–7.
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. CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR* 2009; 58 (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 05/08/10)
4. Blanshard C, *et al.* Treatment of intestinal microsporidiosis with albendazole in patients with AIDS. *AIDS* 1992; 6: 311–13.
5. Dieterich DT, *et al.* Treatment with albendazole for intestinal disease due to *Enterocytozoon bieneusi* in patients with AIDS. *J Infect Dis* 1994; 169: 178–82.
6. Franzen C, *et al.* Intestinal microsporidiosis with *Septata intestinalis* in a patient with AIDS—response to albendazole. *J Infect* 1995; 31: 237–9.
7. Dore GJ, *et al.* Disseminated microsporidiosis due to *Septata intestinalis* in nine patients infected with the human immunodeficiency virus: response to therapy with albendazole. *Clin Infect Dis* 1995; 21: 70–6.
8. Molina J-M, *et al.* Albendazole for treatment and prophylaxis of microsporidiosis due to *Encephalitozoon intestinalis* in patients with AIDS: a randomized double-blind controlled trial. *J Infect Dis* 1998; 177: 1373–7.
9. Bicart-See A, *et al.* Successful treatment with nitazoxanide of *Enterocytozoon bieneusi* microsporidiosis in a patient with AIDS. *Antimicrob Agents Chemother* 2000; 44: 167–8.
10. Molina J-M, *et al.* Fumagillin treatment of intestinal microsporidiosis. *N Engl J Med* 2002; 346: 1963–9.
11. Champion L, *et al.* Fumagillin for treatment of intestinal microsporidiosis in renal transplant recipients. *Am J Transplant* 2010; 10: 1925–30.
12. Metcalfe TW, *et al.* Microsporidial keratoconjunctivitis in a patient with AIDS. *Br J Ophthalmol* 1992; 76: 177–8.
13. Diesenhouse MC, *et al.* Treatment of microsporidial keratoconjunctivitis with topical fumagillin. *Am J Ophthalmol* 1993; 115: 293–8.
14. Garvey MJ, *et al.* Topical fumagillin in the treatment of microsporidial keratoconjunctivitis in AIDS. *Ann Pharmacother* 1995; 29: 872–4.
15. Silverstein BE, *et al.* Microsporidial keratoconjunctivitis in a patient without human immunodeficiency virus infection. *Am J Ophthalmol* 1997; 124: 395–6.
16. Theng J, *et al.* Microsporidial keratoconjunctivitis in a healthy contact lens wearer without human immunodeficiency virus infection. *Ophthalmology* 2001; 108: 976–8.
17. Yee RW, *et al.* Resolution of microsporidial epithelial keratopathy in a patient with AIDS. *Ophthalmology* 1991; 98: 196–201.

Pneumocystis pneumonia

Although *Pneumocystis jirovecii* was formerly classified as a protozoan, it is now accepted to be a fungus. For the management of pneumocystis pneumonia, see p. 567.2.

Toxoplasmosis

Toxoplasmosis[1] is a zoonosis with a worldwide distribution caused by the protozoan *Toxoplasma gondii*, an intestinal parasite of cats for which other mammals may act as intermediate hosts. In man, infection is usually acquired through accidental swallowing of oocysts after contact with infected cat faeces or contaminated soil, from eating raw or undercooked meat from infected animals, or from drinking contaminated water. Congenital transmission may also occur if infection is acquired for the first time during pregnancy.

Toxoplasma infection is common; in immunocompetent individuals it is usually asymptomatic and if symptoms (such as fever, headache, malaise, and lymphadenopathy) do occur they are usually self-limiting, although latent (cystic) disease may become reactivated throughout the host's lifetime. Very rarely myocarditis or encephalitis may occur. Immunocompromised patients may develop serious complications such as encephalitis, chorioretinitis, myocarditis, and pneumonitis. Toxoplasmic encephalitis is the most common presentation in patients with AIDS.

Primary infection during early pregnancy is serious because of the risk of transplacental transmission which may result in fetal death or congenital toxoplasmosis. Primary infection during later pregnancy can also result in congenital infection, although this often only becomes symptomatic later in life. Rarely, reactivation of latent infection in chronically infected severely immunocompromised women has resulted in congenital transmission.[2]

The sequelae in live-born infants with signs of infection are generally severe and include a potentially fatal syndrome in which hydrocephalus, hepatosplenomegaly with jaundice, mental retardation, and chorioretinitis may occur. Congenital disease that becomes clinically evident later in life is usually less severe, but often results in ocular or neurological impairment. Infection in the pregnant woman is usually asymptomatic and antenatal screening programmes have been set up in some countries for the diagnosis of acute infections during pregnancy. However, the value and practicality of such schemes has been debated.[2-7]

Ocular toxoplasmosis causes chorioretinitis and is often a result of congenital infection; patients may be asymptomatic until later in life.

Treatment. Toxoplasmosis in immunocompetent patients is not usually treated unless symptoms are severe. Currently there is no drug active against the cystic form, so any treatment is directed against the acute forms of the disease. Active toxoplasmosis in immunocompromised patients requires prompt treatment.

- Toxoplasmosis is normally treated with a regimen of pyrimethamine plus sulfadiazine;[8,9] folinic acid is also a standard component of regimens including pyrimethamine to counteract associated megaloblastic anaemia.
- Clindamycin plus pyrimethamine and folinic acid has been used as an alternative in patients unable to take the sulfonamide.[8,9]
- Other regimens have been studied and have been found to have activity in toxoplasmic encephalitis, notably co-trimoxazole, atovaquone plus pyrimethamine and folinic acid, or atovaquone plus sulfadiazine, or azithromycin plus pyrimethamine and folinic acid. Atovaquone has also been given alone in patients unable to tolerate pyrimethamine or sulfadiazine.[8]
- Severely ill patients needing parenteral therapy have been given intravenous co-trimoxazole or clindamycin with oral pyrimethamine.[8]

Adjunctive corticosteroids may be given occasionally for treatment of a mass effect associated with focal lesions or oedema, but should be stopped as soon as possible because of their immunosuppressant effect. Anticonvulsants should be given to patients with a history of seizures.[8,9] Acute treatment is ideally continued for 6 weeks, or for longer if disease is extensive or response is incomplete.[8,9]

Immunocompromised patients who have successfully completed a 6-week course of acute therapy should be given chronic *maintenance* therapy, which should ideally be with pyrimethamine plus sulfadiazine and folinic acid,[8,9] but alternatives are pyrimethamine plus clindamycin and folinic acid, co-trimoxazole, or atovaquone, with or without sulfadiazine or pyrimethamine and folinic acid.[8] Chronic maintenance therapy should be lifelong unless immune reconstitution occurs because of antiretroviral therapy, in which case consideration may be given to stopping prophylaxis. It should, however, be restarted if the CD4+ count falls to below 200 cells/microlitre.[8]

The management of maternal and fetal infection may vary considerably from country to country and even within a country.[1] A systematic review[10] of the treatment of women during **pregnancy** involved small studies with variations in period of gestation, duration of follow-up, and other aspects of methodology, making comparison of data problematical; consequently the evidence was inconclusive as to whether treatment was effective in preventing fetal infection or overt neonatal disease. A meta-analysis of individual patients' treatment data reported only a weak association between early treatment and reduced risk of congenital toxoplasmosis. Furthermore, it found no evidence that prenatal treatment significantly reduced the risk of clinical signs and symptoms in infected newborn infants.[11]

If treatment is given, pyrimethamine should not be used to treat primary toxoplasmosis during the first and early second trimester of pregnancy. Spiramycin has been used throughout the first 18 weeks of pregnancy but, although it reduces the risk of congenital transmission, it does not readily penetrate the cerebrospinal space and does not prevent toxoplasmic encephalitis in immunocompromised women. After 14 to 18 weeks of gestation a pyrimethamine regimen with sulfadiazine may be given.[2] Some countries advise that spiramycin be continued throughout the pregnancy, while others recommend changing to the pyrimethamine plus sulfadiazine regimen at 17 weeks of gestation.[1]

When there is evidence of placental or fetal infection acquired in late second or third trimester, treatment is usually with the pyrimethamine plus sulfadiazine regimen; some advise that pyrimethamine plus sulfadiazine treatment may be alternated with courses of spiramycin until term.[1]

In **neonates** with congenital toxoplasmosis, the preferred treatment is also a pyrimethamine plus sulfadiazine regimen.[9] Infants without HIV infection should be treated for 12 months. In infants with mild toxoplasmosis, some experts recommend alternating the pyrimethamine-sulfadiazine regimen with spiramycin on a monthly basis from months 7 to 12, in order to reduce the risk of bone marrow suppression. However, infants with HIV infection and moderate to severe toxoplasmosis should receive the full 12-month regimen of pyrimethamine-sulfadiazine.[9] Longer courses of treatment may be given in cases of extensive disease. A corticosteroid, usually dexamethasone or prednisolone, has been added in children with CNS involvement.[9]

In immunocompetent individuals, **ocular toxoplasmosis** is a self-limiting disease and requires no treatment, unless visual acuity is threatened or there is a large retinal lesion with marked vitritis.[12-14] A systematic review[15] found a lack of evidence to support routine treatment for acute toxoplasma retinochoroiditis in immunocompetent patients, but did find weak evidence to suggest that long-term treatment of patients with chronic recurrent disease may reduce recurrence. All immunocompromised patients should be treated and prolonged treatment is necessary to prevent recrudescence. The best drug regimen is unknown. The most commonly used regimens give pyrimethamine with sulfadiazine or clindamycin (which is concentrated in the choroid). Benefit has been reported from clindamycin with corticosteroids,[16] although corticosteroids should never be used alone since fulminant cases may occur. Spiramycin is not indicated for ocular toxoplasmosis.

Prophylaxis. Primary prophylaxis against *T. gondii* infection has been investigated in AIDS patients and recipients of organ transplants. In HIV-infected adults and adolescents who are seropositive for *Toxoplasma* and who have a CD4+ count of less than 100 cells/microlitre, primary prophylaxis against encephalitis should be given.[8] Primary prophylaxis should also be given to seropositive children with a CD4 percentage less than 15%.[9]

Co-trimoxazole, in regimens designed for pneumocystis pneumonia prophylaxis, was found to be effective and is therefore recommended.[8,9] Alternatively, a regimen using pyrimethamine plus dapsone, or perhaps atovaquone, with or without pyrimethamine, can also be considered.[8] A regimen involving pyrimethamine plus sulfadoxine has also been tried, with promising results.[17]

Toxoplasma-seronegative persons who are not receiving a pneumocystis prophylactic regimen known to be active against toxoplasmic encephalitis should be retested for *Toxoplasma* should their CD4+ count fall below 100 cells/microlitre and if they have seroconverted primary prophylaxis should be started.[8] Primary prophylaxis should be stopped in adult and adolescent patients whose CD4+ count rises in response to antiretroviral therapy to more than 200 cells/microlitre for 3 months or more. If the count subsequently falls to below 200 cells/microlitre it should be restarted.[8] Similarly, primary prophylaxis may be stopped in children whose CD4 percentage rises to above 15% and should be restarted if the CD4 percentage subsequently falls below 15%.[9]

1. Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet* 2004; 363: 1965–76.

2. Montoya JG, Remington JS. Management of Toxoplasma gondii infection during pregnancy. *Clin Infect Dis* 2008; **47**: 554–66.
3. Ambroise-Thomas P, *et al.* La prévention de la toxoplasmose congénitale en France. Évaluation des risques. Résultats et perspectives du dépistage anténatal et du suivi du nouveau-né. *Bull Acad Natl Med* 2001; **185**: 665–83.
4. Logar J, *et al.* Prevention of congenital toxoplasmosis in Slovenia by serological screening of pregnant women. *Scand J Infect Dis* 2002; **34**: 201–4.
5. Gilbert RE, Peckham CS. Congenital toxoplasmosis in the United Kingdom: to screen or not to screen? *J Med Screen* 2002; **9**: 135–41.
6. Pinard JA, *et al.* Maternal serologic screening for toxoplasmosis. *J Midwifery Womens Health* 2003; **48**: 308–16.
7. Ricci M, *et al.* Screening and prevention of congenital toxoplasmosis: an effectiveness study in a population with a high infection rate. *J Matern Fetal Neonatal Med* 2003; **14**: 398–403.
8. 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)
9. CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR* 2009; **58** (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 05/08/10)
10. Peyron F, *et al.* Treatments for toxoplasmosis in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 25/05/05).
11. Thiébaut R, *et al.* SYROCOT (Systematic Review on Congenital Toxoplasmosis) study group. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet* 2007; **369**: 115–22.
12. Rothova A. Ocular involvement in toxoplasmosis. *Br J Ophthalmol* 1993; **77**: 371–7.
13. Nussenblatt RB, Belfort R. Ocular toxoplasmosis: an old disease revisited. *JAMA* 1994; **271**: 304–7. Correction. *ibid.*; **272**: 356.
14. Hay J, Dutton GN. Toxoplasma and the eye. *BMJ* 1995; **310**: 1021–2.
15. Gilbert RE, *et al.* Antibiotics versus control for toxoplasma retinochoroiditis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 25/05/05).
16. Djurković-Djaković O, *et al.* Short-term effects of the clindamycin-steroid regimen in the treatment of ocular toxoplasmosis. *J Chemother* 1995; **7** (suppl 4): 199–201.
17. Schürmann D, *et al.* Twice-weekly pyrimethamine-sulfadoxine effectively prevents Pneumocystis carinii pneumonia and toxoplasmic encephalitis in patients with AIDS. *J Infect* 2001; **42**: 8–15.

Trichomoniasis

Trichomoniasis is caused by invasion of the genito-urinary tract with the protozoan *Trichomonas vaginalis*. Transmission is mainly sexual. Trichomoniasis is a common cause of vaginitis and vaginal discharge but infections vary in severity from asymptomatic (in up to 50% of cases) to an acute inflammatory vaginitis. Men are usually asymptomatic, although they may have urethritis. Asymptomatic infection in either sex should still be treated to prevent sexual transmission and symptomatic infection. *T. vaginalis* infection has been associated with HIV acquisition and adverse pregnancy outcomes, particularly premature rupture of the membranes, preterm delivery, and low birth-weight.

Guidelines for the **treatment** of trichomoniasis have been produced by an expert group in the UK,[1] by WHO,[2] and by the CDC in the USA.[3] Treatment is usually with a nitroimidazole such as metronidazole or tinidazole, often as a single oral dose of 2 g.[1-4] Alternative treatment regimens include standard oral doses of metronidazole or tinidazole given twice daily for 5 to 7 days.[1-3] Sexual partners should also be treated.[1-3] In HIV-infected women with trichomoniasis, there is evidence that metronidazole 500 mg orally given twice daily for 7 days is superior to a single 2-g oral dose; therefore, a multidose treatment regimen should be considered for HIV-infected women.[3]

Some strains of *T. vaginalis* have reduced susceptibility to nitroimidazoles[1-3] and patients who fail to respond to the first course of treatment may be re-treated with a repeat course of the initial regimen[1] or an alternative standard treatment.[2,3] If this fails and re-infection has been excluded patients may be given:

- a broad-spectrum antibacterial (such as erythromycin or amoxicillin) before re-treatment with metronidazole[1]
- oral metronidazole 400 mg three times daily with rectal metronidazole 1 g daily for 7 days or longer (zinc sulfate 1% vaginal douches or vaginal washes with 3% acetic acid may be added to the regimen)[1]
- high dose oral metronidazole[1,3] or tinidazole[3] (2 g) daily for 3 to 5 days
- high dose intravenous metronidazole[1]
- high dose oral tinidazole (2 g) twice daily for 2 weeks, with or without intravaginal tinidazole[1]
- a single dose of oral metronidazole plus intravaginal metronidazole applied at night, each for 3 to 7 days[2]

A patient with metronidazole- and tinidazole-resistant infection was successfully treated with paromomycin.[3] Vaginal preparations of metronidazole are only recommended for the treatment of refractory infections.[2] A trichomoniasis vaccine containing inactivated *Lactobacillus* spp. is available in some countries for the prophylaxis of recurrent vaginal trichomoniasis, see p. 2422.2.

Patients with hypersensitivity to nitroimidazoles can be managed by desensitisation with incremental doses of oral or intravenous metronidazole. Alternative topical therapies have been tried, but cure rates are low (less than 50%).[3,6]

1. Clinical Effectiveness Group, British Association of Sexual Health and HIV. United Kingdom National Guideline on the Management of Trichomonas vaginalis (2007). Available at: http://www.bashh.org/documents/87/87.pdf (accessed 17/07/08)
2. WHO. *Guidelines for the management of sexually transmitted infections.* Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 13/05/04)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]
4. Forna F, Gülmezoglu AM. Interventions for treating trichomoniasis in women. Available in The Cochrane Library; Issue 2. Chichester: John Wiley; 2003 (accessed 14/02/11).
5. Nyirjesy P, *et al.* Paromomycin for nitroimidazole-resistant trichomonosis. *Lancet* 1995; **346**: 1110.
6. Helms DJ, *et al.* Management of trichomonas vaginalis in women with suspected metronidazole hypersensitivity. *Am J Obstet Gynecol* 2008; **198**: 370.e1–7.

African trypanosomiasis

Human African trypanosomiasis (HAT or sleeping sickness)[1] is caused by subspecies of the protozoan *Trypanosoma brucei*, transmitted by the bite of infected tsetse flies (*Glossina* spp.). Infection can follow blood transfusion and congenital trypanosomiasis has also occurred. Infection does not appear to confer immunity.

Infection can be divided into the early, first, or haematolymphatic stage (infection of the bloodstream and lymph nodes), with bouts of fever, lymphadenopathy, pruritus, headache, and muscle and joint pain, and the late, second, or meningoencephalitic stage which starts when the parasite invades the CNS. Signs and symptoms include sleep disturbances, confusion, incoordination, psychiatric disorders, and eventual deterioration of consciousness. Without treatment the patient undergoes progressive neurological degeneration and death.

HAT takes two forms that are clinically distinct, depending on the parasite involved:

- *Trypanosoma brucei gambiense* (Gambian or West African sleeping sickness) occurs in west and central Africa and causes more than 90% of reported cases of HAT. It is a chronic infection and a person may be infected for months or years without major signs or symptoms of the disease; the disease stages are relatively distinct. When symptoms do appear, the patient is often in an advanced disease stage with CNS involvement
- *Trypanosoma brucei rhodesiense* (Rhodesian or East African sleeping sickness) occurs in eastern and southern Africa and causes less than 10% of reported cases of HAT. It is an acute infection with the first signs and symptoms appearing after a few weeks or months; disease stages are indistinct. The disease progresses rapidly and invades the CNS; if left untreated, it will usually lead to death in a matter of weeks or months

Although it has proven impractical to eliminate trypanosomiasis from endemic areas, the intensity of transmission can be reduced by active and passive case detection and treatment.[2] Vector control activities have had some success in controlling *T. b. rhodesiense* disease, but seem to be less effective and less widely applied for the control of *T.b. gambiense*.[3]

The **treatment** of HAT involves the use of 5 drugs depending on the form and stage of the disease:[1-6]

- intramuscular ***pentamidine*** is used for the first stage when caused by *T. b. gambiense*
- intravenous ***suramin*** is used for the first stage when caused by *T. b. rhodesiense* and in areas where pentamidine resistance occurs, suramin may be used for *T. b. gambiense* HAT
- intravenous ***melarsoprol*** is used for the second stage caused by *T. b. rhodesiense* or in second-stage *T. b. gambiense* disease when eflornithine treatment has failed or is unavailable
- intravenous ***eflornithine*** is used for the second stage if caused by *T. b. gambiense*
- oral ***nifurtimox***, used with eflornithine in second-stage disease caused by *T. b. gambiense*, including melarsoprol-refractory disease

The treatment of patients with suramin or pentamidine in the first stage of HAT is relatively easy and safe, but diagnosis is difficult and infection often goes unnoticed since symptoms may be mild or confused with other conditions.[2] Treatment can be curative if started before the CNS has become involved. Most patients, however, are diagnosed after second-stage symptoms have occurred.[2,5] Suramin or pentamidine penetrate the blood-brain barrier poorly and cannot be used to treat second-stage disease, and the other drugs used to treat this stage have limitations.

