Administration in children. Use of cycloserine is licensed in both the UK and USA for children, although age ranges are not specified in licensed product information. For the treatment of drug-resistant tuberculosis the American Academy of Pediatrics (AAP) suggests a dose of 5 to 10 mg/kg twice daily, to a maximum dose of 1 g daily.

The *BNFC* suggests the following doses:

- children aged 2 to 12 years; 5 mg/kg twice daily
- children aged 12 to 18 years; 250 mg twice daily for 2 weeks then adjusted to a maximum dose of 1 g daily

Doses are adjusted according to blood concentrations and response.

Preparations

USP 31: Cycloserine Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Closina; ***Gr.:*** D-cycloserin; Seromycin; ***Hong Kong:*** Seromycin; ***India:*** Cyclorine; ***Thai.:*** Proserine; ***Turk.:*** Siklocap; ***UK:*** Cycloserine; ***USA:*** Seromycin.

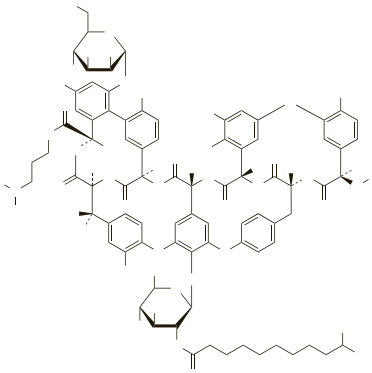
Dalbavancin *(BAN, USAN, rINN)*

A-A-1; BI-397; Dalbavancina; Dalbavancine; Dalbavancinum; MDL-63397; VER-001. 5,31-Dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-{2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl}-38-{[3-(dimethylamino)propyl]carbamoyl}-42-*O*-α-D-mannopyranosyl-15-*N*-methyl(ristomycin A aglicone) (main component).

Дальбаванцин

$C_{88}H_{100}Cl_2N_{10}O_{28}$ = 1816.7.

CAS — 171500-79-1.



Profile

Dalbavancin is a glycopeptide antibacterial under investigation for the treatment of severe infections due to Gram-positive bacteria, including complicated infections of the skin and soft tissues.

◊ References.

1. Lin S-W, *et al.* Dalbavancin: a new option for the treatment of gram-positive infections. *Ann Pharmacother* 2006; **40:** 449–60.
2. Billeter M, *et al.* Dalbavancin: a novel once-weekly lipoglycopeptide antibiotic. *Clin Infect Dis* 2008; **46:** 577–83.
3. Anderson VR, Keating GM. Dalbavancin. *Drugs* 2008; **68:** 639–48.
4. Bailey J, Summers KM. Dalbavancin: a new lipoglycopeptide antibiotic. *Am J Health-Syst Pharm* 2008; **65:** 599–610.

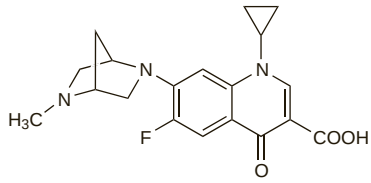
Danofloxacin Mesilate *(BANM, rINNM)*

CP-76136 (danofloxacin); CP-76136-27 (danofloxacin mesilate); Danofloksasiinimesilaatti; Danofloxacin Mesylate *(USAN)*; Danofloxacine, mésilate de; Danofloxacini mesilas; Danofloxacinmesilat; Mesilato de danofloxacino. 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-oxo-3-quinolinecarboxylic acid monomethanesulphonate.

Данофлоксацина Мезилат

$C_{19}H_{20}FN_3O_3,CH_4O_3S$ = 453.5.

CAS — 112398-08-0 (danofloxacin); 119478-55-6 (danofloxacin mesilate).



(danofloxacin)

Profile

Danofloxacin is a fluoroquinolone antibacterial used as the mesilate in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Dapsone *(BAN, USAN, rINN)*

DADPS; Dapson; Dapsona; Dapsonas; Dapsoni; Dapsonum; Dapszon; DDS; Diaminodiphenylsulfone; Diaphenylsulfone; Disulone; NSC-6091; 4,4′-Sulfonylbis-benzenamine; Sulphonyldianiline. Bis(4-aminophenyl) sulphone.

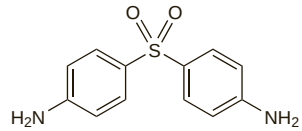
Дапсон

$C_{12}H_{12}N_2O_2S$ = 248.3.

CAS — 80-08-0.

ATC — J04BA02.

ATC Vet — QJ04BA02.



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

Ph. Eur. 6.2 (Dapsone). A white or slightly yellowish-white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in acetone. It dissolves freely in dilute mineral acids. Protect from light.

USP 31 (Dapsone). A white or creamy-white, odourless crystalline powder. Very slightly soluble in water, freely soluble in alcohol; soluble in acetone and in dilute mineral acids. Protect from light.