Intravenous injections with melarsoprol are painful and are associated with severe adverse effects; about 5 to 10% of patients will suffer from reactive encephalopathy during treatment, with an average case-fatality rate of 50%.[2,3,7] Some degree of protection against this toxicity may be provided by prophylaxis with prednisolone.[8,9] High rates of melarsoprol treatment failure (up to 50%) have been reported in several regions, including the Sudan, Uganda, the Democratic Republic of Congo, and Angola.[2]

Eflornithine is also effective and is safer than melarsoprol in the treatment of second-stage *T. b. gambiense* HAT,[10-12] but is not generally used for *T. b. rhodesiense* HAT[3] because of reduced susceptibility of the parasite.[2] Eflornithine is difficult to use as it needs to be given by slow intravenous infusion every 6 hours for 14 days, and requires close patient monitoring. If relapse occurs after treatment with eflornithine, use of melarsoprol should be considered.[4]

There is concern that long-term use of eflornithine monotherapy may result in the development of resistance, and it is less effective in areas with a high prevalence of HIV infection.[10] Oral nifurtimox has been used for treatment of late stage *T.b. gambiense* HAT,[13,14] but is considered not effective enough to be used as monotherapy.[2] However, promising results have been obtained from a randomised controlled study[15] for the treatment of second stage *T.b. gambiense* infection with oral nifurtimox for 10 days plus intravenous eflornithine (given 12-hourly for 7 days). Combination therapy (NECT) required fewer eflornithine doses and the duration of treatment was reduced. Furthermore, resistance was also less likely to develop as the drugs have different modes of action.[2] Given the high incidence of adverse effects with melarsoprol, NECT was considered a candidate to replace it, although the combination still requires access to appropriate healthcare facilities.[7]

Patients should be seen every 6 months for a follow-up period of at least 2 years, to ascertain if treatment has been successful.

Various potential antitrypanosomal drugs are under investigation, including diamidine derivatives[16] and the nitroimidazole fexinidazole.[17]

1. Brun R, *et al.* Human African trypanosomiasis. *Lancet* 2010; **375**: 148–59.
2. WHO. 17th Expert Committee on the Selection and Use of Essential Medicines. *Proposal for the inclusion of nifurtimox-eflornithine combination as a treatment for stage 2 Trypanosoma brucei gambiense human african trypanosomiasis (sleeping sickness) in the WHO Model List of Essential Medicines: Drugs for Neglected Diseases Initiative (DNDi).* Geneva: WHO, 2009. Available at: http://www.who.int/selection_medicines/committees/expert/17/application/DNDi_Appli.pdf (accessed 07/04/09)
3. Legros D, *et al.* Treatment of human African trypanosomiasis—present situation and needs for research and development. *Lancet Infect Dis* 2002; **2**: 437–40.
4. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 14/02/11)
5. Barrett MP, *et al.* Human African trypanosomiasis: pharmacological re-engagement with a neglected disease. *Br J Pharmacol* 2007; **152**: 1155–71.
6. 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)
7. 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 28/01/11).
8. Pepin J, *et al.* Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* 1989; **i**: 1246–50.
9. Pepin J, *et al.* Risk factors for encephalopathy and mortality during melarsoprol treatment of Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1995; **89**: 92–7.
10. Chappuis F, *et al.* Eflornithine is safer than melarsoprol for the treatment of second-stage Trypanosoma brucei gambiense human African trypanosomiasis. *Clin Infect Dis* 2005; **41**: 748–51.
11. Balasegaram M, *et al.* Melarsoprol versus eflornithine for treating late-stage Gambian trypanosomiasis in the Republic of the Congo. *Bull WHO* 2006; **84**: 783–91.
12. Priotto G, *et al.* Safety and effectiveness of first line eflornithine for Trypanosoma brucei gambiense sleeping sickness in Sudan: cohort study. *BMJ* 2008; **336**: 705–8.
13. 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.
14. Pepin 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.
15. 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.
16. Paine MF, *et al.* Diamidines for human African trypanosomiasis. *Curr Opin Investig Drugs* 2010; **11**: 876–83.
17. Torreele E, *et al.* Fexinidazole—a new oral nitroimidazole drug candidate entering clinical development for the treatment of sleeping sickness. *PLoS Negl Trop Dis* 2010; **4**: e923.

American trypanosomiasis

American trypanosomiasis (Chagas' disease)[1-7] is a zoonosis caused by *Trypanosoma cruzi*, carried by Central or South American reduviid or triatomine bugs. Infected bugs defecate on the human host while feeding on blood and metacyclic trypanosomes that are shed enter the host through broken skin or by direct penetration of mucous membranes such as the conjunctiva. Infection may also occur through blood transfusion or less commonly transplanted organs; vertical transmission from infected mother to fetus can also occur. In endemic areas infection is usually acquired in childhood. Control measures include case detection and treatment, vector control by insecticide

applications within domestic buildings, and screening of blood donors.

In the early *acute phase* of infection parasites are present in the blood; clinical symptoms may or may not be apparent and most people recover spontaneously within 4 to 8 weeks. Symptomatic infection in the acute phase is characterised by fever, malaise, rash, lymphadenopathy, and hepatosplenomegaly. A swelling or chagoma may occur at the site of infection, which is often on the face; if this site is the conjunctiva a unilateral periorbital oedema occurs (Romañas sign). More rarely acute heart failure or meningoencephalitis occur and may be fatal in children. After a few months an asymptomatic latent or *indeterminate phase* develops and parasitaemia falls to low or undetectable levels. In 10 to 20 years about 15 to 30% of chronically infected persons develop *chronic* Chagas' disease (also called the chronic symptomatic phase) which is characterised by irreversible alterations of heart muscle (Chagasic cardiomyopathy) and gastrointestinal disease (mainly enlargement of the oesophagus or the rectosigmoid colon). In immunocompromised patients (including those with HIV infection) symptomatic reactivation of chronic, latent *T. cruzi* may occur.

Available treatment is generally unsatisfactory but, despite their toxicity, oral nifurtimox or oral benznidazole are of value especially in the acute phase; it is not certain whether trypanocidal treatment during the indeterminate phase can prevent the development of chronic disease although favourable results were obtained in a small study in children given benznidazole.[8] A systematic review[9] found that when given either nifurtimox or benznidazole, parasitological cure occurred in about 60 to 85% of patients in the acute phase and in more than 90% of congenitally infected infants treated in their first year of life. Although it is generally felt that there is no benefit from treatment in the chronic phase, treatment during the early chronic phase was reported to be beneficial,[10] and long-term follow-up of patients who had received benznidazole showed a reduction in cardiac complications and parasitaemia.[11]

Following a systematic review[9] it has been suggested that indications for treatment with benznidazole or nifurtimox include all cases of acute and congenital infection, reactivated infection, and all children 18 years of age or less with chronic infection; antitrypanocidal treatment should also generally be offered to adults aged 19 to 50 without advanced Chagasic cardiomyopathy, and may be considered in older adults although the risks of drug therapy are greater in the last group. It is not recommended for advanced Chagasic cardiomyopathy, since the existing pathology will not benefit, but the potential to reduce development of cardiomyopathy should be considered in patients with gastrointestinal involvement. In laboratory workers at risk of an infection after an accident, treatment with benznidazole for 10 days should be started immediately.[1]

Guidelines for the treatment of opportunistic infection in HIV-infected patients in the USA[12] suggest treatment with benznidazole or nifurtimox to reduce parasitaemia and prevent clinical symptoms in those with acute, early chronic, and reactivated disease. Re-treatment with either one of these drugs is recommended for HIV-infected patients who do not respond or who relapse after their initial therapy. Disease reactivation is also a problem in patients undergoing organ transplantation and the risk depends mainly on the degree of immunosuppression. Many experts advise close post-transplantation laboratory and clinical monitoring and treatment if reactivation is shown.[9,13] Some experts suggest treatment should be given to patients in whom future immunosuppression is anticipated, such as previously untreated *T. cruzi*-infected patients awaiting organ transplantation, or HIV-infected patients.[9]

The efficacy of treatment varies from country to country and may be linked to variations in the sensitivity of different strains of *T. cruzi*. Treatment is said to be successful when both parasitaemia and serological tests become negative and remain so for at least one year after the end of treatment.

Allopurinol, allopurinol riboside, and itraconazole have been tried for the treatment of American trypanosomiasis since they have shown trypanocidal activity in laboratory and *animal* studies; a prodrug of ravuconazole, E-1224, is also being studied. Initial clinical studies reported that oral allopurinol (600 or 900 mg daily for 60 days) was as effective as nifurtimox or benznidazole in reducing parasitaemia during the indeterminate phase and was better tolerated.[14] However, a later randomised, placebo-controlled study[15] in a small number of patients with chronic Chagas' disease reported that oral allopurinol was no more effective in clearing infection than placebo. A placebo-controlled study[16] in 404 patients with chronic Chagas' disease treated with either oral itraconazole (6 mg/kg daily for 120 days), oral allopurinol (8.5 mg/kg daily for 60 days), or placebo reported parasitologic cure in 44% and ECG normalisation in 36.5% of patients treated with allopurinol; for those given itraconazole a parasitologic cure of 53% and ECG normalisation of 48.2% was reported. A follow-up study[17] of the cardiac benefits in patients with chronic Chagas' disease 9 years after treatment with either oral itraconazole or oral allopurinol found that itraconazole and allopurinol were equally effective at reversing ECG changes but itraconazole appeared more protective against developing new ECG abnormalities in patients with a normal ECG at baseline. A further evaluation 11 years after treatment concluded that itraconazole was no less effective at preventing cardiomyopathy than allopurinol but had fewer adverse effects.[18] Posaconazole has also been tried.[19]

1. WHO. Control of Chagas disease: second report of the WHO expert committee. *WHO Tech Rep Ser 905* 2002. Available at: http://libdoc.who.int/trs/WHO_TRS_905.pdf (accessed 17/07/08)
2. Barrett MP, *et al.* The trypanosomiases. *Lancet* 2003; 362: 1469–80.
3. Yacoub S, *et al.* Neglected tropical cardiomyopathies: I. Chagas disease: myocardial disease. *Heart* 2008; 94: 244–8.
4. Rassi A, *et al.* Chagas disease. *Lancet* 2010; 375: 1388–1402.
5. Lescure F-X, *et al.* Chagas disease: changes in knowledge and management. *Lancet Infect Dis* 2010; 10: 556–70.
6. Rassi A, *et al.* Challenges and opportunities for primary, secondary, and tertiary prevention of Chagas' disease. *Heart* 2009; 95: 524–34.
7. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. *N Engl J Med* 2011; 364: 2527–34.
8. Sosa Estani S, *et al.* Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas' disease. *Am J Trop Med Hyg* 1998; 59: 526–9.
9. Bern C, *et al.* Evaluation and treatment of Chagas disease in the United States: a systematic review. *JAMA* 2007; 298: 2171–81.
10. de Andrade ALSS, *et al.* Randomised trial of efficacy of benznidazole in treatment of early Trypanosoma cruzi infection. *Lancet* 1996; 348: 1407–13.
11. Viotti R, *et al.* Treatment of chronic Chagas' disease with benznidazole: clinical and serologic evolution of patients with long-term follow-up. *Am Heart J* 1994; 127: 151–62.
12. 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)
13. Altclas JD, *et al.* Organ transplantation and Chagas disease. *JAMA* 2008; 299: 1134.
14. Gallerano RH, *et al.* Therapeutic efficacy of allopurinol in patients with chronic Chagas' disease. *Am J Trop Med Hyg* 1990; 43: 159–66. Correction. *ibid.* 1991; 44: 580.
15. Rassi A, *et al.* Specific treatment for Trypanosoma cruzi: lack of efficacy of allopurinol in the human chronic phase of Chagas disease. *Am J Trop Med Hyg* 2007; 76: 58–61.
16. Apt W, *et al.* Treatment of chronic Chagas' disease with itraconazole and allopurinol. *Am J Trop Med Hyg* 1998; 59: 133–8.
17. Apt W, *et al.* Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the regression and prevention of electrocardiographic abnormalities during 9 years of follow-up. *Ann Trop Med Parasitol* 2003; 97: 23–9.
18. Apt W, *et al.* Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the results of clinical and parasitological examinations 11 years post-treatment. *Ann Trop Med Parasitol* 2005; 99: 733–41.
19. Apt W. Current and developing therapeutic agents in the treatment of Chagas disease. *Drug Des Devel Ther* 2010; 4: 243–53.

Acetarsol *(BAN, rINN)*

Acetaminohydroxyphenylarsonsäure; Acétarsol; Acetarsolum; Acetarsona; Acetarsone; Acetphenarsinum; Asetarsoli; Osarsolum; Ацетарсол.

3-Acetamido-4-hydroxyphenylarsonic acid.

$C_8H_{10}AsNO_5$=275.1

CAS — 97-44-9.

ATC — A07AX02; G01AB01; P01CD02.

ATC Vet — QA07AX02; QG01AB01; QP51AD05.

UNII — 806529YU1N.

Profile

Acetarsol, a pentavalent organic arsenical derivative, has been given orally in the treatment of intestinal amoebiasis and vaginally in the treatment of trichomoniasis, but the use of pentavalent arsenical compounds has generally been abandoned in favour of more effective and less toxic drugs. For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p. 2448.3.

Acetarsol suppositories were once tried in the treatment of proctitis. Acetarsol lithium and acetarsol sodium have been included in some preparations for minor mouth infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Osarbon (Осарбон); Osarcid (Осарцид).

Aminitrozole *(BAN, rINN)*

Acinitrazole; Aminitrozol; Aminitrozolum; CL-5279; Nithiamide (USAN); Nithiamide; Аминитрозол.

N-(5-Nitrothiazol-2-yl)acetamide.

$C_5H_5N_3O_3S$=187.2

CAS — 140-40-9.

UNII — 9CBM60191Z.

Profile

Aminitrozole is an antiprotozoal that is used topically, often with sulfanilamide (p. 368.1), in the treatment of susceptible skin and soft tissue infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ukr.*: Nitacid (Нитацид); Streptonitol (Стрептонитол).

Amprolium Hydrochloride *(BANM, rINNM)*

Amprolii Hydrochloridum; Amprolio, hidrocloruro de; Amprolium, Chlorhydrate d'; Hidrocloruro de amprolio; Амполия Гидрохлорид.

1-(4-Amino-2-propylpyrimidin-5-ylmethyl)-2-methylpyridinium chloride hydrochloride.

$C_{14}H_{19}ClN_4HCl$=315.2

CAS — 121-25-5 (amprolium); 137-88-2 (amprolium hydrochloride).

Pharmacopoeias. In *Fr.* and *US* for veterinary use only. Also in *BP(Vet)*.

BP(Vet) 2014: (Amprolium Hydrochloride). A white or almost white, odourless or almost odourless powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform; very slightly soluble in ether.

USP 36: (Amprolium). A white to light yellow powder. Freely soluble in water, in alcohol, in dimethylformamide and in methyl alcohol; sparingly soluble in dehydrated alcohol; practically insoluble in acetone, in butyl alcohol, and in isopropyl alcohol.

Profile

Amprolium hydrochloride is an antiprotozoal used in veterinary practice, for the treatment and control of coccidiosis caused by *Eimeria* spp. It is a structural analogue of thiamine and prolonged high doses may cause thiamine deficiency. Neurological symptoms reported after overdose in *dogs* were treatable with intravenous or intramuscular thiamine.

Pentavalent Antimony Compounds

Antimonio pentavalente, compuestos de; Пятивалентные Сурьмы Соединений.

Meglumine Antimonate

Antimoniato de meglumina; Antimony Meglumine; Meglumine Antimoniate; Protostib; RP-2168; Меглумина Антимонат.

1-Deoxy-1-methylamino-D-glucitol antimonate.

$C_7H_{18}NO_8Sb$=366.0

CAS — 133-51-7.

ATC — P01CB01.

ATC Vet — QP51AB01.

UNII — 75G4TW236W.

Sodium Stibogluconate *(BAN, rINN)*

Estibogluconato de sodio; Natrii Stibogluconas; Natriumstiboglukonaatti; Natriumstiboglukonat; Sod. Stiboglu.; Sodium Antimony Gluconate; Sodyum Stiboglukonat; Stibogluconat-Natrium; Stibogluconate de Sodium; Натрия Стибоглюконат.

CAS — 16037-91-5.

ATC — P01CB02.

ATC Vet — QP51AB02.

UNII — V08350159D.

Description. A pentavalent antimony compound of indefinite composition. It has been represented by the formula $C_6H_9Na_2O_9Sb$ but usually there are less than 2 atoms of Na for each atom of Sb. Solutions may be sterilised by autoclaving.

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

BP 2014: (Sodium Stibogluconate). It is mainly the disodium salt of μ-oxy-bis[gluconato(3-)O^2,O^3,O^4-hydroxoantimony]. It contains not less than 30.0% and not more than 34.0% of antimony(V), calculated with reference to the dried and methanol-free substance. It is a colourless, odourless or almost odourless, mostly amorphous powder. Very soluble in water; practically insoluble in alcohol and in ether. A solution in water containing 10% of pentavalent antimony has a pH of 5.0 to 5.6 after autoclaving.

Uses and Administration

Pentavalent antimony, as sodium stibogluconate or meglumine antimonate, is used as first-line treatment for most forms of leishmaniasis (see below). Cutaneous and diffuse cutaneous leishmaniasis caused by *Leishmania aethiopica* infections do not respond to standard treatment with pentavalent antimony compounds, but may respond slowly if higher doses are used.

For systemic use, meglumine antimonate or sodium stibogluconate may be given by deep intramuscular injection or by intravenous injection. Intravenous injections must be given very slowly (over at least 5 minutes) and preferably through a fine needle to avoid thrombophlebitis; as with trivalent antimony compounds, they should be stopped immediately if coughing, vomiting, or substernal pain occurs. Both products may be injected intralesionally. Meglumine antimonate and sodium stibogluconate are given as solutions containing the equivalent of pentavalent antimony 85 mg/mL and 100 mg/mL respectively. Doses are expressed in terms of the equivalent amount of pentavalent antimony.

Local variations exist in treatment schedules but WHO recommends the following regimens:

- In **visceral leishmaniasis**, initial treatment is based on daily intramuscular injection of pentavalent antimony 20 mg/kg (but see below) usually given for 28 days. The length of treatment varies from one endemic area to another, but is continued until no parasites are detected in consecutive splenic aspirates taken at 14-day intervals. Patients who relapse are re-treated at the same dose.
- Early non-inflamed lesions of **cutaneous leishmaniasis** due to all forms of *Leishmania* except *L. aethiopica*, *L. amazonensis*, and *L. braziliensis* may be treated by infiltration with intralesional injections of 1 to 3 mL of sodium stibogluconate or meglumine antimonate (about 100 to 300 mg of pentavalent antimony), repeated once or twice if necessary at intervals of 1 to 2 days. Systemic therapy with intramuscular pentavalent antimony 10 to 20 mg/kg daily is given if the lesions are more severe and continued until a few days after clinical and parasitological cure is achieved. In cutaneous leishmaniasis due to *L. braziliensis*, prolonged systemic treatment with intramuscular pentavalent antimony 20 mg/kg daily for a minimum of 4 weeks is indicated. Similar doses are required for **diffuse cutaneous leishmaniasis** due to *L. amazonensis* and are continued for several months after clinical improvement occurs. Relapses should be expected until immunity develops.
- In **mucocutaneous leishmaniasis**, daily doses of intramuscular pentavalent antimony 20 mg/kg are given for a minimum of 4 weeks; if the response is poor, 10 to 15 mg/kg may be given every 12 hours for the same period. Relapses are well known and have generally been associated with inadequate or interrupted treatment; they are treated with the same drug given for at least twice as long as the original treatment. Only when that fails should alternative treatment be given.

Administration in children. Doses of pentavalent antimony products, such as meglumine antimonate and sodium stibogluconate, for the treatment of leishmaniasis in children are usually the same as those for adults, see Uses and Administration, above. However, for those children with visceral leishmaniasis and weighing less than 10 kg the minimum daily dose is 200 mg.

Leishmaniasis. The main treatment for leishmaniasis (p. 922.1) is a pentavalent antimony compound such as meglumine antimonate or sodium stibogluconate. A maximum daily dose of 850 mg was initially recommended by WHO and is still recommended in the UK licensed product information. However, higher doses of antimony compounds have been tried in order to overcome the unresponsiveness of leishmaniasis to therapy. In the USA, the use of 20 mg/kg daily of pentavalent antimony has been recommended, without restriction to an 850-mg maximum daily dose;[1] this is now also the dose currently suggested by WHO. At 20 mg/kg daily the most common adverse effects are musculoskeletal disorders, elevated liver enzyme values, and T-wave changes on the ECG, and the CDC recommends that the ECG, blood chemistry, and blood count should be monitored throughout therapy if resources permit.[1] Severe cardiotoxicity is rare at this dose but fatal cardiotoxicity has been reported with doses of up to 60 mg/kg daily (see under Effects on the Heart, below). Drug-resistant strains of *Leishmania infantum* have been associated with unresponsiveness to treatment with meglumine antimonate.[2] It was suggested[3] that the use of suboptimal doses may be increasing the prevalence of drug-resistant strains of the parasite. However, low doses of antimony compounds (5 mg/kg daily for 30 days) have produced long-term cure in patients with cutaneous *L. braziliensis* infection followed for up to 10 years.[4]

INTRALESIONAL ADMINISTRATION. Intralesional infiltration of 3 doses of sodium stibogluconate on alternate days or once weekly was more effective than daily treatment in a study of 96 patients with cutaneous leishmaniasis in Saudi Arabia.[5] Others have reported on the use of intralesional stibogluconate in cases from Israel[6] and twice-weekly intralesional sodium stibogluconate has been suggested for the treatment of cutaneous leishmaniasis caused by *L. tropica* in India.[7] Local infiltration of meglumine antimonate in usual doses of 150 to 900 mg (maximum 1.5 g) once each week for up to 6 weeks produced microbiological and clinical cures in all of 45 patients in Italy with cutaneous leishmaniasis.[8]

1. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg* 1992; **46**: 296–306.
2. Faraut-Gambarelli F, *et al.* In vitro and in vivo resistance of Leishmania infantum to meglumine antimoniate: a study of 37 strains collected from patients with visceral leishmaniasis. *Antimicrob Agents Chemother* 1997; **41**: 827–30.
3. Grogl M, *et al.* Drug resistance in leishmaniasis: its implication in systemic chemotherapy of cutaneous and mucocutaneous disease. *Am J Trop Med Hyg* 1992; **47**: 117–26.
4. Oliveira-Neto MP, *et al.* A low-dose antimony treatment in 159 patients with American cutaneous leishmaniasis: extensive follow-up studies (up to 10 years). *Am J Trop Med Hyg* 1997; **57**: 651–5.
5. Tallab TM, *et al.* Cutaneous leishmaniasis: schedules for intralesional treatment with sodium stibogluconate. *Int J Dermatol* 1996; **35**: 594–7.
6. Solomon M, *et al.* Treatment of cutaneous leishmaniasis with intralesional sodium stibogluconate. *J Eur Acad Dermatol Venereol* 2009; **23**: 1189–92.
7. Bumb RA, *et al.* Efficacy of short-duration (twice weekly) intralesional sodium stibogluconate in treatment of cutaneous leishmaniasis in India. *Br J Dermatol* 2010; 854–8.
8. Aste N, *et al.* Intralesional treatment of cutaneous leishmaniasis with meglumine antimoniate. *Br J Dermatol* 1998; **138**: 370–1.

Adverse Effects, Treatment, and Precautions

As for Trivalent Antimony Compounds, p. 151.3.

Adverse effects are generally less frequent and less severe with the pentavalent antimony compounds sodium stibogluconate and meglumine antimonate than with trivalent compounds such as antimony sodium tartrate. Nevertheless, similar precautions should be observed, especially in patients on high-dose therapy.

Intramuscular injections of sodium stibogluconate can be painful and intravenous use has been associated with thrombophlebitis. Elevations in serum lipase and amylase usually occur during treatment and symptomatic pancreatitis has been reported in some patients. Successful treatment of mucocutaneous leishmaniasis may cause severe inflammation around the lesion and involvement of the pharynx or trachea may be life-threatening.

Common adverse effects of pentavalent antimony are anorexia, vomiting, nausea, malaise, arthralgia and myalgia, headache, lethargy, and abdominal pain. ECG changes are dose-dependent and most commonly include T-wave flattening and inversion and prolonged *QT* interval. Renal damage is a rarely reported toxic effect. Serious adverse effects have involved the liver, musculoskeletal system, pancreas, or the heart;[1,2] when they occur it is prudent to interrupt the course temporarily.[1] Pentavalent antimony is usually well tolerated,[1] although a study[2] of 96 patients treated with sodium stibogluconate for leishmaniasis reported significant, but generally reversible, adverse effects; treatment was interrupted in 28% of the patients.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 21/01/09)
2. Aronson NE, *et al.* Safety and efficacy of intravenous sodium stibogluconate in the treatment of leishmaniasis: recent US military experience. *Clin Infect Dis* 1998; **27**: 1457–64.

Breast feeding. The amount of antimony distributed into the breast milk of a patient given sodium stibogluconate was considered not to constitute a hazard and oral absorption was not detected in an *animal* study.[1] The last available guidance from the American Academy of Pediatrics also considered that the use of antimony is usually compatible with breast feeding.[2] Others, however, have felt that more safety evaluation was required before antimony could be considered completely safe during breast feeding.[3]

1. Berman JD, *et al.* Concentration of Pentostam in human breast milk. *Trans R Soc Trop Med Hyg* 1989; **83**: 784–5.
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 02/06/04)
3. Verschoyle RD. Comment. *Trop Dis Bull* 1990; **87**: 919.

Effects on the blood. Although thrombocytopenia is associated with leishmaniasis, there are also case reports associating it with sodium stibogluconate.[1,2] Eosinophilia and lymphocytosis were common in a small study in Brazilian patients given intravenous or intralesional meglumine antimonate for cutaneous leishmaniasis.[3]

1. Braconier JH, Mörner H. Recurrent episodes of thrombocytopenia during treatment with sodium stibogluconate. *J Antimicrob Chemother* 1993; **31**: 187–8.
2. Hepburn NC. Thrombocytopenia complicating sodium stibogluconate therapy for cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1993; **87**: 691.
3. Neves DB, *et al.* Antimony in plasma and skin of patients with cutaneous leishmaniasis—relationship with side effects after treatment with meglumine antimoniate. *Trop Med Int Health* 2009; **14**: 1515–22.

Effects on the heart. The ECG was monitored during 65 courses of treatment with sodium stibogluconate in 59 Kenyan patients with leishmaniasis.[1] ECG abnormalities developed during 35 treatment courses. They were qualitatively similar to those previously described during treatment with trivalent antimonial drugs, but occurred less frequently and later during the course of treatment. The most common abnormality was inversion and/or decreased amplitude of T waves. Incidence was related to total daily dose and duration of treatment. One patient died suddenly during the 4th week of treatment with antimony 60 mg/kg daily. Other deaths probably related to cardiotoxicity have been reported in patients receiving 60 mg/kg daily[2] and 30 mg/kg daily.[3] It has been recommended[1] that for treatment with sodium stibogluconate ECGs should be obtained every 3 to 4 days in patients given antimony 20 mg/kg daily for more than 20 days or a higher dose for more than 10 days. If Stokes-Adams attacks or ventricular tachyarrhythmias develop, sodium stibogluconate should be stopped and appropriate treatment given. A retrospective study[4] in patients treated with sodium stibogluconate for mostly cutaneous leishmaniasis found that the mean QT_c interval steadily increased throughout the period of treatment, reaching a potentially toxic threshold by the third week, but cardiotoxicity was seen only in one elderly patient who had hypokalaemia and pre-existing cardiovascular morbidity. Identification before treatment of factors that may increase cardiovascular risk is important. For further information on the cumulative cardiotoxicity of sodium stibogluconate and amphotericin B see Antifungals, under Interactions, p. 928.1.

1. Chulay JD, *et al.* Electrocardiographic changes during treatment of leishmaniasis with pentavalent antimony (sodium stibogluconate). *Am J Trop Med Hyg* 1985; **34**: 702–9.
2. Bryceson ADM, *et al.* Visceral leishmaniasis unresponsive to antimonial drugs II: response to high dosage sodium stibogluconate or prolonged treatment with pentamidine. *Trans R Soc Trop Med Hyg* 1985; **79**: 705–14.
3. Thakur CP. Harmful effect of high stibogluconate treatment of kala-azar in India. *Trans R Soc Trop Med Hyg* 1986; **80**: 672–3.
4. Lawn SD, *et al.* Electrocardiographic and biochemical adverse effects of sodium stibogluconate during treatment of cutaneous and mucosal leishmaniasis among returned travellers. *Trans R Soc Trop Med Hyg* 2006; **100**: 264–9.

Effects on the kidneys. Sodium stibogluconate given for 10 days to 16 young men with cutaneous leishmaniasis had no apparent adverse effect on glomerular or tubular renal function.[1] However, evidence of renal tubular dysfunction has been reported in patients with mucocutaneous leishmaniasis given meglumine antimonate or sodium stibogluconate for 30 days or more[2] and acute renal failure has occurred in patients both with,[3] and without,[4] pre-existing renal impairment, the latter resulting in death.

1. Jolliffe DS. Nephrotoxicity of pentavalent antimonials. *Lancet* 1985; **i**: 584.
2. Veiga JPR, *et al.* Renal tubular dysfunction in patients with mucocutaneous leishmaniasis treated with pentavalent antimonials. *Lancet* 1983; **ii**: 569.
3. Balzan M, Fenech F. Acute renal failure in visceral leishmaniasis treated with sodium stibogluconate. *Trans R Soc Trop Med Hyg* 1992; **86**: 515–16.
4. Rodrigues MLO, *et al.* Nephrotoxicity attributed to meglumine antimoniate (Glucantime) in the treatment of generalized cutaneous leishmaniasis. *Rev Inst Med Trop Sao Paulo* 1999; **41**: 33–7.

Effects on the liver. WHO has reported that when serious adverse effects occur with sodium stibogluconate they often involve the liver or the heart.[1] There have been reports of disturbed liver function[2,3] in patients given sodium stibogluconate, although there has also been a report[4] that signs of altered liver function, which may be a feature of visceral leishmaniasis, improved during treatment with sodium stibogluconate.

1. WHO. Control of the leishmaniases. *WHO Tech Rep Ser 793* 1990. Available at: http://libdoc.who.int/trs/WHO_TRS_793.pdf (accessed 17/07/08)
2. Ballou WR, *et al.* Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii**: 13–16.
3. Hepburn NC, *et al.* Hepatotoxicity of sodium stibogluconate in leishmaniasis. *Lancet* 1993; **342**: 238–9.
4. Misbahuddin M, *et al.* Stibogluconate for leishmaniasis. *Lancet* 1993; **342**: 804.

Effects on the musculoskeletal system. Arthralgia is common with pentavalent antimony compounds. It is usually dose-dependent[1] but a patient has been described who had symptoms early in treatment.[2] Palindromic arthropathy with effusion was associated with sodium stibogluconate treatment in another patient.[3]

1. Ballou WR, *et al.* Safety and efficacy of high-dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii**: 13–16.
2. Castro C, *et al.* Severe arthralgia, not related to dose, associated with pentavalent antimonial therapy for mucosal leishmaniasis. *Trans R Soc Trop Med Hyg* 1990; **84**: 362.

3. Donovan KL, *et al.* Pancreatitis and palindromic arthropathy with effusions associated with sodium stibogluconate treatment in a renal transplant recipient. *J Infect* 1990; 21: 107–10.

Effects on the nervous system. Peripheral neuropathy developed in a patient about 8 days after starting therapy with sodium stibogluconate.[1] The symptoms were generally reversible when treatment was stopped (after 17 days), although there was some slight persistent hypoaesthesia in the toes. An interaction with a single dose of amitriptyline, taken on the second day of stibogluconate therapy, seemed unlikely but could not be ruled out. Two cases of cerebellar ataxia have been reported during treatment with sodium stibogluconate for visceral leishmaniasis; toxicity might have been partly due to the neurological manifestations of the disease.[2]

1. Brummitt CF, *et al.* Reversible peripheral neuropathy associated with sodium stibogluconate therapy for American cutaneous leishmaniasis. *Clin Infect Dis* 1996; 22: 878–9.
2. Khalil EA, *et al.* Antimony-induced cerebellar ataxia. *Saudi Med J* 2006; 27: 90–2.

Effects on the pancreas. Pancreatitis has been associated with sodium stibogluconate treatment.[1-3] Stopping treatment usually resulted in resolution of pancreatitis.

1. Donovan KL, *et al.* Pancreatitis and palindromic arthropathy with effusions associated with sodium stibogluconate treatment in a renal transplant recipient. *J Infect* 1990; 21: 107–10.
2. Gasser RA, *et al.* Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. *Clin Infect Dis* 1994; 18: 83–90.
3. Domingo P, *et al.* Treatment of Indian kala-azar with pentavalent antimony. *Lancet* 1995; 345: 584–5.

Interactions

Antifungals. Cardiotoxicity, including some fatalities, has been reported in about 8 to 17% of patients treated with the standard dose of sodium stibogluconate for visceral leishmaniasis, and patients may remain at risk for cardiotoxicity for about 2 months after stopping treatment due to its slow terminal elimination phase. In contrast, cardiotoxicity is uncommon with *amphotericin B*, although it may occur in patients with pre-existing cardiopulmonary disease or electrolyte abnormalities. Cumulative cardiotoxicity, resulting in sudden clinical deterioration and death, has been reported in 3 previously stable young children given intravenous amphotericin B up to 15 days after stopping treatment with sodium stibogluconate for the treatment of visceral leishmaniasis.[1] One child had a documented ventricular tachycardia on day 2 of amphotericin B treatment, while the other children had signs and symptoms suggestive of a fatal arrhythmia on days 4 and 6 of treatment with amphotericin B. It was suggested that sodium stibogluconate increased the susceptibility of the myocardium to damage by amphotericin B. A rest period of about 14 days (or longer if ECG changes persist) and correction of electrolyte abnormalities was advised when switching treatment from sodium stibogluconate to amphotericin B.[1]

1. Maheshwari A, *et al.* Cumulative cardiac toxicity of sodium stibogluconate and amphotericin B in treatment of kala-azar. *Pediatr Infect Dis J* 2011; 30: 180–1.

Pharmacokinetics

The pentavalent antimony compounds are poorly absorbed from the gastrointestinal tract but are rapidly absorbed and distributed by the intravenous and the intramuscular routes, which have similar pharmacokinetics. Elimination occurs in two phases; a rapid initial phase, in which the majority of a dose is excreted via the kidneys within 12 hours, and a slower phase, possibly reflecting reduction to trivalent antimony. The elimination half-life of the initial phase is about 2 hours and that of the slow terminal phase is about 33 to 76 hours. Accumulation occurs on daily use and maximum tissue concentrations may not be reached for 7 days or more. Antimony has been detected in breast milk (see Breast Feeding, p. 927.2).

References.

1. Rees PH, *et al.* Renal clearance of pentavalent antimony (sodium stibogluconate). *Lancet* 1980; II: 226–9.
2. Chulay JD, *et al.* Pharmacokinetics of antimony during treatment of visceral leishmaniasis with sodium stibogluconate or meglumine antimoniate. *Trans R Soc Trop Med Hyg* 1988; 82: 69–72.
3. Al Jaser M, *et al.* Pharmacokinetics of antimony in patients treated with sodium stibogluconate for cutaneous leishmaniasis. *Pharm Res* 1995; 12: 113–16.
4. Cruz A, *et al.* Pharmacokinetics of antimony in children treated for leishmaniasis with meglumine antimoniate. *J Infect Dis* 2007; 195: 602–8.
5. Zaghloul IY, *et al.* Clinical efficacy and pharmacokinetics of antimony in cutaneous leishmaniasis patients treated with sodium stibogluconate. *J Clin Pharmacol* 2010; 50: 1230–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Glucantime; *Fr.*: Glucantime; *Gr.*: Glucantime; *Israel*: Pentostam; *Spain*: Glucantime; *UK*: Pentostam; *Venez.*: Glucantime.

Pharmacopoeial Preparations
BP 2014: Sodium Stibogluconate Injection.

Atovaquone *(BAN, USAN, rINN)*

566C; 566C80; Atovacuona; Atovakon; Atovakvon; Atovakvoni; Atovaquonum; BW-566C; BW-566C80; BW-A566C; Atobaxon.

2-[*trans*-4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

$C_{22}H_{19}O_3Cl$=366.8.

CAS — 95233-18-4.

ATC — P01AX06.

UNII — Y883P1Z2LT.

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

Ph. Eur. 8: (Atovaquone). A yellow, crystalline powder. Practically insoluble in water; sparingly soluble in dichloromethane; very slightly soluble in methyl alcohol. It shows polymorphism.

USP 36: (Atovaquone). A yellow powder. Insoluble in water; slightly soluble in alcohol, in butanediol, in ethyl acetate, in glycerol, in octanol, and in macrogol 200; sparingly soluble in acetone, in di-*n*butyl adipate, in dimethyl sulfoxide, and in macrogol 400; soluble in chloroform; freely soluble in *N*-methylpyrrolidone and in tetrahydrofuran; very slightly soluble in 0.1N sodium hydroxide. Store in airtight containers. Protect from light.

Uses and Administration

Atovaquone is a hydroxynaphthoquinone antiprotozoal that is also active against the fungus *Pneumocystis jirovecii*. It is used in the treatment and prophylaxis of pneumocystis pneumonia in patients unable to tolerate co-trimoxazole, and with proguanil in the treatment and prophylaxis of malaria. As well as these established uses atovaquone is also used in other protozoal infections including babesiosis and toxoplasmosis. For further information see below.

In the treatment of mild to moderate **pneumocystis pneumonia**, atovaquone is given orally in a dose of 750 mg with food twice daily as a suspension, for 21 days. For prophylaxis 1500 mg of the suspension is given once daily with food.

For the *prophylaxis* of falciparum **malaria** in adults over 40 kg oral atovaquone 250 mg with oral proguanil hydrochloride 100 mg is given once daily. The course should start 1 to 2 days before travel to the malarious area, continue daily throughout exposure, and for 7 days after leaving the area.

In the *treatment* of uncomplicated falciparum malaria in adults over 40 kg oral atovaquone 1 g with oral proguanil hydrochloride 400 mg is given as a single daily dose for 3 days.

For details of doses in children, see below.

Atovaquone with proguanil is one of the antimalarial drug combinations recommended by some experts to be carried as a *standby* for the emergency treatment of malaria. The dose recommended for self-treatment is the same as that for treatment of uncomplicated falciparum malaria.

Reviews.

1. Haile LG, Flaherty JF. Atovaquone: a review. *Ann Pharmacother* 1993; 27: 1488–94.
2. Artymowicz RJ, James VE. Atovaquone: a new antipneumocystis agent. *Clin Pharm* 1993; 12: 563–70.
3. Spencer CM, Goa KL. Atovaquone: a review of its pharmacological properties and therapeutic efficacy in opportunistic infections. *Drugs* 1995; 50: 176–96.
4. Baggish AL, Hill DR. Antiparasitic agent atovaquone. *Antimicrob Agents Chemother* 2002; 46: 1163–73.
5. McKeage K, Scott LJ. Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. *Drugs* 2003; 63: 597–623.
6. Marra F, *et al.* Atovaquone-proguanil for prophylaxis and treatment of malaria. *Ann Pharmacother* 2003; 37: 1266–75.
7. Boggild AK, *et al.* Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). *Am J Trop Med Hyg* 2007; 76: 208–23.

Administration in children. Children may be given atovaquone with proguanil for the *prophylaxis* of falciparum **malaria** in the following licensed oral doses, based on the adult dose of 250 mg of atovaquone daily:

- children weighing 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- over 40 kg: the adult dose The course should start 1 to 2 days before travel to the malarious area, continue daily throughout exposure, and for 7 days after leaving the area.

Licensed oral doses of atovaquone with proguanil for the *treatment* of uncomplicated falciparum malaria, based on the adult dose of 1 g of atovaquone daily for 3 days, are:

- children weighing 5 to 8 kg: one-eighth the adult dose
- 9 to 10 kg: three-sixteenths the adult dose
- 11 to 20 kg: one-quarter the adult dose
- 21 to 30 kg: half the adult dose
- 31 to 40 kg: three-quarters the adult dose
- over 40 kg: the adult dose

For doses in children with **babesiosis** or for prophylaxis of **pneumocystis pneumonia** see below.