Stability. A study[1] of the stability of two extemporaneous oral suspensions of dapsone prepared from commercially available tablets found them to be stable for 3 months when stored at 4° and at 25°.

1. Nahata MC, *et al.* Stability of dapsone in two oral liquid dosage forms. *Ann Pharmacother* 2000; **34:** 848–50.

Adverse Effects

Varying degrees of dose-related haemolysis and methaemoglobinaemia are the most frequently reported adverse effects of dapsone, and occur in most patients given more than 200 mg daily; doses of up to 100 mg daily do not cause significant haemolysis, but patients with G6PD deficiency are affected by doses above about 50 mg daily.

Although agranulocytosis has been reported rarely with dapsone when used alone, reports have been more common when it has been used with other drugs in the prophylaxis of malaria. Deaths due to agranulocytosis, aplastic anaemia, and other blood dyscrasias have been reported.

Rash and pruritus may develop. Serious cutaneous hypersensitivity reactions occur rarely and include maculopapular rash, exfoliative dermatitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Fixed drug eruptions have occurred.

A 'dapsone syndrome' may occur after 4 to 8 weeks of treatment and resembles mononucleosis in its presentation (see Hypersensitivity Reactions, below).

Peripheral neuropathy with motor loss has been reported in patients on dapsone for dermatological conditions. Peripheral neuropathy may occur as part of leprosy reaction states and is not an indication to stop dapsone.

Other adverse effects occur infrequently and include nausea, vomiting, anorexia, headache, hepatitis, insomnia, psychosis, and tachycardia.

Carcinogenicity. A survey of 1678 leprosy patients admitted for treatment to the National Hansen's Disease Center in the USA between 1939 and 1977 indicated that, although dapsone has been implicated as a carcinogen in *animals*, the use of dapsone did not appear to affect significantly the risk of cancer in these patients.[1] The International Agency for Research on Cancer concluded[2] that there was limited evidence for the carcinogenicity of dapsone in *animals* and insufficient data to be able to classify the carcinogenic risk in humans.

1. Brinton LA, *et al.* Cancer mortality among patients with Hansen's disease. *J Natl Cancer Inst* 1984; **72:** 109–14.
2. IARC/WHO. Some pharmaceutical drugs. *IARC monographs on the evaluation of carcinogenic risks to humans volume 24* 1980. Also available at: http://monographs.iarc.fr/ENG/Monographs/vol24/volume24.pdf Updated 07/04/88. (accessed 03/10/07)

Effects on the blood. *Haemolysis* is the most frequent serious adverse effect of dapsone and may occur at doses of 200 mg or higher daily.[1] Red blood cells may contain Heinz bodies and there is a reduction in their life span. Well-known risk factors include G6PD deficiency, methaemoglobin reductase deficiency, and haemoglobin M trait; haemoglobin E trait may also increase susceptibility to haemolytic reactions.[2] Haemolytic anaemia has been reported in a neonate after ingestion of dapsone in breast milk.[3]

Methaemoglobinaemia, although common, is rarely symptomatic.[1] However, severe cyanosis was associated with methaemoglobinaemia after an inadvertent overdose with dapsone in an HIV-positive patient with suspected pneumocystis pneumonia.[4] Methaemoglobinaemia has also been reported in an HIV-negative patient with severe renal impairment, who had previously undergone liver and kidney transplantations and who was receiving dapsone for prophylaxis of pneumocystis pneumonia.[5] The metabolite dapsone hydroxylamine is probably responsible for the methaemoglobinaemia and haemolysis associated with dapsone. Studies have shown[6,7] that use of dapsone with cimetidine, which inhibits production of the *N*-hydroxy metabolite, has resulted in a decrease in methaemoglobin levels, at least in the short term.

Agranulocytosis has occurred rarely on use of dapsone in leprosy and skin disease. More cases have been observed when used for malaria prophylaxis[8] (see also under Pyrimethamine, p.610) and dermatitis herpetiformis.[9] The reaction is usually self-limiting once the drug is withdrawn, but fatalities have occurred.[9,10]

Aplastic anaemia has been reported.[11,12] Of 11 fatalities attributed to dapsone reported to the British and Swedish adverse reaction registers[13] between 1968 and 1988, seven were due to white blood cell dyscrasias; none were attributed to red cell dyscrasias, although such reactions formed almost half of all serious reactions reported for dapsone.

Pure red cell aplasia has been reported in an elderly patient taking oral dapsone daily for granuloma annulare.[14]

Thrombocytosis was reported in a patient with AIDS receiving dapsone prophylactically.[15]

See also Hypoalbuminaemia, below.