Babesiosis. Atovaquone 750 mg twice daily with azithromycin 500 to 1000 mg on day 1 followed by 250 mg once daily thereafter, both orally for 7 to 10 days, has been recommended by some experts[1] in the USA for the treatment of babesiosis infections; higher doses of azithromycin should be used in immunocompromised patients (see Babesiosis, under Uses and Administration of Azithromycin, p. 221.3). Children may be given atovaquone 20 mg/kg (maximum 750 mg) twice daily with azithromycin 10 mg/kg (maximum 500 mg) on day 1 followed by 5 mg/kg (maximum 250 mg) once daily thereafter, both orally for 7 to 10 days.[1,2] In a prospective, randomised study[3] involving 58 patients with babesiosis (p. 920.2), atovaquone with azithromycin was found to be as effective as, and associated with fewer adverse effects than, standard therapy with quinine and clindamycin. Atovaquone with azithromycin, both given for 10 days, was also effective in the treatment of an 8-month-old child with transfusion-associated babesiosis.[4] However, the emergence of resistance to the combination has been reported in immunocompromised patients.[5]

1. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 43: 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 23/08/13)
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Krause PJ, *et al.* Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; 343: 1454–8.
4. Raju M, *et al.* Atovaquone and azithromycin treatment for babesiosis in an infant. *Pediatr Infect Dis J* 2007; 26: 181–3.
5. Wormser GP, *et al.* Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with *Babesia microti* infection. *Clin Infect Dis* 2010; 50: 381–6.

Malaria. Atovaquone with proguanil (*Malarone*) is used in the treatment and prophylaxis of uncomplicated malaria caused by *Plasmodium falciparum* (see p. 644.1).

Atovaquone, a blood schizontocide, is associated with an unacceptably high rate of recrudescence when used alone[1] for *treatment* but is more successful in malaria when used with proguanil,[2,3] including that produced by multidrug-resistant strains.[4] Use of the combination to treat *P. ovale* and *P. malariae* malarias has also been studied.[5] Atovaquone with proguanil followed by primaquine may also be effective for the treatment of *P. vivax* malaria.[6] Some authorities recommend this combination as an alternative treatment option in patients not responsing to chloroquine monotherapy[7] or for those with chloroquine-resistant infections.[7,8]

1. Chiodini PL, *et al.* Evaluation of atovaquone in the treatment of patients with uncomplicated Plasmodium falciparum malaria. *J Antimicrob Chemother* 1995; 36: 1073–5.
2. Looareesuwan S, *et al.* Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am J Trop Med Hyg* 1996; 54: 62–6.
3. Radloff PD, *et al.* Atovaquone and proguanil for Plasmodium falciparum malaria. *Lancet* 1996; 347: 1511–14.
4. Sabcharoen A, *et al.* Efficacy and pharmacokinetics of atovaquone and proguanil in children with multidrug-resistant Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg* 1998; 92: 201–6.
5. Radloff PD, *et al.* Atovaquone plus proguanil is an effective treatment for Plasmodium ovale and P. malariae malaria. *Trans R Soc Trop Med Hyg* 1996; 90: 682.
6. Looareesuwan S, *et al.* Atovaquone and proguanil hydrochloride followed by primaquine for treatment of plasmodium vivax malaria in Thailand. *Trans R Soc Trop Med Hyg* 1999; 93: 637–40.
7. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (updated April 2011). Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf (accessed 27/07/11)
8. Lalloo DG, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines. *J Infect* 2007; 54: 111–21. Correction. [primaquine dose]. Corrected version available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947343507 (accessed 15/11/10)

Pneumocystis pneumonia. Atovaquone is one alternative to co-trimoxazole for the treatment of pneumocystis pneumonia (p. 567.2). In open studies, a clinical response to atovaquone was reported in 78% of patients with mild to moderate disease and in 56% of patients with severe disease who were intolerant of, or who failed to respond to, both co-trimoxazole and pentamidine.[1] Comparative studies have shown atovaquone to be less effective than co-trimoxazole[2] and probably less effective than pentamidine,[3,4] but to produce fewer treatment-limiting adverse effects than either.

Atovaquone is also an alternative to co-trimoxazole for both primary or secondary *prophylaxis*, and was as effective as dapsone[5] or inhaled pentamidine[6] in studies in patients intolerant of co-trimoxazole. Atovaquone 30 mg/kg daily plus azithromycin 5 mg/kg daily was found to be possibly as

effective as co-trimoxazole in prophylaxis of pneumocystis pneumonia in HIV-infected children.[7]

1. White A, *et al.* Clinical experience with atovaquone on a treatment investigational new drug protocol for Pneumocystis carinii pneumonia. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; **9**: 280–5.
2. Hughes W, *et al.* Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. *N Engl J Med* 1993; **328**: 1521–7.
3. Dohn MN, *et al.* Oral atovaquone compared with intravenous pentamidine for Pneumocystis carinii pneumonia in patients with AIDS. *Ann Intern Med* 1994; **121**: 174–80.
4. Lederman MM, van der Horst C. Atovaquone for Pneumocystis carinii pneumonia. *Ann Intern Med* 1995; **122**: 314.
5. El-Sadr WM, *et al.* Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998; **339**: 1889–95.
6. Chan C, *et al.* Atovaquone suspension compared with aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis* 1999; **180**: 369–76.
7. Hughes WT, *et al.* Comparison of atovaquone and azithromycin with trimethoprim-sulfamethoxazole for the prevention of serious bacterial infections in children with HIV infection. *Clin Infect Dis* 2005; **40**: 136–45.

Toxoplasmosis. Atovaquone, either alone or with pyrimethamine or sulfadiazine, has produced encouraging results for treatment[1-4] or long-term suppression[4-6] of toxoplasmosis (p. 924.2) in patients with AIDS. US guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents[4] suggest atovaquone with either pyrimethamine or sulfadiazine may be considered as an alternate regimen for treatment of toxoplasmosis; atovaquone may be given alone in patients unable to tolerate pyrimethamine and sulfadiazine. Atovaquone with or without pyrimethamine can be considered as an alternate regimen for primary prophylaxis, while atovaquone, with or without either pyrimethamine or sulfadiazine, may be considered as an alternate regimen for secondary prophylaxis of toxoplasmosis.[4] However, failure of atovaquone prophylaxis following haematopoietic stem-cell transplantation has been reported.[7] It has also been tried for the treatment of toxoplasmic retinochoroiditis in immunocompetent patients.[8]

For details of doses used with pyrimethamine for the prevention of toxoplasmosis, see under Pyrimethamine, p. 663.1.

1. Kovacs JA, *et al.* Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. *Lancet* 1992; **340**: 637–8.
2. Torres RA, *et al.* Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1997; **24**: 422–9.
3. Chirgwin K, *et al.* Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. *Clin Infect Dis* 2002; **34**: 1243–50.
4. 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)
5. Katlama C, *et al.* Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. *AIDS* 1996; **10**: 1107–12.
6. Winterhalter S, *et al.* Does atovaquone prolong the disease-free interval of toxoplasmic retinochoroiditis? *Graefes Arch Clin Exp Ophthalmol* 2010; **248**: 1187–92.
7. Garcia de la Fuente I, *et al.* Acute disseminated fatal toxoplasmosis after haploidentical stem cell transplantation despite atovaquone prophylaxis in a young man. *Pediatr Infect Dis J* 2010; **29**: 1059–60.

Adverse Effects and Precautions

The most common adverse effects associated with the use of atovaquone plus proguanil are headache, coughing, and gastrointestinal effects such as nausea, diarrhoea, and vomiting. Other commonly occurring adverse effects include anorexia, depression, dizziness, fever, insomnia, rashes, raised liver enzyme values, hyponatraemia, and haematological disturbances such as anaemia and neutropenia. Rare cases of allergic reactions (such as angioedema, anaphylaxis, urticaria, and vasculitis), cholestasis, and hepatitis have been reported. Hepatic failure requiring liver transplantation has also been reported. Similar adverse effects have been reported in patients taking atovaquone without proguanil for prevention and treatment of pneumocystis pneumonia. Atovaquone should be avoided in patients with gastrointestinal disorders that may limit absorption of the drug. In patients with severe renal impairment, atovaquone plus proguanil is contra-indicated for the prophylaxis of malaria; it should be used with caution in the treatment of malaria.

Effects on the skin. Stevens-Johnson syndrome has been reported[1] in a patient after a few days of taking atovaquone with proguanil for malaria prophylaxis. A case[2] of bullous erythema multiforme has also been reported in a patient given atovaquone with proguanil for malaria treatment; pruritus occurred after the first and second doses and bullae developed after the third dose.

1. Emberger M, *et al.* Stevens-Johnson syndrome associated with Malarone antimalarial prophylaxis. Abstract: *Clin Infect Dis* 2003; **37**: 158. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/375073 (accessed 17/07/08)
2. Remich SA, *et al.* Bullous erythema multiforme after treatment with Malarone, a combination antimalarial composed of atovaquone and proguanil hydrochloride. *Trop Doct* 2008; **38**: 190–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies atovaquone 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 atovaquone with either metoclopramide, tetracycline, rifampicin, or rifabutin results in decreases in plasma-atovaquone concentrations. Reduced concentrations of atovaquone with proguanil have been reported in HIV-positive patients also taking efavirenz or ritonavir-boosted atazanavir or lopinavir. Other drugs which have produced small reductions in plasma-atovaquone concentrations include aciclovir, antidiarrhoeals, benzodiazepines, cephalosporins, laxatives, opioids, and paracetamol.

Atovaquone is reported to decrease the metabolism of zidovudine resulting in moderate increases in zidovudine plasma concentrations. A decrease in trough concentrations of indinavir, and in the area under the indinavir time-concentration curve has been reported when atovaquone was also given. Small decreases in the plasma concentrations of co-trimoxazole (not considered to be clinically significant) have been noted in patients taking atovaquone. There is a theoretical possibility that atovaquone could displace other highly protein-bound drugs from plasma-protein binding sites.

Anticoagulants. For reference to a case of atovaquone increasing the effect of *warfarin*, see Antiprotozoals, p. 1532.3.

Pharmacokinetics

Atovaquone is a highly lipophilic compound with a low aqueous solubility. Oral bioavailability of atovaquone shows considerable interindividual variation. Bioavailability from commercial oral liquid formulations is better than from tablets and can be further improved if taken with food, particularly meals with a high fat content. The absolute bioavailability of the tablet and liquid formulations is 23% and 47% respectively, when taken with food. Atovaquone is more than 99% bound to plasma proteins. There is indirect evidence that atovaquone may undergo limited metabolism, however, no specific metabolites have been identified. It has a long plasma half-life of 2 to 3 days in adults and 1 to 2 days in children, thought to be due to enterohepatic recycling. It is excreted almost exclusively in faeces as unchanged drug.

References.

1. Rolan PE, *et al.* Examination of some factors responsible for a food-induced increase in absorption of atovaquone. *Br J Clin Pharmacol* 1994; **37**: 13–20.
2. Dixon R, *et al.* Single-dose and steady-state pharmacokinetics of a novel microfluidized suspension of atovaquone in human immunodeficiency virus-seropositive patients. *Antimicrob Agents Chemother* 1996; **40**: 556–60.
3. Hussein Z, *et al.* Population pharmacokinetics of atovaquone in patients with acute malaria caused by Plasmodium falciparum. *Clin Pharmacol Ther* 1997; **61**: 518–30.
4. Rolan PE, *et al.* Disposition of atovaquone in humans. *Antimicrob Agents Chemother* 1997; **41**: 1319–21.
5. Thapar MM, *et al.* Time-dependent pharmacokinetics and drug metabolism of atovaquone plus proguanil (Malarone) when taken as chemoprophylaxis. *Eur J Clin Pharmacol* 2002; **58**: 19–27.
6. McGready R, *et al.* The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. *Eur J Clin Pharmacol* 2003; **59**: 545–52.
7. Na-Bangchang K, *et al.* The pharmacokinetics and pharmacodynamics of atovaquone and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. *Eur J Clin Pharmacol* 2005; **61**: 573–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Wellvone; ***Belg.***: Wellvone; ***Canad.***: Mepron; ***Fr.***: Wellvone; ***Ger.***: Wellvone; ***Gr.***: Wellvone; ***Ital.***: Wellvone; ***Jpn***: Samtirel; ***Neth.***: Wellvone; ***Port.***: Wellvone; ***S.Afr.***: Wellvone; ***Spain***: Wellvone; ***Swed.***: Wellvone; ***Switz.***: Wellvone; ***UK***: Wellvone; ***USA***: Mepron.

Multi-ingredient Preparations. ***Austral.***: Malarone; ***Austria***: Malarone; ***Belg.***: Malarone; ***Canad.***: Malarone; ***Chile***: Malarone; ***Cz.***: Malarone; ***Denm.***: Malarone; ***Fin.***: Malarone; ***Fr.***: Malarone; ***Ger.***: Malarone; ***Gr.***: Malarone; ***Hong Kong***: Malarone; ***Hung.***: Malarone; ***Irl.***: Malarone; ***Israel***: Malarone; ***Ital.***: Malarone; ***Jpn***: Malarone; ***Malaysia***: Malarone; ***Neth.***: Malarone; ***Norw.***: Malarone; ***NZ***: Malarone; ***Pol.***: Malarone; ***Port.***: Malarone; ***S.Afr.***: Malanil; ***Singapore***: Malarone; ***Spain***: Malarone; ***Swed.***: Malarone; ***Switz.***: Malarone; ***Thai.***: Malanil; ***UK***: Malarone; Reprapog; ***USA***: Malarone.

Pharmacopoeial Preparations
USP 36: Atovaquone Oral Suspension.

Azanidazole *(BAN, USAN, rINN)*

Azanidazol; Azanidazolo; Azanidazolum; F-4; Азанидазол.

4-[(*E*)-2-(1-Methyl-5-nitroimidazol-2-yl)vinyl]pyrimidin-2-ylamine.

$C_{10}H_{10}N_6O_2$=246.2

CAS — 62973-76-6.

ATC — G01AF13; P01AB04.

ATC Vet — QG01AF13; QP51AA04.

UNII — YP2Y0DRX4S.

Profile

Azanidazole is a 5-nitroimidazole derivative similar to metronidazole (p. 936.1) and has been used in the treatment of trichomoniasis in usual oral doses of 200 mg twice daily or 250 mg once daily intravaginally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Triclose.

Benznidazole *(rINN)*

Benznidazol; Benznidazolum; Ro-7-1051; Бензнидазол.

N-Benzyl-2-(2-nitroimidazol-1-yl)acetamide.

$C_{12}H_{12}N_4O_3$=260.3

CAS — 22994-85-0.

ATC — P01CA02.

UNII — YC42NRJ1ZD.

Pharmacopoeias. In *Int.* –

Uses and Administration

Benznidazole is a 2-nitroimidazole derivative with antiprotozoal activity. It is of value in the treatment of American trypanosomiasis (Chagas' disease—see below), especially during the early acute stage of the disease.

In the *acute* stage of the disease, uncomplicated cases in patients weighing up to 40 kg may be given benznidazole orally in a dose of 7.5 mg/kg daily while those weighing more than 40 kg should be given 5 mg/kg daily. Patients with acute meningoencephalitis should be given a dose of up to 25 mg/kg daily. Benznidazole should be given orally in equally divided doses every 8 or 12 hours and is usually given for 60 days (but see also American Trypanosomiasis, below).

Trypanosoma cruzi infected organ transplant donors should be treated for 2 weeks before the donation and recipients for 2 weeks after it. In laboratory workers at risk of an infection after an accident, treatment with benznidazole (7 to 10 mg/kg daily) for 10 days should be started immediately.

Treatment of patients in the *chronic* phase of the disease with oral benznidazole (5 mg/kg daily in equally divided doses every 8 or 12 hours) may be considered in areas where transmission by the vector has been interrupted and the 60-day treatment course can be completed under medical supervision.

For details of doses in children, see below.

Administration in children. For the treatment of the acute phase of American trypanosomiasis (Chagas' disease) in children, benznidazole may be given orally at a dose of 5 to 10 mg/kg daily in two equally divided doses for 60 days. In congenital cases, full-term neonates are given 10 mg/kg daily; treatment is started at a dose of 5 mg/kg daily and may be increased to 10 mg/kg daily after 3 days of treatment if the patient does not develop leucopenia or thrombocytopenia.

American trypanosomiasis. Available treatment for American trypanosomiasis (p. 925.3) is generally unsatisfactory, but benznidazole is of value especially in the acute phase. Guidelines[1,2] recommend that benznidazole should be given for 60 days. Although the duration of treatment has not been studied in patients co-infected with HIV, a treatment course of 30 to 60 days is recommended in these patients.[3] Treatment is usually confined to the acute phase of the disease. However, therapy during the early chronic phase was reported to be beneficial[4] (although a meta-analysis[5] suggested that benefit in late chronic phase was probably marginal); prospective long-term follow-up in patients with indeterminate- or chronic-stage disease who had received benznidazole has

shown that treatment may reduce the risk for progression of heart disease and reduce parasitaemia.[6]

1. WHO. Control of Chagas disease: second report of the WHO expert committee. *WHO Tech Rep Ser 905* 2002. Available at: http://libdoc.who.int/trs/WHO_TRS_905.pdf (accessed 17/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. 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)
4. de Andrade ALSS, *et al.* Randomised trial of efficacy of benznidazole in treatment of early Trypanosoma cruzi infection. *Lancet* 1996; 348: 1407–13.
5. Pérez-Molina JA, *et al.* Use of benznidazole to treat chronic Chagas' disease: a systematic review with a meta-analysis. *J Antimicrob Chemother* 2009; 64: 1139–47.
6. Viotti R, *et al.* Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial. *Ann Intern Med* 2006; 144: 724–34.

Adverse Effects

Benznidazole has adverse effects similar to those of metronidazole (p. 937.3).

The most commonly reported adverse effect is a hypersensitivity reaction characterised by dermatitis with cutaneous eruptions (usually appearing 5 to 10 days after starting treatment), fever, generalized oedema, lymphadenopathy, and joint and muscle pain. The most severe adverse effects are bone marrow depression, thrombocytopenic purpura, and agranulocytosis. Other reported adverse effects include polyneuropathy, paraesthesia, and peripheral neuropathy.

Like metronidazole, benznidazole is considered to be mutagenic and should be avoided during pregnancy. Patients are also advised not to drink alcoholic beverages while taking benznidazole.

A study[1] involving 20 patients with chronic American trypanosomiasis given benznidazole 5 mg/kg daily had to be stopped because of the high incidence of rashes and neurological symptoms. A severe, debilitating pain syndrome has also been reported in a patient after treatment with benznidazole for 5 weeks.[2]

1. Apt W, *et al.* Clinical trial of benznidazole and an immunopotentiator against Chagas disease in Chile. *Trans R Soc Trop Med Hyg* 1986; 80: 1010.
2. Moll C, *et al.* Severe invalidating pain syndrome associated with benznidazole therapy for Chagas' disease. *Clin Rheumatol* 2008; 27: 269–70.

Pharmacokinetics

Benznidazole is absorbed from the gastrointestinal tract after oral doses (>90% bioavailability) and is widely distributed throughout the body. More than 40% of the drug is bound to plasma protein. The peak plasma concentration occurs after 3 to 4 hours and the half-life is about 12 hours. It is metabolised in the liver and more than 70% of the metabolites are excreted by the kidneys; about 30% of a dose is excreted in the faeces.

References.

1. Raaflaub J, Ziegler WH. Single-dose pharmacokinetics of the trypanosomicide benznidazole in man. *Arzneimittelforschung* 1979; 29: 1611–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Radanil; *Braz.*: Rochagan†; *Ecuad.*: Ragonil.

Buparvaquone *(BAN, rINN)*

Buparvacuona; Buparvaquonum; BW-720C; Бупарвахон.
trans-2-(4-*tert*-Butylcyclohexylmethyl)-3-hydroxy-1,4-naphthoquinone.
$C_{21}H_{26}O_3$=326.4
CAS — 88426-33-9.
ATC Vet — QP51AX22.
UNII — 0354RT7LG4.

Profile

Buparvaquone is an antiprotozoal used in veterinary practice for the treatment of theileriosis in cattle. Topical formulations are being evaluated for the treatment of visceral and cutaneous leishmaniasis.

Carnidazole *(BAN, USAN, pINN)*

Carnidazol; Carnidazolum; R-25831; R-28096 (carnidazole hydrochloride); Карнидазол.
O-Methyl [2-(2-methyl-5-nitroimidazol-1-yl)ethyl]thiocarbamate.
$C_8H_{12}N_4O_3S$=244.3
CAS — 42116-76-7.
ATC Vet — QP51AA09.
UNII — RH5K1819JG.

Profile

Carnidazole is a 5-nitroimidazole derivative similar to metronidazole. It is used in veterinary practice for the treatment and prevention of trichomoniasis in pigeons.

Clazuril *(BAN, USAN, rINN)*

Clazurilo; Clazurilum; Klatsurili; Klazuril; R-62690; Клазурил.
(±)-[2-Chloro-4-(4,5-dihydro-3,5-dioxo-*as*-triazin-2(3*H*)-yl)phenyl]-(*p*-chlorophenyl)acetonitrile.
$C_{17}H_{10}Cl_2N_4O_2$=373.2
CAS — 101831-36-1.
ATC Vet — QP51AJ02.
UNII — O8W0R05772.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Clazuril for Veterinary Use; Clazuril BP(Vet) 2014). A white or light yellow powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; freely soluble in dimethylformamide. Protect from light.

Profile

Clazuril is an antiprotozoal used in veterinary practice for the treatment and prophylaxis of coccidiosis in pigeons.

Clefamide *(BAN, rINN)*

Chlorphenoxamide; Clefamida; Cléfamide; Clefamidum; Клефамид.
2,2-Dichloro-*N*-(2-hydroxyethyl)-*N*-[4-(4-nitrophenoxy)benzyl]acetamide.
$C_{17}H_{16}Cl_2N_2O_5$=399.2
CAS — 3576-64-5.
ATC — P01AC02.
UNII — 4AZ2VBK4EK.

Profile

Clefamide is an antiprotozoal that has been used as a luminal amoebicide in the treatment of *Entamoeba histolytica* infections.

Clopidol *(BAN, USAN, rINN)*

Clopidolum; Clopindol; Meticlorpindol; Клопидол.
3,5-Dichloro-2,6-dimethylpyridin-4-ol.
$C_7H_7Cl_2NO$=192.0
CAS — 2971-90-6.
UNII — 8J763HFF5N.

Profile

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

Decoquinate *(BAN, USAN, rINN)*

Décoquinate; Decoquinato; Decoquinatum; HC-1528; M&B-15497; Декохинат.
Ethyl 6-decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate.
$C_{24}H_{35}NO_5$=417.5
CAS — 18507-89-6.
ATC Vet — QP51AX14.
UNII — 534I52PVWH.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP (Vet).*

BP(Vet) 2014: (Decoquinate). A cream to buff-coloured, odourless or almost odourless, microcrystalline powder. Insoluble in water; practically insoluble in alcohol; very slightly soluble in chloroform and in ether.

USP 36: (Decoquinate). Store in airtight containers.

Profile

Decoquinate is an antiprotozoal used in veterinary practice for the treatment and prophylaxis of coccidiosis in calves and lambs, and for prophylaxis of coccidiosis in chickens. It is also used for prevention of abortions due to toxoplasmosis in sheep.

Dehydroemetine Hydrochloride *(BANM, rINNM)*

BT-436; Dehidroemetina, hidrocloruro de; Déhydroémétine Chlorhydrate de; 2,3-Dehydroemetine Hydrochloride; Dehydroemetini Hydrochloridum; DHE; Hidrocloruro de dehidroemetina; Ro-1-9334; Дегидроэметина Гидрохлорид.
2,3-Didehydro-6′,7′,10,11-tetramethoxyemetan dihydrochloride; 3-Ethyl-1,6,7,11b-tetrahydro-9,10-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl)-4*H*-benzo[*a*]quinolizine dihydrochloride.
$C_{29}H_{38}N_2O_4$,2HCl=551.5
CAS — 4914-30-1 (dehydroemetine); 2228-39-9 (dehydroemetine hydrochloride).

NOTE. The name DHE has been used to denote a preparation of dihydroergotamine mesilate.

Pharmacopoeias. In *Int.*

Profile

Dehydroemetine, a synthetic derivative of emetine (p. 932.3), is a tissue amoebicide with similar actions and uses, although probably of a lower toxicity.

Dehydroemetine should be avoided in patients with cardiac, renal, or neuromuscular disease and patients should be monitored for cardiotoxicity during treatment.

When used in the treatment of amoebiasis (p. 919.1) dehydroemetine hydrochloride is given by intramuscular injection in a dose of 1 mg/kg daily (maximum daily dose of 60 mg), generally for 6 to 10 days, but for no more than 5 days in children. A dose of 500 micrograms/kg has been suggested for elderly or severely ill patients. At least 6 weeks should elapse before treatment is repeated. After treatment with dehydroemetine, patients should receive a luminal amoebicide to eliminate organisms from the colon. Patients with hepatic abscesses may be given supplementary treatment with chloroquine. Dehydroemetine has also been used with metronidazole.

Administration in children. Doses of dehydroemetine for the treatment of amoebiasis in children are the same as those for adults, although it may be used for shorter periods, see above.

Liver fluke infections. Dehydroemetine has been given[1,2] in the treatment of the liver fluke infection fascioliasis (see p. 146.2).

1. Farid Z, *et al.* Treatment of acute toxaemic fascioliasis. *Trans R Soc Trop Med Hyg* 1988; 82: 299.
2. Cruz López O, *et al.* Fasciolosis hepática diagnosticada en fase de estado. *Rev Gastroenterol Mex* 2006; 71: 59–62.

Diaveridine *(BAN, USAN, rINN)*

BW-49-210; Diaveridina; Diavéridine; Diaveridinum; NSC-408735; Диаверидин.
5-Veratrylpyrimidine-2,4-diyldiamine.
$C_{13}H_{16}N_4O_2$=260.3
CAS — 5355-16-8.
ATC Vet — QP51AX18.
UNII — 7KVX81XA87.

Pharmacopoeias. In *Fr.* for veterinary use.

Profile

Diaveridine is an antiprotozoal used in veterinary practice for the control of coccidiosis in poultry.

Diclazuril *(BAN, USAN, rINN)*

Diclazurilo; Diclazurilum; Diklatsurili; Diklazuril; R-64433; Диклазурил.
(±)-4-Chlorophenyl[2,6-dichloro-4-(2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-2-yl)phenyl]acetonitrile.
$C_{17}H_9Cl_3N_4O_2$=407.6
CAS — 101831-37-2.
ATC Vet — QP51AJ03.
UNII — K110K1B1VE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Diclazuril for Veterinary Use; Diclazuril BP(Vet) 2014). A white or light yellow powder. Practically insoluble in water, in alcohol, and in dichloromethane; sparingly soluble in dimethylformamide. Protect from light.

USP 36: (Diclazuril). White to yellow powder. Practically insoluble in water, in alcohol, and in dichloromethane; sparingly soluble in dimethylformamide.

Profile

Diclazuril is an antiprotozoal that has been tried in AIDS patients for the management of diarrhoea associated with

protozoal infection. It is used in veterinary practice for the control of coccidiosis.

References.
1. Kayembe K. *et al.* Diclazuril for Isospora belli infections in AIDS. *Lancet* 1989; i: 1397.
2. Connolly GM. *et al.* Diclazuril in the treatment of severe cryptosporidial diarrhoea in AIDS patients. *AIDS* 1990; 4: 700–701.
3. Menichetti F. *et al.* Diclazuril for cryptosporidiosis in AIDS. *Am J Med* 1991; 90: 271–2.
4. Limson-Pobre RNR. *et al.* Use of diclazuril for the treatment of isosporiasis in patients with AIDS. *Clin Infect Dis* 1995; 20: 201–2.

Diiodohydroxyquinoline *(INN)*

Diiodohidroxiquinoleína; Diiodohydroxyquin; Diiodohydroxyquinoléine; Di-iodohydroxyquinoline (BAN); Diiodohydroxyquinolinum; Diiodoidrossichinolina; Di-iodoxychinolinum; Diiodoxyquinoléine; Diiyodohidroksikinolin; Dijodhydroxikinolin; Dijodihydroksikinoliini; Iodoquinol (USAN); Yodoquinol; Дийодогидроксихинолин.

5,7-Di-iodoquinolin-8-ol.

$C_9H_5I_2NO$=397.0

CAS — 83-73-8.

ATC — G01AC01.

ATC Vet — QG01AC01.

UNII — 63W7IE88K8.

Pharmacopoeias. In *US.*

USP 36: (Iodoquinol). A light yellowish to tan, microcrystalline powder, not readily wetted in water, odourless or has a faint odour. Practically insoluble in water; sparingly soluble in alcohol and in ether.

Uses and Administration

Diiodohydroxyquinoline, a halogenated hydroxyquinoline, is a luminal amoebicide acting mainly in the bowel lumen and is used in the treatment of intestinal amoebiasis, (p. 919.1) although less toxic amoebicides such as diloxanide furoate or paromomycin are usually preferred, especially in children (see Precautions, below). It is given alone in the treatment of asymptomatic cyst passers, or as follow-up treatment after an amoebicide that acts in the tissues, such as metronidazole, in patients with symptomatic (invasive) amoebiasis. The usual oral dosage is 630 or 650 mg three times daily for 20 days.

For details of doses in children, see below.

Diiodohydroxyquinoline has also been given in the treatment of *Dientamoeba fragilis* infections, in balantidiasis (p. 920.3) as an alternative to tetracycline, and has been tried in *Blastocystis hominis* infections (p. 920.3).

Diiodohydroxyquinoline was formerly used in the treatment of acrodermatitis enteropathica; it is reported to act by enhancing zinc absorption and has now been superseded by oral zinc therapy.

Diiodohydroxyquinoline is claimed to have some antibacterial and antifungal activity and has been used topically (but see Children, under Precautions, below).

Administration in children. Diiodohydroxyquinoline is licensed in the USA and some other countries for the treatment of amoebiasis in children; however, there is concern over its safety in children (see Children, under Precautions, below).

For the treatment of asymptomatic amoebiasis (including asymptomatic cyst passers) and as follow-up treatment after a tissue amoebicide in the management of symptomatic intestinal or invasive amoebiasis, diiodohydroxyquinoline is given in the usual oral dose of 10 to 13.3 mg/kg three times daily (to a maximum of 1.95 g daily) for 20 days.

Adverse Effects

Major concerns have been expressed about the safety of the halogenated hydroxyquinolines since the recognition of severe neurotoxicity with clioquinol (p. 273.1). In Japan, the epidemic development of subacute myelo-opticoneuropathy (SMON) in the 1960s was associated with the ingestion of normal or high doses of clioquinol for prolonged periods and the sale of clioquinol and related hydroxyquinolines was subsequently banned there. Symptoms of SMON are mainly those of peripheral neuropathy, including optic atrophy, and myelopathy. Abdominal pain and diarrhoea often precede neurological symptoms such as paraesthesias in the legs, progressing to paraplegia in some patients, and loss of visual acuity sometimes leading to blindness. Cerebral disturbances, including confusion and retrograde amnesia, have also been reported. Although many patients improved when clioquinol was withdrawn, others had residual disability.

It was suggested that the Japanese epidemic might have been due to genetic susceptibility, but a few cases of SMON associated with clioquinol or related hydroxyquinoline derivatives, including broxyquinoline and diiodohydroxyquinoline, have been reported elsewhere.

Diiodohydroxyquinoline has also been associated with gastrointestinal effects such as abdominal cramps, nausea, and diarrhoea. Adverse effects which may be attributable to the iodine content of diiodohydroxyquinoline include pruritus ani, skin eruptions, and enlargement of the thyroid gland. Fever, chills, headache, and vertigo have also occurred.

Effects on the nervous system. Hypertensive encephalopathy and seizures have been reported in a 10-year-old boy taking oral diiodohydroxyquinoline for a *Dientamoeba fragilis* infection.[1] Fourteen days after starting treatment the boy had abdominal cramps and muscle pain. Four days later a pins-and-needles sensation in his feet, ataxic gait, foot drop, stiff legs, general weakness, and headache developed. These symptoms were shortly followed by tonic-clonic seizures and results from additional investigations indicated a hypertensive encephalopathy. Five months after stopping diiodohydroxyquinoline, results from a neurologic examination were normal, but the boy still had tingling and sensitivities in his legs.

1. Health Canada. Iodoquinol: suspected association with hypertensive encephalopathy and seizures. *Can Adverse React News* 2006; 16 (3): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/cam-bcei_v16n3-eng.pdf (accessed 11/02/09)

Precautions

Diiodohydroxyquinoline is contra-indicated in patients known to be hypersensitive to iodine or halogenated hydroxyquinolines and in those with hepatic or renal impairment. It should be used with caution in thyroid disease and may interfere with determinations of protein-bound iodine in tests for thyroid function for up to 6 months after therapy. Its use is best avoided in patients with neurological disorders. Long-term use should be avoided.

Children. Last available guidance from the Committee on Drugs of the American Academy of Pediatrics[1] considered that there was a potential risk of toxicity to infants and children from clioquinol and diiodohydroxyquinoline applied topically. Since alternative effective preparations are available for dermatitis, the Committee recommended that products containing either of these compounds should not be used.

WHO considers that the use of halogenated hydroxyquinolines for the treatment of acute diarrhoea or amoebiasis in children cannot be justified.[2] There is no evidence of their efficacy in acute diarrhoea and they have been associated with severe neurological effects. On the rare occasions when a luminal amoebicide is required, other less toxic and more effective agents are available.

1. Kaufman RE. *et al.* American Academy of Pediatrics Committee on Drugs. Clioquinol (iodochlorhydroxyquin, Vioform) and Iodoquinol (diiodohydroxyquin): blindness and neuropathy. *Pediatrics* 1990; 86: 797–8. [Re-affirmed October 2006, Retired January 2011] Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;86/5/797.pdf (accessed 15/02/11)
2. WHO. The rational use of drugs in the management of acute diarrhoea in children. Geneva: WHO, 1990.

Pharmacokinetics

Diiodohydroxyquinoline is poorly absorbed from the gastrointestinal tract. Concern has been expressed about possible absorption after application to the skin (see Children, under Precautions, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Diodoquin; *Mex.*: Ameban; Antidifar; Carsuquin; Diamebᵗ; Diodoquin; Diyosulᵗ; Entero-Diyod; Entodibaᵗ; Exoquin; Quinosul; Versamiv; *Turk.*: Floraquin; *USA*: Aloquin; *Sebaquin*; Yodoxin; *Venez.*: Diodoquin.

Multi-ingredient Preparations. *Arg.*: Hipoglos Cicatrizante; *Chile*: Dexagin; *Hong Kong*: Anlinaᵗ; *India*: Enteroguanidine; *Mex.*: Ameban; Amebyl; Bontal; Coralzul; Depofin; Dialginᵗ; Diodolina; Dipecfur; Facetin-D; Farmeban; Flagenase 400; Flagocilᵗ; Lambliquin; Metodine; Metrodiyod; Norecil; Novagcon; Stomfler Plus; Threchopᵗ; *S.Afr.*: Vagarsol; Viocort; Viodorᵗ; *Thai.*: Coccila; Disento; Gynecon-T; Gynecon; Gynocoᵗ; Gynovaᵗ; Gyonep; Gyracon; Nystin; Patarver; Quinradon-Nᵗ; Vagicin; VG Med; *USA*: Alcortin A; Hydro-Iodoquinol; Vytone.

Pharmacopoeial Preparations
USP 36: Iodoquinol Tablets.

Diloxanide Furoate *(BANM, rINNM)*

Diloksanid Furoat; Diloxanida, furoato de; Diloxanide, Furoate de; Diloxanidi Furoas; Furoato de diloxanida; Дилоксанида Фуроат.

4-(*N*-Methyl-2,2-dichloroacetamido)phenyl 2-furoate.

$C_{14}H_{11}Cl_2NO_4$=328.1

CAS — 579-38-4 (diloxanide); 3736-81-0 (diloxanide furoate).

ATC — P01AC01.

UNII — YP4NZ2IW34.

Pharmacopoeias. In *Br., Int.*, and *US.*

BP 2014: (Diloxanide Furoate). A white or almost white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Protect from light.

USP 36: (Diloxanide Furoate). A white or almost white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Diloxanide furoate, a dichloroacetamide derivative, is a luminal amoebicide acting mainly in the bowel lumen and is used in the treatment of intestinal amoebiasis (p. 919.1). It is given alone in the treatment of asymptomatic cyst passers or after an amoebicide that acts in the tissues, such as metronidazole, in patients with symptomatic (invasive) amoebiasis.

Diloxanide furoate is given orally in a dosage of 500 mg three times daily for 10 days. The course of treatment may be repeated if necessary.

For details of doses in children, see below.

Administration in children. Diloxanide furoate may be given orally to children for the treatment of asymptomatic amoebiasis (including asymptomatic cyst passers) and as follow-up treatment after a tissue amoebicide in the management of symptomatic (invasive) amoebiasis in dose of 20 mg/kg daily; in 3 divided doses, for 10 days. UK licensed product information stipulates diloxanide furoate may only be given to children weighing more than 25 kg while the *BNFC* suggests it may be given to children from the age of 1 month.

Adverse Effects

Flatulence is the most common adverse effect during treatment with diloxanide furoate. Vomiting, pruritus, and urticaria may occasionally occur.

Pharmacokinetics

Diloxanide furoate is hydrolysed before absorption from the gastrointestinal tract. The resulting diloxanide is readily absorbed and excreted mainly in the urine as the glucuronide; less than 10% of a dose appears in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Amicline.

Multi-ingredient Preparations. *India*: Aldezol-DF; Amebis Forte; Amicline Plus; Antibic-DF; Aristogyl Plus; Dialox; DLotin MPS; Dyrade-M; Eldazole; Entamizole†; Entrolate; Idometrin-D; Metrogyl Compound; Metron-DF; Novogyl-MPS; Qugyl; Tinidafyl Plus; Wotinex.

Pharmacopoeial Preparations
BP 2014: Diloxanide Tablets.

Dimetridazole *(BAN, pINN)*

Dimetridatsoli; Dimetridazol; Dimétridazole; Dimetridazolum; Диметридазол.

1,2-Dimethyl-5-nitroimidazole.

$C_5H_7N_3O_2$=141.1

CAS — 551-92-8.

ATC Vet — QP51AA07.

UNII — K59P7XN88X.

Pharmacopoeias. In *Fr.* for veterinary use. Also in *BP(Vet).*

BP(Vet) 2014: (Dimetridazole). An almost white to brownish-yellow, odourless or almost odourless powder which darkens on exposure to light. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; slightly soluble in ether. Protect from light.

Profile

Dimetridazole is a 5-nitroimidazole derivative similar to metronidazole. It is used in veterinary practice for the control of various protozoal infections in birds, fish, and reptiles. It has also been used for swine dysentery. Dimetridazole is considered to be potentially carcinogenic and use in food-producing animals has been banned in some countries.

Diminazene Aceturate (BANM, rINNM)

Aceturato de diminazeno; Diminazène, Acéturate de; Diminazeni Aceturas; Diminazeno, aceturato de; Диминазена Ацетурат.

1,3-Bis(4-amidinophenyl)triazene bis(*N*-acetylglycinate).

$C_{27}H_{29}N_9O_6$=575.5

CAS — 536-71-0 (diminazene); 908-54-3 (diminazene aceturate).

UNII — J8RSAD85NO.

NOTE. Diminazene aceturate is often referred to by its veterinary proprietary name Berenil.

Profile

Diminazene aceturate, an aromatic diamidine derivative related to pentamidine, is an antiprotozoal used in veterinary practice in the treatment of trypanosomiasis and babesiosis. It has also been tried in human infections.

Dinitolmide (BAN, rINN)

Dinitolmida; Dinitolmidum; Dinitrotoluamida; Dinitrotoluamide; Methyldinitrobenzamide; Динитолмид.

3,5-Dinitro-o-toluamide.

$C_8H_7N_3O_5$=225.2

CAS — 148-01-6.

ATC Vet — QP51AX12.

UNII — AOX68RY47V.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Dinitolmide). A cream to light tan powder. Practically insoluble in water; slightly soluble in alcohol, in chloroform, and in ether; soluble in acetone.

Profile

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

Eflornithine Hydrochloride

(BANM, USAN, rINNM)

DFMO; α-Difluoromethylornithine Hydrochloride; Éflornithine; Chlorhydrate d'; Eflornithini Hydrochloridum; Eflornitina, hidrocloruro de; Hidrocloruro de, eflornitina; MDL-71782; MDL-71782A; RMI-71782; Эфлорнитина Гидрохлорид.

2-(Difluoromethyl)-DL-ornithine monohydrochloride monohydrate.

$C_6H_{12}F_2N_2O_2$,HCl,H_2O=236.6

CAS — 67037-37-0 (eflornithine); 96020-91-6 (eflornithine hydrochloride).

ATC — D11AX16; P01CX03.

ATC Vet — QD11AX16.

UNII — 4NH22NDW9H.

Uses and Administration

Eflornithine is an antiprotozoal that acts as an irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis; trypanosomes are more susceptible to the effects of eflornithine than are humans, probably because of their slower turnover of this enzyme.

Eflornithine is used in **African trypanosomiasis** due to *Trypanosoma brucei gambiense* (see below). It is effective in the late stage of the disease (when there is CNS involvement).

In the treatment of African trypanosomiasis, eflornithine hydrochloride is given by intravenous infusion. The dose is 100 mg/kg every 6 hours for at least 14 days. Each dose should be given over a period of at least 45 minutes. Dosage should be reduced in patients with renal impairment.

Eflornithine hydrochloride is also applied topically twice daily for the reduction of unwanted **facial hair** in women (see Hirsutism, below). It is available as a cream containing 15% eflornithine hydrochloride monohydrate; in the UK this content is expressed as 11.5% eflornithine and in the USA as 13.9% anhydrous eflornithine hydrochloride.

Oral formulations of eflornithine are under investigation for the treatment of familial adenomatous polyposis (see Malignant Neoplasms of the Colon and Rectum, p. 706.3).

Cryptosporidiosis. Eflornithine has been tried in the treatment of cryptosporidiosis (p. 921.1) in AIDS patients.[1]

1. Rolston KVI, *et al.* Intestinal cryptosporidiosis treated with eflornithine: a prospective study among patients with AIDS. *J Acquir Immune Defic Syndr* 1989; 2: 426–30.

Hirsutism. Topical eflornithine hydrochloride applied twice daily as a 13.9% cream is effective in reducing the growth of unwanted facial hair in females (see Hirsutism, p. 2262.1), although it must be used indefinitely to prevent regrowth.[1] Its action is thought to be due to the irreversible inhibition of ornithine decarboxylase in hair follicles. It has also been used successfully with laser hair removal.[2]

1. Barman Balfour JA, McClellan K. Topical eflornithine. *Am J Clin Dermatol* 2001; 2: 197–201.
2. Hamzavi I, *et al.* A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. *J Am Acad Dermatol* 2007; 57: 54–9.

Malignant neoplasms. Eflornithine has antimetabolic activity and is being studied as a potential chemopreventive agent in patients at high risk of a variety of malignant diseases, including cancer of the bladder, breast, cervix, colon, oesophagus, prostate, and skin.[1,2] It has been investigated with NSAIDs such as sulindac in the prevention of colon cancer.

1. Meyskens FL, Gerner EW. Development of difluoromethylornithine (DFMO) as a chemoprevention agent. *Clin Cancer Res* 1999; 5: 945–51.
2. Raul F. Revival of 2-(difluoromethyl)ornithine (DFMO), an inhibitor of polyamine biosynthesis, as a cancer chemopreventive agent. *Biochem Soc Trans* 2007; 35: 353–5.

African trypanosomiasis. Eflornithine is effective in the treatment of *Trypanosoma brucei gambiense* infections (p. 925.2), and is particularly valuable in providing an alternative to melarsoprol in meningoencephalitic disease.[1-3] Eflornithine 100 mg/kg intravenously every 6 hours for 7 days, rather than the standard 14 days, produced long-term responses in 42 of 47 patients who had relapsed after other treatment regimens.[4] Similar positive results in relapsing cases were obtained with a short 7-day course in a multicentre randomised controlled study,[5] although this short course was inferior to the 14-day course for new cases, in whom it could not be recommended. A patient who had relapsed after treatment with melarsoprol and eflornithine given singly was cured when the drugs were given together.[6] Eflornithine given for 4 days followed by 3 daily injections of melarsoprol, was associated with a cure rate of 93% in 42 patients with melarsoprol-resistant Gambian trypanosomiasis. Efficacy and toxicity were considered to be similar to a 7-day course of eflornithine monotherapy.[7] Promising results have been reported from use of eflornithine 400 mg/kg daily (200 mg/kg every 12 hours) intravenously for 7 days with oral nifurtimox 15 mg/kg daily (5 mg/kg every 8 hours) for 10 days;[8,9] this drug combination has now been included in the WHO List of Essential Medicines for the treatment of human African trypanosomiasis.[10]

Eflornithine is not effective when given alone in *T. b. rhodesiense* infections, and early reports of its use with suramin were not encouraging.[11]

1. Chappuis F, *et al.* Eflornithine is safer than melarsoprol for the treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis. *Clin Infect Dis* 2005; 41: 748–51.
2. Balasegaram M, *et al.* Melarsoprol versus eflornithine for treating late-stage Gambian trypanosomiasis in the Republic of the Congo. *Bull WHO* 2006; 84: 783–91.
3. Priotto G, *et al.* Safety and effectiveness of first line eflornithine for *Trypanosoma brucei gambiense* sleeping sickness in Sudan: cohort study. *BMJ* 2008; 336: 705–8.
4. Khonde N, *et al.* A seven days course of eflornithine for relapsing Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1997; 91: 212–13.
5. Pepin J, *et al.* Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. *Bull WHO* 2000; 78: 1284–95.
6. Simarro PP, Asumu PN. Gambian trypanosomiasis and synergism between melarsoprol and eflornithine: first case report. *Trans R Soc Trop Med Hyg* 1996; 90: 315.
7. Mpia B, Pépin J. Combination of eflornithine and melarsoprol for melarsoprol-resistant Gambian trypanosomiasis. *Trop Med Int Health* 2002; 7: 775–9.
8. 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.
9. 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.
10. 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)
11. 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 and Precautions

Intravenous eflornithine commonly causes myelosuppression that may lead to anaemia, leucopenia, and thrombocytopenia. Some patients have had hearing loss and alopecia. Gastrointestinal disturbances, especially diarrhoea, may occur. Seizures have occurred in about 8% of patients given eflornithine but they may have been related to the disease rather than treatment.

Dosage should be reduced in patients with renal impairment.

Acne and skin irritation, such as erythema or a stinging or burning sensation, has been reported after topical application of eflornithine; however, adverse effects are generally mild and usually resolve without medical treatment or stopping eflornithine.

Effects on the ears. A study in 58 patients[1] given oral eflornithine alone or with interferon alfa for the treatment of metastatic melanoma found that hearing loss was related to the cumulative dose of eflornithine and was worse in patients with pre-existing hearing deficit. Temporary hearing loss usually occurs with daily doses above 2 g/m² and when the cumulative dose exceeds 250 g/m². A case of irreversible hearing loss has been reported in a patient with Barrett's oesophagus after taking [oral] eflornithine 500 mg/m² daily for about 13 weeks (cumulative dose of 45 g/m²) for the prevention of oesophageal cancer.[2]

1. Croghan MK, *et al.* Dose-related α -difluoromethylornithine ototoxicity. *Am J Clin Oncol* 1991; 14: 331–5.
2. Lao CD, *et al.* Irreversible ototoxicity associated with difluoromethylornithine. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 1250–2.

Effects on the heart. An AIDS patient with pneumocystis pneumonia had a fatal cardiac arrest during an intravenous infusion of eflornithine 100 mg/kg over 1 hour.[1] Sudden death after infusion of eflornithine had occurred in several other critically ill patients with AIDS.

1. Barbarash RA, *et al.* Alpha-difluoromethylornithine infusion and cardiac arrest. *Ann Intern Med* 1986; 105: 141–2.

Pharmacokinetics

Eflornithine hydrochloride is absorbed from the gastrointestinal tract. After intravenous doses about 80% is excreted unchanged in the urine in 24 hours. The terminal elimination half-life is about 3 hours. It is distributed to the CSF.

Less than 1% of a dose is absorbed after topical application.

References.

1. Haegele KD, *et al.* Kinetics of α -difluoromethylornithine: an irreversible inhibitor of ornithine decarboxylase. *Clin Pharmacol Ther* 1981; 30: 210–17.
2. Milord F, *et al.* Eflornithine concentrations in serum and cerebrospinal fluid of 63 patients treated for Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1993; 87: 473–7.
3. Malhotra B, *et al.* Percutaneous absorption and pharmacokinetics of eflornithine HCl 13.9% cream in women with unwanted facial hair. *J Clin Pharmacol* 2001; 41: 972–8.
4. Na-Bangchang K, *et al.* The pharmacokinetics of eflornithine (alpha-difluoromethylornithine) in patients with late-stage T.b. gambiense sleeping sickness. *Eur J Clin Pharmacol* 2004; 60: 269–78.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vaniqa; *Austral.*: Vaniqa; *Austria*: Vaniqa; *Belg.*: Vaniqa; *Canad.*: Vaniqa; *Chile*: Sessor; Vaniqa; *Cz.*: Vaniqa; *Denm.*: Vaniqa; *Fr.*: Vaniqa; *Ger.*: Vaniqa; *India*: Eflora; Elyn; *Irl.*: Vaniqa; *Israel*: Vaniqa; *Ital.*: Vaniqa; *Neth.*: Vaniqa; *Norw.*: Vaniqa; *Pol.*: Vaniqa; *Port.*: Vaniqa; *Spain*: Vaniqa; *Swed.*: Vaniqa; *Switz.*: Vaniqa; *UK*: Vaniqa; *USA*: Ornidyl†; Vaniqa.

Emetine Hydrochloride (BANM)

Cloridrato de Emetina; Emet. Hydrochlor.; Emetiinihydrokloridi; Emetina, hidrocloruro de; Emetin-dihydrochlorid; Émétine, chlorhydrate d'; Emetine Dihydrochloride; Emetinhidroklorid; Emetinhydroklorid; Emetini Chloridum; Emetini Dihydrochloridum; Emetini hydrochloridum; Emetino hidrochloridas; Emetyny dichlorowodorek; Ipecine Hydrochloride; Methylcephaëline Hydrochloride; Эметина Гидрохлорид.

6',7',10,11-Tetramethoxyemetan dihydrochloride heptahydrate; (2*S*,3*R*,11b*S*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-[(1*R*)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl]-2*H*-benzo[*a*]quinolizine dihydrochloride heptahydrate.

$C_{29}H_{40}N_2O_4$,2HCl,$7H_2O$=679.7

CAS — 483-18-1 (emetine); 316-42-7 (anhydrous emetine hydrochloride); 7083-71-8 (emetine hydrochloride, hydrate); 79300-08-6 (emetine hydrochloride, heptahydrate).

ATC — P01AX02.

UNII — U52OG12P96 (anhydrous emetine hydrochloride); J636CC0C64 (emetine hydrochloride heptahydrate); 07DUYSKQBX (emetine hydrochloride pentahydrate).

Pharmacopoeias. In *Chin.* and *Viet.*

Eur. has a monograph for Emetine Hydrochloride Pentahydrate;

Int. permits the heptahydrate or pentahydrate in the same monograph. *US* has a monograph for the anhydrous salt.

Ph. Eur. 8: (Emetine Hydrochloride Pentahydrate). A white or slightly yellow crystalline powder. Freely soluble in water and in alcohol. A 2% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 36: (Emetine Hydrochloride). The hydrochloride of an alkaloid obtained from ipecacuanha, or prepared by methylation of cephaëline, or prepared synthetically. Anhydrous emetine hydrochloride is a white or slightly yellowish, odourless, crystalline powder. Freely soluble in

water and 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

Emetine, an alkaloid of ipecacuanha (p. 1667.2), is a tissue amoebicide acting mainly in the bowel wall and in the liver. It has been given by deep subcutaneous or intramuscular injection in the treatment of severe invasive amoebiasis (p. 919.1), including hepatic amoebiasis in patients who do not respond to metronidazole, but safer drugs have generally replaced it. Emetine was formerly given orally as emetine and bismuth iodide.

Emetine has also been included in combination preparations for the symptomatic relief of cough.

Adverse Effects

Emetine hydrochloride is commonly associated with muscle pain and weakness around the injection site; there may be necrosis and abscess formation. After injection, diarrhoea and nausea and vomiting, sometimes with dizziness and headache, are common. There may be more generalised myalgia and weakness, and, more rarely, mild sensory disturbances. Eczematous, urticarial, and purpuric skin lesions have been reported.

Cardiotoxicity may be marked by precordial pain, dyspnoea, tachycardia, and hypotension. ECG changes, particularly flattening or inversion of the T-wave and prolongation of the QT interval, occur in many patients. Accumulation after large doses or prolonged use may cause lesions of the heart, gastrointestinal tract, kidneys, liver, and skeletal muscle. Severe acute degenerative myocarditis may occur and give rise to sudden cardiac failure and death. In some patients cardiotoxic effects have appeared after the completion of treatment with therapeutic doses.

Emetine hydrochloride is very irritant and contact with mucous membranes should be avoided.

Precautions

Emetine is contra-indicated in cardiac, renal, or neuromuscular disease, in pregnancy, and in children except in severe amoebic dysentery unresponsive to other drugs. It should be used with great caution in old or debilitated patients. Patients given emetine should be closely supervised; ECG monitoring is advisable during treatment.

Pharmacokinetics

After injection emetine hydrochloride is concentrated in the liver, and to some extent in kidney, lung, and spleen. Excretion is slow and detectable amounts may persist in urine 40 to 60 days after treatment has been stopped.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Spirbon†; *Hung.*: Radipon†; *Switz.*: Sano Tuss.

Pharmacopoeial Preparations
USP 36: Emetine Hydrochloride Injection.

Ethopabate *(BAN)*

Etopabato; Этопабат.
Methyl 4-acetamido-2-ethoxybenzoate.
$C_{12}H_{15}NO_4$=237.3
CAS — 59-06-3.
ATC Vet — QP51AX17.
UNII — F4X3L6068O.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP (Vet)*.

BP(Vet) 2014: (Ethopabate). A white or pinkish-white powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in chloroform and in methyl alcohol; slightly soluble in ether.

USP 36: (Ethopabate). A white or pinkish-white, odourless or practically odourless, powder. Very slightly soluble in water; soluble in dehydrated alcohol, in acetone, in methyl alcohol, and in acetonitrile; slightly soluble in ether; sparingly soluble in dichloromethane, in dioxan, in ethyl acetate, and in isopropyl alcohol. Protect from light.

Profile

Ethopabate is an antiprotozoal used in veterinary practice for the control of coccidiosis in poultry.

Etofamide *(rINN)*

Ethychlordiphene; Etofamida; Étofamide; Etofamidum; K-430; Этофамид.
2,2-Dichloro-*N*-(2-ethoxyethyl)-*N*-[4-(4-nitrophenoxy)benzyl] acetamide.
$C_{19}H_{20}Cl_2N_2O_5$=427.3
CAS — 25287-60-9.
ATC — P01AC03.
UNII — 03F36JH2TU.

Profile

Etofamide, a dichloroacetamide derivative, is a luminal amoebicide with actions and uses similar to those of diloxanide furoate (p. 931.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Kitnos; *Mex.*: Kitnos; *Philipp.*: Kitnos.

Fumagillin *(BAN, rINN)*

Fumagilina; Fumagillini; Fumagilline; Fumagillinum; Фумагиллин.
4-(1,2-Epoxy-1,6-dimethylhex-4-enyl)-5-methoxy-1-oxaspiro [2.5]oct-6-yl hydrogen deca-2,4,6,8-tetraenedioate.
$C_{26}H_{34}O_7$=458.6
CAS — 23110-15-8.
ATC — P01AX10.
ATC Vet — QP51AX23.
UNII — 7OW73204U1.

Profile

Fumagillin is an alicyclic antibiotic produced by certain strains of *Aspergillus fumigatus*. It has activity against microsporidia and is used in veterinary practice to control *Nosema apis* infection in honeybees.

Fumagillin is given in an oral dose of 20 mg three times daily for 14 days in the treatment of diarrhoea due to intestinal microsporidial infection (see below) with *Enterocytozoon bieneusi* in patients with HIV infection. It has also been tried in humans in the topical treatment of microsporidial keratoconjunctivitis. It was formerly given orally in the treatment of intestinal amoebiasis, but produced an unacceptably high frequency of adverse effects. Analogues of fumagillin have been studied for effects on angiogenesis in solid tumours.

Microsporidiosis. As discussed on p. 924.1, topical treatment of microsporidial keratoconjunctivitis has been disappointing. There have been several reports of successful treatment in individual patients using fumagillin topically,[1-3] usually as a solution of bicyclohexylammonium fumagillin containing the equivalent of fumagillin 70 micrograms/mL.

Oral fumagillin has been effective in the treatment of diarrhoea due to intestinal microsporidial infection with *Enterocytozoon bieneusi* in immunocompromised patients, including those with HIV infection[4-6] and solid organ transplant recipients.[6-8] US guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents[9] recommend the use of topical fumagillin plus oral albendazole for microsporidial eye infections.

1. Rosberger DF, *et al.* Successful treatment of microsporidial keratoconjunctivitis with topical fumagillin in a patient with AIDS. *Cornea* 1993; 12: 261–5.
2. Diesenhouse MC, *et al.* Treatment of microsporidial keratoconjunctivitis with topical fumagillin. *Am J Ophthalmol* 1993; 115: 293–8.
3. Garvey MJ, *et al.* Topical fumagillin in the treatment of microsporidial keratoconjunctivitis in AIDS. *Ann Pharmacother* 1995; 29: 872–4.
4. Molina J-M, *et al.* Potential efficacy of fumagillin in intestinal microsporidiosis due to Enterocytozoon bieneusi in patients with HIV infection: results of a drug screening study. *AIDS* 1997; 11: 1603–10.
5. Molina J-M, *et al.* Trial of oral fumagillin for the treatment of intestinal microsporidiosis in patients with HIV infection. *AIDS* 2000; 14: 1341–8.
6. Molina J-M, *et al.* Fumagillin treatment of intestinal microsporidiosis. *N Engl J Med* 2002; 346: 1963–9.
7. Lantermier F, *et al.* Microsporidiosis in solid organ transplant recipients: two Enterocytozoon bieneusi cases and review. *Transpl Infect Dis* 2009; 11: 83–8.
8. Champion L, *et al.* Fumagillin for treatment of intestinal microsporidiosis in renal transplant recipients. *Am J Transplant* 2010; 10: 1925–30.
9. 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)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Flisint.

Furazolidone *(BAN, rINN)*

Furatsolidoni; Furazolidon; Furazolidona; Furazolidonum; Nifurazolidonum; Фуразолидон.
3-(5-Nitrofurfurylideneamino)-2-oxazolidone.
$C_8H_7N_3O_5$=225.2
CAS — 67-45-8.
ATC — G01AX06.
ATC Vet — QG01AX06; QJ01XE90.
UNII — SJ9CPU3RE0.

Pharmacopoeias. In *Br.*, *Fr.*, and *US*.

BP 2014: (Furazolidone). A yellow odourless or almost odourless crystalline powder. Very slightly soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. The filtrate from a 1% suspension in water has a pH of 4.5 to 7.0. Protect from light.

USP 36: (Furazolidone). A yellow, odourless, crystalline powder. Practically insoluble in water, in alcohol, and in carbon tetrachloride. Store in airtight containers. Protect from light and avoid exposure to direct sunlight.

Uses and Administration

Furazolidone is a nitrofuran derivative with antiprotozoal and antibacterial activity. It is active against the protozoan *Giardia intestinalis* (*Giardia lamblia*) and against a range of enteric bacteria *in vitro*, including staphylococci, enterococci, *Escherichia coli*, *Salmonella* spp., *Shigella* spp., and *Vibrio cholerae*. Furazolidone is bactericidal and appears to act by interfering with bacterial enzyme systems. Resistance is reported to be limited. It is used in the treatment of giardiasis (p. 921.3) and cholera (p. 184.2). It has been suggested for other bacterial gastrointestinal infections, but antibacterial therapy is regarded as unnecessary in mild and self-limiting gastro-enteritis (see p. 182.2).

Furazolidone is given orally in a dose of 100 mg four times daily. It is usually given for 2 to 5 days, but may be given for up to 7 days in some patients, or for up to 10 days for giardiasis.

For details of doses in children see below.

Administration in children. For the treatment of giardiasis, cholera, and other diarrhoeal diseases caused by susceptible organisms, children and infants from 1 month of age may be given oral furazolidone at a dose of 1.25 to 1.5 mg/kg four times daily for 2 to 5 days. Some patients may need 7 days of treatment, or up to 10 days for giardiasis.

Peptic ulcer disease. Furazolidone is not one of the main antibacterials used in *Helicobacter pylori* eradication regimens for peptic ulceration (p. 1816.2), but there are some studies suggesting its efficacy in adults,[1-7] children,[8,9] and in patients unresponsive to standard first- or second-line eradication regimens.[10-14]

1. Xiao S-D, *et al.* High cure rate of Helicobacter pylori infection using tripotassium dicitrato bismuthate, furazolidone and clarithromycin triple therapy for 1 week. *Aliment Pharmacol Ther* 1999; 13: 311–15.
2. Liu W-Z, *et al.* Furazolidone-containing short-term triple therapies are effective in the treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 1999; 13: 317–22.
3. Dani R, *et al.* Omeprazole, clarithromycin and furazolidone for the eradication of Helicobacter pylori in patients with duodenal ulcer. *Aliment Pharmacol Ther* 1999; 13: 1647–52.
4. Graham DY, *et al.* Furazolidone combination therapies for Helicobacter pylori infection in the United States. *Aliment Pharmacol Ther* 2000; 14: 211–15.
5. Liu W-Z, *et al.* A new quadruple therapy for Helicobacter pylori using tripotassium dicitrato bismuthate, furazolidone, josamycin and famotidine. *Aliment Pharmacol Ther* 2000; 14: 1519–22.
6. Fakheri H, *et al.* Clarithromycin vs furazolidone in quadruple therapy regimens for the treatment of Helicobacter pylori in a population with a high metronidazole resistance rate. *Aliment Pharmacol Ther* 2001; 15: 411–16.
7. Lu H, *et al.* One-week regimens containing ranitidine bismuth citrate, furazolidone and either amoxicillin or tetracycline effectively eradicate Helicobacter pylori: a multicentre, randomized, double-blind study. *Aliment Pharmacol Ther* 2001; 15: 1975–9.
8. Kawakami E, *et al.* Furazolidone-based triple therapy for H pylori gastritis in children. *World J Gastroenterol* 2006; 12: 5544–9.
9. Machado RS, *et al.* Furazolidone, tetracycline and omeprazole: a low-cost alternative for Helicobacter pylori eradication in children. *J Pediatr (Rio J)* 2008; 84: 160–5.
10. Silva FM, *et al.* Omeprazole, furazolidone, and tetracycline: an eradication treatment for resistant H. pylori in Brazilian patients with peptic ulcer disease. *Rev Hosp Clin Fac Med Sao Paulo* 2002; 57: 205–8.
11. Isakov V, *et al.* Furazolidone-based triple 'rescue therapy' vs. quadruple 'rescue therapy' for the eradication of Helicobacter pylori resistant to metronidazole. *Aliment Pharmacol Ther* 2002; 16: 1277–82.
12. Elsig JN, *et al.* A furazolidone-based quadruple therapy for Helicobacter pylori retreatment in patients with peptic ulcer disease. *Clinics* 2005; 60: 485–8.
13. Qasim A, *et al.* Rifabutin- and furazolidone-based Helicobacter pylori eradication therapies after failure of standard first- and second-line eradication attempts in dyspepsia patients. *Aliment Pharmacol Ther* 2005; 21: 91–6.
14. Pelga GEG, *et al.* Quadruple therapy with furazolidone for retreatment in patients with peptic ulcer disease. *World J Gastroenterol* 2008; 14: 6224–7.

Adverse Effects

Adverse effects of furazolidone are usually mild and transient. The most common involve the gastrointestinal tract and include nausea and vomiting. Dizziness, drowsiness, headache, and a general malaise have also been reported.

Allergic reactions, most commonly skin reactions such as rashes or angioedema, may occur. There have been instances of acute pulmonary reactions, similar to those seen with the structurally related drug nitrofurantoin, and of hepatotoxicity. Agranulocytosis has been reported rarely. Haemolytic anaemia may occur in patients with G6PD deficiency given furazolidone.

Darkening of the urine has been attributed to the presence of metabolites.

Precautions

Furazolidone should be used with caution in those with G6PD deficiency because of the risk of haemolytic anaemia. It should not be given to infants under 1 month of age since their enzyme systems are immature.

Interactions

A disulfiram-like reaction has been reported in patients taking alcohol while on furazolidone therapy; alcohol should be avoided during, and for a short period after, treatment with furazolidone.

A metabolite of furazolidone is an MAOI and the cautions advised for these drugs regarding use with other drugs, especially indirect-acting sympathomimetic amines, and the consumption of food and drink containing tyramine, should be followed (see Phenelzine Sulfate, p. 444.3 and p. 445.1). However, there appear to be no reports of hypertensive crises in patients receiving furazolidone and it has been suggested that, since furazolidone inhibits monoamine oxidase gradually over several days, the risks are small if treatment is limited to a 5-day course. Toxic psychosis has been reported in a patient receiving furazolidone and amitriptyline (see Antiprotozoals, under Interactions of Amitriptyline, p. 406.3). Omeprazole modestly decreases serum concentrations of furazolidone; other proton pump inhibitors could interact similarly.

Pharmacokinetics

Although furazolidone has been considered to be largely unabsorbed when given orally, the occurrence of systemic adverse effects and coloured metabolites in the urine suggest that this may not be the case. Rapid and extensive metabolism, possibly in the intestine, has been proposed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Giardil; ***Braz.***: Giarlam; Neo Furasil; ***Chile***: Furoxona; ***India***: Furoxone; ***Indon.***: Diralox; Neo Prodiar; ***Mex.***: Furoxona; Fuxol; Kaodin; Salmocide†; ***Philipp.***: Diafuran; Diapectolin; Furoxone; ***Thai.***: Furasian; Furion; ***Turk.***: Furoksan; ***Venez.***: Furoxil; Furoxona.

Multi-ingredient Preparations. ***Braz.***: Colestase; ***Chile***: Furazolidona; ***Hong Kong***: Berber CO†; Enterodin Compound†; ***India***: Aldiamycin; Alfumet; Amibex; Anaerid-F; Aristogyl-F; Aristogyl-F; C-Met; Dependal-M; Diaglow; Enterofuran-M; Flagyl-F; Pumestar; Inseptin-MF; Kaltin MF; Lomofen; Lomostop-MF; Megyl-F; Metrogyl-F; ***Mex.***: Caopectar†; Colfur†; Coralzul; Dialgin†; Dibapec Compuesto†; Estibal; Exofur; Furoxona CP; Kapecfuran; Neokap; Optazol; Reuginal; Solfurol; Threchop†; Yodozona; ***Spain***: Desinvag†; ***Thai.***: Coccila; Coccila; Diaropect; Diaropect; Difuran; Diocin; Disento PF; Disento; Furamed; Furasian; Furopectal; Furopectin; Patarlin; Profura; Suratin.

Pharmacopoeial Preparations
USP 36: Furazolidone Oral Suspension; Furazolidone Tablets.

Halofuginone Hydrobromide

(BANM, USAN, rINNM)

Halofuginona, hidrobromuro de; Halofuginone, Bromhydrate d'; Halofuginoni Hydrobromidum; Hidrobromuro de halofuginona; RU-19110; Галофугинона Гидробромид.

(±)-*trans*-7-Bromo-6-chloro-3-[3-(3-hydroxy-2-piperidyl)acetonyl]quinazolin-4(3*H*)-one hydrobromide.

$C_{16}H_{17}BrClN_3O_3,HBr$=495.6

CAS — 55837-20-2 (halofuginone); 64924-67-0 (halofuginone hydrobromide).

UNII — PTC2969MV1.

Profile

Halofuginone is an antiprotozoal used as the hydrobromide in veterinary practice for the prevention of coccidiosis in poultry and for the treatment and prevention of cryptosporidiosis in calves. It is also under investigation for use in neoplastic disease in humans and in the treatment of scleroderma (p. 1942.3).

Imidocarb *(BAN, rINN)*

BRN-0964732; Imidocarbe; Imidocarbo; Imidocarbum; Имидокарб.

1,3-Bis[3-(2-imidazolin-2-yl)phenyl]urea.

$C_{19}H_{20}N_6O$=348.4

CAS — 27885-92-3.

ATC Vet — QP51AE01.

UNII — 8US53K0VDH.

Imidocarb Dipropionate *(BANM, rINNM)*

Dipropionato de imidocarbo; Imidocarbe, Dipropionate d'; Imidocarbi Dipropionas; Имидокарба Дипропионат.

$C_{19}H_{20}N_6O,2C_3H_6O_2$=496.6

CAS — 55750-06-6.

UNII — ZSM1M03SHC.

Imidocarb Hydrochloride *(BANM, USAN, rINNM)*

4A65; Hidrocloruro de imidocarbo; Imidocarbe, Chlorhydrate d'; Imidocarbi Hydrochloridum; Имидокарба Гидрохлорид.

3,3'-Di(2-imidazolin-2-yl)carbanilide dihydrochloride.

$C_{19}H_{20}N_6O,2HCl$=421.3

CAS — 5318-76-3.

UNII — KCC1V76AH8.

Profile

Imidocarb has antiprotozoal and antibacterial activity and is used as the dipropionate in veterinary practice in the treatment of babesiosis and anaplasmosis. Imidocarb hydrochloride has also been used.

Isometamidium Chloride *(BAN, rINN)*

Cloruro de Isometamidio; Isometamidii Chloridum; Isometamidio, cloruro de; Isometamidium; Isométamidium, Chlorure d'; Изометамидия Хлорид.

8-[3-(*m*-Amidinophenyl)-2-triazeno]3-amino-5-ethyl-6-phenylphenanthridinium chloride.

$C_{28}H_{26}ClN_7$=496.0

CAS — 34301-55-8.

UNII — 7NH28I651F.

Profile

Isometamidium is an antiprotozoal used as the chloride in veterinary practice for the control of trypanosomiasis.

Lasalocid *(BAN, USAN, rINN)*

Lasalocide; Lasalócido; Lasalocidum; Ro-02-2985; Лазалоцид.

6-[(3*R*,4*S*,5*S*,7*R*)-7-((2*S*,3*S*,5*S*)-5-Ethyl-5-[(2*R*,5*R*,6*S*)-5-ethyltetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl]tetrahydro-3-methyl-2-furyl}4-hydroxy-3,5-dimethyl-6-oxononyl]-2-hydroxy-*m*-toluic acid.

$C_{34}H_{54}O_8$=590.8

CAS — 11054-70-9; 25999-31-9.

ATC Vet — QP51AH02.

UNII — W7V2ZZ2FWB.

Lasalocid Sodium *(BANM, rINNM)*

Lasalocid sódico; Lasalocide Sodique; Lasalocidum Natricum; Лазалоцид Натрий.

$C_{34}H_{53}NaO_8$=612.8

CAS — 25999-20-6.

ATC Vet — QP51AH02.

UNII — W2S5C71Y3G.

Profile

Lasalocid, an antibiotic produced by *Streptomyces lasaliensis*, is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in birds.

Maduramicin *(BAN, USAN, rINN)*

CL-273703; Maduramicin Ammonium; Maduramicina; Maduramicine; Maduramicinum; Мадурамицин.

Ammonium (2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2-hydroxy-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*,5'*R*)-octahydro-2-methyl-3'-[(2*R*,4*S*,5*S*,6*S*)-tetrahydro-4,5-dimethoxy-6-methyl-2*H*-pyran-2-yl]oxy}-5'-[(2*S*,3*S*,5*R*,6*S*)-tetrahydro-6-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-yl](2,2'-bifuran-5-yl)-1,6-dioxaspiro[4.5]dec-7-yl ethyl}-4,5-dimethoxy-3-methyl-2*H*-pyran-2-acetate.

$C_{47}H_{80}O_{17},NH_3$=934.2

CAS — 84878-61-5.

ATC Vet — QP51AX10.

UNII — 5U912U22T2.

NOTE. The name maduramicin has also been used to denote the acid.

Profile

Maduramicin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry. Accidental ingestion by humans has resulted in muscle weakness, polyneuropathy, myonecrosis and rhabdomyolysis, and acute renal failure; fatalities have been reported.

Melarsoprol *(BAN, rINN)*

Mel B; Melarsen Oxide-BAL; Mélarsoprol; Melarsoprolum; RP-3854; Меларсопрол.

2-[4-(4,6-Diamino-1,3,5-triazin-2-ylamino)phenyl]-1,3,2-dithiarsolan-4-ylmethanol.

$C_{12}H_{15}AsN_6OS_2$=398.3

CAS — 494-79-1.

ATC — P01CD01.

ATC Vet — QP51AD04.

UNII — ZF3786Q2E8.

Uses and Administration

Melarsoprol, a trivalent arsenical derivative, is a trypanocide that appears to act by inhibiting trypanosomal pyruvate kinase. It is effective in the treatment of all stages of African trypanosomiasis due to *Trypanosoma brucei gambiense* or *T brucei rhodesiense* (see below), but because of its toxicity its use is usually reserved for stages of the disease involving the CNS. Resistance has been reported to develop.

Patients undergoing therapy with melarsoprol should be treated in hospital. Melarsoprol is given by intravenous injection as a 3.6% solution in propylene glycol. The injection should be given slowly, care being taken to prevent leakage into the surrounding tissues, and the patient should remain supine and fasting for several hours after the injection.

Treatment protocols vary, but in general melarsoprol is given in low doses initially (0.36 to 1.8 mg/kg daily), especially in children and debilitated patients, increased gradually to the maximum daily dose of 3.6 mg/kg. For **intermittent** cyclic therapy, doses are given daily for 3 or 4 days and the course repeated 2 or 3 times with an interval of 7 to 10 days between courses. Since massive destruction of parasites resulting in a Jarisch-Herxheimer reaction is particularly dangerous during treatment with melarsoprol, several doses of suramin or pentamidine may be given to induce the reaction before melarsoprol is started.

An alternative 10-day **consecutive** treatment course of intravenous melarsoprol 2.2 mg/kg daily, for the treatment of *T. b. gambiense*, has been endorsed by many authorities, since it shortens patients' time in hospital and reduces the total amount of drug given. See also below.

Melarsonyl potassium is a water-soluble derivative of melarsoprol which was formerly used as an alternative to melarsoprol but was probably more toxic and less effective.

African trypanosomiasis. Melarsoprol, which is effective against both *Trypanosoma brucei gambiense* and *T. b. rhodesiense*, is usually only given to treat the meningoencephalitic stage of African trypanosomiasis (p. 925.2) because it may produce potentially fatal encephalopathy. However, protection against this toxicity may be provided by prophylaxis with prednisolone.[1,2] Therapy with melarsoprol and eflornithine was reported to be effective in a patient who had not responded to either drug alone.[3] A study[4] to evaluate the efficacy and toxicity of a combination of eflornithine for 4 days followed by 3 daily injections of melarsoprol in 42 patients with melarsoprol-resistant Gambian trypanosomiasis, was associated with cure in 93% of patients. Efficacy and toxicity were considered to be similar to a 7-day course of eflornithine monotherapy. A comparative study[5] in 500 patients with second-stage infection with *T. b. gambiense* found that an alternative dosage regimen of melarsoprol 2.2 mg/kg daily, as a single course over 10 consecutive days, was similar in efficacy to intermittent cyclic regimens of 1.2 to 3.6 mg/kg daily for 3 or 4 days repeated twice over a 26-day period with 7-day intervals between series, although there was no difference between the regimens in the incidence of associated encephalopathy. Follow-up involving 442 of these patients indicated that results of the 2 regimens continued to be comparable; relapse after 1 year occurred in 3% of those given standard treatment and in 2% given alternative treatment; relapse rates after 2 years were

reported to be 5% and 6% respectively.[6] A further uncontrolled, multinational drug-utilisation study[7] in 2020 patients with late-stage African trypanosomiasis treated with the 10-day consecutive melarsoprol regimen reported a 93.9% cure rate 24 hours after completing treatment and an 86.2% cure rate after 2 years, however, nearly half of the patients were lost to follow-up. The overall reported fatality rate was 5.9%; encephalopathic syndrome was reported for 8.7% of patients and it was fatal in about half of all cases.

1. Pepin J, *et al.* Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* 1989; i: 1246–50.
2. Pepin J, *et al.* Risk factors for encephalopathy and mortality during melarsoprol treatment of Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1995; 89: 92–7.
3. Simarro PP, Asumu PN. Gambian trypanosomiasis and synergism between melarsoprol and eflornithine: first case report. *Trans R Soc Trop Med Hyg* 1996; 90: 315.
4. Mpia B, Pépin J. Combination of eflornithine and melarsoprol for melarsoprol-resistant Gambian trypanosomiasis. *Trop Med Int Health* 2002; 7: 775–9.
5. Burri C, *et al.* Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by Trypanosoma brucei gambiense: a randomised trial. *Lancet* 2000; 355: 1419–25.
6. Schmid C, *et al.* Efficacy of 10-day melarsoprol schedule 2 years after treatment for late-stage gambiense sleeping sickness. *Lancet* 2004; 364: 789–90.
7. Schmid C, *et al.* Effectiveness of a 10-day melarsoprol schedule for the treatment of late-stage human African trypanosomiasis: confirmation from a multinational study (IMPAMEL II). *J Infect Dis* 2005; 191: 1922–31.

Adverse Effects and Treatment

Adverse effects are common and may be severe during the treatment of African trypanosomiasis with melarsoprol. It may be difficult to distinguish between effects of the disease, Jarisch-Herxheimer reactions resulting from the release of antigens from trypanosomes killed by melarsoprol, and adverse effects due to the drug's arsenic content or to hypersensitivity. For the adverse effects of arsenic and their treatment, see Arsenic Trioxide, p. 2448.3.

A severe febrile reaction may occur after the first injection of melarsoprol, especially in patients with large numbers of trypanosomes in their blood. For those patients receiving intermittent cyclic treatment it is common practice to give 2 or 3 injections of suramin or pentamidine before starting melarsoprol therapy.

The most serious adverse effect is reactive encephalopathy, which occurs in about 3 to 10% of patients treated with melarsoprol and is usually seen between the end of the first 3- or 4-day course of injections and the start of the second course in those patients receiving intermittent cyclic treatment and from day 8 to 10 in those receiving the 10-day consecutive schedule. (For further information on treatment schedules see Uses and Administration, p. 934.3.) Encephalopathy may be sudden in onset or develop slowly. Symptoms include fever, headache, tremor, slurring of speech, convulsions, and coma; death has occurred in up to 5% of patients treated with melarsoprol. Less commonly, haemorrhagic encephalopathy may occur. The prophylactic use of corticosteroids has been suggested during treatment courses of melarsoprol (see African Trypanosomiasis, p. 934.3). Treatment of reactive encephalopathy has included the use of corticosteroids, hypertonic solutions to combat cerebral oedema, anticonvulsants such as diazepam, and subcutaneous adrenaline; dimercaprol has been given on the assumption that encephalopathy resulted from arsenic poisoning, but has not generally been of benefit.

Hypersensitivity reactions to melarsoprol may occur during the second and subsequent courses of treatment. Desensitisation with gradually increasing doses of melarsoprol has been attempted; corticosteroids may help to control symptoms during this procedure. Some authorities consider that the use of small doses of melarsoprol may increase the risk of resistance.

Melarsoprol injection is very irritant and extravasation during intravenous use should be avoided. Vomiting and abdominal colic may occur if it is injected too rapidly. Other adverse effects reported include agranulocytosis, hypertension, peripheral neuropathy, proteinuria, severe diarrhoea, myocardial damage, exfoliative dermatitis, and renal and hepatic disturbances.

References.
1. Pepin J, *et al.* Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* 1989; i: 1246–50.
2. Pepin J, Milord F. African trypanosomiasis and drug-induced encephalopathy: risk factors and pathogenesis. *Trans R Soc Trop Med Hyg* 1991; 85: 222–4.
3. Pepin J, *et al.* Risk factors for encephalopathy and mortality during melarsoprol treatment of Trypanosoma brucei gambiense sleeping sickness. *Trans R Soc Trop Med Hyg* 1995; 89: 92–7.

Precautions

Use of melarsoprol in febrile patients has been associated with an increased incidence of reactive encephalopathy, and therefore it should not be given during epidemics of influenza. Intercurrent infections such as malaria and pneumonia should be treated before melarsoprol is used. Severe haemolytic reactions have been reported in patients with G6PD deficiency. It may precipitate erythema nodosum when given to patients with leprosy.

Patients should be in hospital when they are treated with melarsoprol and dosage decided after taking into account their general condition.

Treatment of pregnant women with trypanosomiasis should be deferred until after delivery. Pregnant women with meningoencephalitis may be treated with pentamidine (*Trypanosoma brucei gambiense*) or suramin (*T. b. rhodesiense*).

Pharmacokinetics

Melarsoprol is reported to be unreliably absorbed if given orally and is usually given by intravenous injection. A small amount penetrates into the CSF where it has a local trypanocidal action. It is a prodrug and is rapidly metabolised to the active form, melarsen oxide. Melarsoprol itself has a plasma half-life of 30 minutes and is excreted in the faeces and urine.

The pharmacokinetics of melarsoprol have not been fully evaluated. Using biological assay and atomic absorption spectrometry, the terminal half-life of melarsoprol was originally calculated to be 35 hours and low trypanocidal activity was detected in the CSF. These methods, however, cannot distinguish melarsoprol from other substances such as melarsoprol metabolites that also have trypanocidal activity. When the terminal half-life was calculated by high-performance liquid chromatography (HPLC), melarsoprol was found to be eliminated from the plasma within 1 hour.[1,2] Based on these findings it is thought that melarsoprol is rapidly eliminated from the plasma and transformed into metabolites with trypanocidal activity.[1] Melarsen oxide has been identified by HPLC as a metabolite; the peak plasma concentration was reached 15 minutes after a dose and the half-life of free melarsen oxide was 3.9 hours.[2]

1. Bronner U, *et al.* Discrepancy in plasma melarsoprol concentrations between HPLC and bioassay methods in patients with T. gambiense sleeping sickness indicates that melarsoprol is metabolized. *Trop Med Int Health* 1998; 3: 913–7.
2. Keiser J, *et al.* Investigations of the metabolites of the trypanocidal drug melarsoprol. *Clin Pharmacol Ther* 2000; 67: 478–88.

Mepacrine Hydrochloride *(BANM, rINNM)*

Acrichinum; Acrinamine; Antimalarinae Chlorhydras; Chinacrina; Hidrocloruro de atatabrina; Hidrocloruro de mepacrina; Hidrocloruro de quinacrina; Mepacrina, hidrocloruro de; Mépacrine, Chlorhydrate de; Mepacrini Hydrochloridum; Mepakrin Hidroklorür; Quinacrine Hydrochloride; Менакрина Гидрохлорид.

6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride dihydrate.

$C_{23}H_{30}ClN_3O,2HCl,2H_2O$=508.9

CAS — 83-89-6 (mepacrine); 69-05-6 (anhydrous mepacrine dihydrochloride); 6151-30-0 (mepacrine dihydrochloride dihydrate).

ATC — P01AX05.

UNII — G6242H2NAA (mepacrine hydrochloride dihydrate); 81A613ZZ6X (anhydrous mepacrine hydrochloride).

Uses and Administration

Mepacrine is a 9-aminoacridine antiprotozoal used as the hydrochloride mainly as an alternative to the nitroimidazoles in the treatment of giardiasis (p. 921.3).

In giardiasis, mepacrine hydrochloride is given orally in doses of 100 mg three times daily after food for 5 to 7 days.

For details of doses in children, see below.

Mepacrine hydrochloride may also be used for the treatment of some cutaneous forms of lupus erythematosus and for SLE (see below). It has also been used locally in the treatment of some forms of cutaneous leishmaniasis, as a sterilisation technique for contraception, and in the management of malignant pleural effusions. For further information on such uses see below. It was formerly used to treat malaria.

The mesilate was also formerly used.

Mepacrine is under investigation for the treatment of variant Creutzfeldt-Jakob Disease.

Administration in children. As an alternative drug for the treatment of giardiasis, mepacrine hydrochloride may be given orally to children at a dose of 2 mg/kg three times daily after food (to a maximum 300 mg daily) for 5 days.

Contraception. Sterilisation with intra-uterine mepacrine has been attempted as an irreversible method of contraception (p. 2232.3). It produces occlusion of the fallopian tube and has been reported to be an effective non-surgical means of female sterilisation,[1] although it may be less effective than other methods.[2] There has been speculation about the risk of cancer from this technique but there appeared to be no evidence to confirm such a risk.[3-5] However, the method remains controversial and a full evaluation of its safety and efficacy has been recommended.[6] The Indian government has banned the use of mepacrine for sterilisation.[7]

1. Hieu DT, *et al.* 31 781 Cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342: 213–17.
2. Sokal DC, *et al.* Contraceptive effectiveness of two insertions of quinacrine: results from 10-year follow-up in Vietnam. *Contraception* 2008; 78: 61–5.
3. Anonymous. Death of a study: WHO, what, and why. *Lancet* 1994; 343: 987–8.
4. Hieu DT. Quinacrine method of family planning. *Lancet* 1994; 343: 1040.
5. Sokal DC, *et al.* Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. *Contraception* 2008; 78: 66–72.
6. Benagiano G. Sterilisation by quinacrine. *Lancet* 1994; 344: 689.
7. WHO. *Pharmaceuticals: restrictions in use and availability.* Geneva: WHO, 2001. Available at: http://whqlibdoc.who.int/hq/2001/EDM_QSM_2001.3.pdf (accessed 6/03/09)

Leishmaniasis. Mepacrine has historically been suggested for intralesional injection in the treatment of early noninflamed nodular lesions of cutaneous leishmaniasis (p. 922.1) due to *Leishmania tropica, L. major, L. mexicana, L. panamensis,* or *L. peruviana.*[1] The suggested course of treatment was 3 intralesional injections of a 5% solution of mepacrine given at intervals of 3 to 5 days. However, local infiltration of drugs can be difficult and painful.

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)

Lupus erythematosus. Mepacrine may be added to the treatment regimen of patients with some forms of cutaneous lupus erythematosus. Treatment is usually started with hydroxychloroquine and if no improvement occurs after about 2 months mepacrine is added at an initial dosage of 100 mg daily. If this combination treatment is effective the dose of both drugs may be decreased after 1 month to reduce any adverse effects. Chloroquine may be used as an alternative to hydroxychloroquine and can also be combined with mepacrine.[1,2] Mepacrine has also been used as monotherapy, in a similar dose, in patients with visual disorders in whom treatment with hydroxychloroquine or chloroquine was considered unsuitable.[2]

Mepacrine has also been used as an alternative to standard treatments in SLE (p. 1613.3). A small study[3] reported that 5 of 6 patients with SLE unresponsive to treatment with hydroxychloroquine plus prednisone and either azathioprine or methotrexate, had complete remission of their disease when mepacrine (100 mg daily) was added to their existing treatment. Other small studies[4,5] in patients with stable SLE disease found that the addition of mepacrine to their current treatment reduced the SLE disease activity index and lowered serum levels of B lymphocyte activating factor and anticardiolipin antibody titres in some patients.

1. Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. *Dermatol Ther* 2007; 20: 160–74.
2. González-Sixto B, *et al.* Aspectos prácticos de la quinacrina como tratamiento del lupus eritematoso cutáneo: serie de casos. *Actas Dermosifiliogr* 2010; 101: 54–8.
3. Toubi E, *et al.* The benefit of combining hydroxychloroquine with quinacrine in the treatment of SLE patients. *Lupus* 2000; 9: 92–5.
4. Toubi E, *et al.* Quinacrine added to ongoing therapeutic regimens attenuates anticardiolipin antibody production in SLE. *Lupus* 2003; 12: 297–301.
5. Toubi E, *et al.* The reduction of serum B-lymphocyte activating factor levels following quinacrine add-on therapy in systemic lupus erythematosus. *Scand J Immunol* 2006; 63: 299–303.

Sclerotherapy. Intrapleural instillations of mepacrine hydrochloride or mesilate have been used as sclerosants in the management of malignant pleural effusions (p. 700.1) and recurrent pneumothorax but the treatment is associated with pain and a high frequency of toxic effects.

Adverse Effects

The most common adverse effects associated with mepacrine are dizziness, headache, and gastrointestinal disturbances such as nausea and vomiting. Reversible yellow discoloration of the skin, conjunctiva, and urine may occur during long-term use or after large doses; blue/black discoloration of the palate and discoloration of the nails have also been reported. Doses such as those used in the treatment of giardiasis may occasionally cause transient acute toxic psychosis. CNS stimulation and convulsions have been reported at high parenteral doses. Retinopathy similar to that seen with chloroquine (p. 651.2) and chronic dermatoses, including severe exfoliative dermatitis and lichenoid eruptions, have also occurred after prolonged use of mepacrine. Aplastic anaemia has also been reported after long term use, often preceded by such dermatoses. Hepatitis and hepatic necrosis occur rarely.

Effects on the nervous system. Two patients had convulsions a few hours after mepacrine hydrochloride 400 mg was given intrapleurally for malignant effusions.

One developed status epilepticus and died and the other was successfully treated with anticonvulsants.[1]

1. Borda I, Krant M. Convulsions following intrapleural administration of quinacrine hydrochloride. *JAMA* 1967; 201: 1049–50.

Precautions

Mepacrine should be used with caution in elderly patients or patients with a history of psychosis, or in the presence of hepatic disease. Mepacrine can cause exacerbation of psoriasis and should be avoided in psoriatic patients.

Interactions

Mepacrine has been reported to produce a mild disulfiram-like reaction (see p. 2496.1) when taken with alcohol.

Theoretically, mepacrine may increase the plasma concentrations of primaquine resulting in a higher risk of toxicity, and it has been recommended that these drugs should not be used together.

Pharmacokinetics

Mepacrine is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur in 1 to 3 hours. It is widely distributed throughout the body. It accumulates in body tissues, particularly the liver, and is liberated slowly. Protein binding is 85%. It is excreted slowly mainly in the urine, with an elimination half-life of 5 days, and is still detectable in the urine after 2 months. Mepacrine crosses the placenta.

Intrapleural administration. Peak plasma concentrations of mepacrine far above those associated with CNS effects were rapidly attained in 3 of 4 patients after intrapleural instillation of a solution of mepacrine hydrochloride and remained at these levels for several hours.[1]

1. Björkman S, *et al.* Pharmacokinetics of quinacrine after intrapleural instillation in rabbits and man. *J Pharm Pharmacol* 1989; 41: 160–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Maladin.

Methyl Benzoquate *(BAN)*

AY-20385; ICI-55052; Metilbenzocuato; Nequinate (pINN); Nequinate (USAN); Néquinate; Nequinato; Nequinatum; Нехинат.

Methyl 7-benzyloxy-6-butyl-1,4-dihydro-4-oxoquinoline-3-carboxylate.

$C_{22}H_{23}NO_4$=365.4

CAS — 13997-19-8.

UNII — 91ZE013933.

Profile

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

Metronidazole *(BAN, USAN, rINN)*

Bayer-5360; Metronidatsoli; Metronidazol; Metronidazolas; Métronidazole; Metronidazolo; Metronidazolum; NSC-50364; RP-8823; SC-10295; Метронидазол.

2-(2-Methyl-5-nitroimidazol-1-yl)ethanol.

$C_6H_9N_3O_3$=171.2

CAS — 443-48-1.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

UNII — 140QMO216E.

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

Ph. Eur. 8: (Metronidazole). A white or yellowish, crystalline powder. Slightly soluble in water, in alcohol, in acetone, and in dichloromethane. Protect from light.

USP 36: (Metronidazole). White to pale yellow, odourless crystals or crystalline powder. It darkens on exposure to light. Sparingly soluble in water and in alcohol; slightly soluble in chloroform and in ether; soluble in dilute hydrochloric acid (1 in 2). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. See below.

Metronidazole Benzoate *(BAN, rINNM)*

Benzoato de metronidazol; Benzoyl Metronidazole; Metronidatsolibentsoaatti; Metronidazol, benzoato de; Metronidazolbensoat; Metronidazolbenzoat; Metronidazol-benzoát; Métronidazole, benzoate de; Metronidazoli Benzoas; Metronidazolo benzoatas; RP-9712; Метронидазола Бензоат.

2-(2-Methyl-5-nitroimidazol-1-yl)ethyl benzoate.

$C_{13}H_{13}N_3O_4$=275.3

CAS — 13182-89-3.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

UNII — A355C835XC.

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

Ph. Eur. 8: (Metronidazole Benzoate). White or slightly yellowish, crystalline powder or flakes. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 36: (Metronidazole Benzoate). A white to slightly yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane; very slightly soluble in solvent ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Metronidazole Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de metronidazol; Metronidazol, hidrocloruro de; Métronidazole, Chlorhydrate de; Metronidazoli Hydrochloridum; SC-32642; Метронидазола Гидрохлорид.

$C_6H_9N_3O_3$.HCl=207.6

CAS — 69198-10-3.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

UNII — 76JC1633UF.

Incompatibility. Solutions of metronidazole hydrochloride have a low pH, usually of less than 2.0, before dilution and neutralisation for intravenous use. These undiluted solutions react with aluminium in equipment such as needles and produce reddish-brown discoloration, and a precipitate has been reported with ready-to-use preparations of metronidazole hydrochloride, although this occurred after contact for 6 hours or more.[1,2]

Several studies have assessed the compatibility of antibacterial injections and other drugs when added to metronidazole solution for intravenous infusion.[3-7] Results have varied according to the criteria applied and the preparations and conditions used. Physical incompatibilities due to the low pH of metronidazole injections appear to be more of a problem than chemical incompatibility. Regardless of these studies, it is generally recommended that other drugs should not be added to intravenous solutions of metronidazole or its hydrochloride. Specific information on the compatibility of individual formulations may be found in the manufacturers' literature.

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; 42: 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; 42: 2660.
3. Bisaillon S, Sarrazin R. Compatibility of several antibiotics or hydrocortisone when added to metronidazole solution for intravenous infusion. *J Parenter Sci Technol* 1983; 37: 129–32.
4. Gupta VD, Stewart KR. Chemical stabilities of hydrocortisone sodium succinate and several antibiotics when mixed with metronidazole injection for intravenous infusion. *J Parenter Sci Technol* 1985; 39: 145–8.
5. Gupta VD, *et al.* Chemical stabilities of cefamandole nafate and metronidazole when mixed together for intravenous infusion. *J Clin Hosp Pharm* 1985; 10: 379–83.
6. Barnes AR. Chemical stabilities of cefuroxime sodium and metronidazole in an admixture for intravenous infusion. *J Clin Pharm Ther* 1990; 15: 187–96.
7. Nahata MC, *et al.* Stability of metronidazole and ceftizoxime sodium in ready-to-use metronidazole bags stored at 4 and 25 degrees C. *Am J Health-Syst Pharm* 1996; 53: 1046–8.

Uses and Administration

Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa (see Antimicrobial Action, p. 939.3); it also has a radiosensitising effect and has been tried in the treatment of malignant neoplasms. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of metronidazole has been reduced.

Metronidazole is used in the treatment of susceptible protozoal infections such as amoebiasis, balantidiasis, *Blastocystis hominis* infections, giardiasis, and trichomoniasis; it has also been tried in leishmaniasis and microsporidiosis. For details of these infections and their treatment see under Choice of Antiprotozoal, p. 919.1. Metronidazole is also used in the treatment and prophylaxis of anaerobic bacterial infections. Specific bacterial infections treated with metronidazole include acute necrotising ulcerative gingivitis, bacterial vaginosis, pelvic inflammatory disease, urethritis (nongonococcal), tetanus, and antibiotic-associated colitis. For details of these infections and their treatment see under Choice of Antibacterial, p. 172.2.

Metronidazole is used to eradicate *Helicobacter pylori* in peptic ulcer disease (with other antimicrobials, and either bismuth compounds or proton pump inhibitors) and in the management of malodorous tumours and ulcers where there is anaerobic infection. It is also used in the treatment of rosacea and of dracunculiasis (guinea-worm infection) and has been given orally in the treatment of hepatic encephalopathy and perianal Crohn's disease; a topical ointment containing 10% metronidazole is also used in investigation for the treatment of perianal Crohn's disease. See also below for these miscellaneous uses.

ADMINISTRATION AND DOSAGE. Metronidazole is given orally in tablets, capsules, or extended release tablets or, as metronidazole benzoate, in oral suspension; the tablets are taken with or after food and the suspension at least 1 hour before food. Extended-release tablets should be given at least 1 hour before or 2 hours after meals. Metronidazole is also given rectally in suppositories, intravaginally as a gel or cream, applied topically as a cream or gel, or given by intravenous infusion of metronidazole or metronidazole hydrochloride. Doses are expressed in terms of metronidazole base.

In **amoebiasis**, metronidazole acts as an amoebicide at all sites of infection with *Entamoeba histolytica*. Because of its rapid absorption it is probably less effective against parasites in the bowel lumen and is therefore used with a luminal amoebicide such as diloxanide furoate or diiodohydroxyquinoline in the treatment of symptomatic (invasive) amoebiasis. For the treatment of invasive intestinal amoebiasis, metronidazole is given in oral doses of 800 mg every 8 hours for 5 days; for extra-intestinal amoebiasis (including liver abscess) a dose of 400 to 800 mg every 8 hours for 5 to 10 days is given.

In **balantidiasis** and ***Blastocystis hominis* infection**, metronidazole has been given orally in a dose of 750 mg three times daily for 5 and 10 days, respectively.

In **giardiasis**, the usual oral dose of metronidazole is 2 g once daily for 3 successive days, or 400 mg three times daily for 5 days, or 500 mg twice daily for 7 to 10 days.

In **trichomoniasis**, metronidazole is given orally either as a single 2-g dose, as a 7-day course of 200 mg every 8 hours, or at a dose of 400 to 500 mg every 12 hours for 5 to 7 days. Sexual partners should also be treated. If treatment needs to be repeated, an interval of 4 to 6 weeks between courses has been recommended. Vaginal preparations containing metronidazole are available for the treatment of vaginal trichomoniasis in some countries.

Bacterial vaginosis is treated similarly to vaginal trichomoniasis with which it may co-exist; metronidazole is usually given orally as a single 2-g dose or as a 5 to 7-day course of 400 or 500 mg twice daily. Alternatively it may be applied locally as 5 g of a 0.75% gel once or twice daily for 5 days.

In **acute necrotising ulcerative gingivitis**, metronidazole 200 to 250 mg three times daily is given orally for 3 days; similar doses are used in acute oral infections. A 25% dental gel has also been used as an adjunct to the treatment of chronic periodontal infections.

For the treatment of most **anaerobic bacterial infections**, metronidazole is given orally in an initial dose of 800 mg followed by 400 mg every 8 hours, usually for about 7 days. A regimen of 500 mg every 8 hours is an alternative. When oral therapy is precluded metronidazole may be given intravenously, 500 mg being infused as 100 mL of a 5 mg/mL solution at a rate of 5 mL/minute every 8 hours, or rectally as a 1-g suppository every 8 hours for 3 days; if rectal use needs to be continued for more than 3 days, the dose should be reduced to 1 g 12 hourly. Alternative adult doses of metronidazole are 7.5 mg/kg every 6 to 8 hours orally or 15 mg/kg by intravenous infusion followed by 7.5 mg/kg every 6 hours, doses being infused over 1 hour; by either route a total dose of 4 g in 24 hours should not be exceeded. In mixed anaerobic and aerobic infections metronidazole is given with the appropriate antibacterials.

For details of doses in children, see p. 937.1.

For the **prevention of postoperative anaerobic bacterial infections**, especially in patients undergoing abdominal or gynaecological surgery, metronidazole is given orally, intravenously, or rectally in doses similar to those used for treatment, usually with a beta-lactam or an aminoglycoside antibacterial. Various schedules have been employed. In the UK, licensed doses for adults are:

- orally 400 mg every 8 hours in the 24 hours before surgery followed postoperatively by intravenous or rectal dosage until oral therapy is possible
- by intravenous infusion, 500 mg shortly before operation and repeated every 8 hours, oral doses of 200 or 400 mg every 8 hours being substituted as soon as possible
- by rectum, 1 g every 8 hours starting 2 hours before surgery.

The *BNF*, however, recommends that oral doses should be started only 2 hours before the operation and that the

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