1. Jopling WH. Side-effects of antileprosy drugs in common use. *Lepr Rev* 1983; **54:** 261–70.
2. Lachant NA, Tanaka KR. Case report: dapsone-associated Heinz body hemolytic anemia in a Cambodian woman with hemoglobin E trait. *Am J Med Sci* 1987; **294:** 364–8.
3. Sanders SW, *et al.* Hemolytic anemia induced by dapsone transmitted through breast milk. *Ann Intern Med* 1982; **96:** 465–6.
4. Seaton RA, *et al.* Blue and breathless. *Hosp Med* 1999; **60:** 530.
5. Ward KE, McCarthy MW. Dapsone-induced methemoglobinemia. *Ann Pharmacother* 1998; **32:** 549–53.
6. Coleman MD, *et al.* The use of cimetidine as a selective inhibitor of dapsone N-hydroxylation in man. *Br J Clin Pharmacol* 1990; **30:** 761–7.
7. Rhodes LE, *et al.* Cimetidine improves the therapeutic/toxic ratio of dapsone in patients on chronic dapsone therapy. *Br J Dermatol* 1995; **132:** 257–62.
8. Firkin FC, Mariani AF. Agranulocytosis due to dapsone. *Med J Aust* 1977; **2:** 247–51.
9. Cockburn EM, *et al.* Dapsone-induced agranulocytosis: spontaneous reporting data. *Br J Dermatol* 1993; **128:** 702–3.
10. Barss P. Fatal dapsone agranulocytosis in a Melanesian. *Lepr Rev* 1986; **57:** 63–6.
11. Foucauld J, *et al.* Dapsone and aplastic anemia. *Ann Intern Med* 1985; **102:** 139.
12. Meyerson MA, Cohen PR. Dapsone-induced aplastic anaemia in a woman with bullous systemic lupus erythematosus. *Mayo Clin Proc* 1994; **69:** 1159–62.
13. Björkman A, Phillips-Howard PA. Adverse reactions to sulfa drugs: implications for malaria chemotherapy. *Bull WHO* 1991; **69:** 297–304.
14. Borrás-Blasco J, *et al.* Pure red cell aplasia associated with dapsone therapy. *Ann Pharmacother* 2005; **39:** 1137–8.
15. Wynn RF, *et al.* Case report of dapsone-related thrombocytosis in an AIDS patient. *Am J Med* 1995; **98:** 602.

Effects on the eyes. There have been rare reports[1-4] of ocular toxicity, usually resulting in permanent loss of visual acuity, after overdoses with dapsone. Toxic effects included blurring of vision,[1,2] optic atrophy,[1] ischaemic retinopathy, ischaemic optic neuropathy,[3] and bilateral macular infarction.[4] These effects were thought to be due to acute hypoxia and obstruction with red cell fragments. A case of anterior ischaemic optic neuropathy[5] has also been reported in a patient taking usual doses of dapsone for dermatitis herpetiformis.

1. Daneshmend TK. The neurotoxicity of dapsone. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 43–58.
2. Alexander TA, *et al.* Presumed DDS ocular toxicity. *Indian J Ophthalmol* 1989; **37:** 150–1.

3. Seo M-S, *et al.* Dapsone maculopathy. *Korean J Ophthalmol* 1997; **11:** 70–3.
4. Chakrabarti M, *et al.* Bilateral macular infarction due to diaminodiphenyl sulfone (4,4′ DDS) toxicity. *Retina* 1999; **19:** 83–4.
5. Chalioulias K, *et al.* Anterior ischaemic optic neuropathy associated with Dapsone. *Eye* 2006; **20:** 943–5.

Effects on the liver. Toxic hepatitis and cholestatic jaundice have been reported by licensed product information to occur early in dapsone therapy. Jaundice may also form part of the dapsone syndrome (see Hypersensitivity Reactions, below). Deterioration in liver function tests during dapsone treatment has been noted in a patient with dermatitis herpetiformis and primary sclerosing cholangitis.[1]

1. Kirby B, *et al.* Abnormal liver function tests induced by dapsone in a patient with dermatitis herpetiformis and primary sclerosing cholangitis. *Br J Dermatol* 1999; **141:** 172–3.

Effects on the lungs. Hypersensitivity reactions to dapsone usually affect the skin, but there have been rare reports of dapsone hypersensitivity presenting with fever, wheezing, and pulmonary eosinophilia.[1-4] Pulmonary eosinophilia occurred in one patient taking dapsone for urticaria[1] and in another taking dapsone as part of the WHO multidrug treatment regimen for leprosy.[2] In both patient symptoms resolved when dapsone was stopped and occurred again on rechallenge. Another patient[3] known to develop fever and wheezing when taking dapsone for leprosy was given a dapsone challenge for 5 days. He became acutely ill and had a high absolute eosinophil count; symptoms resolved 2 weeks after stopping dapsone.

1. Jaffuel D, *et al.* Eosinophilic pneumonia induced by dapsone. *BMJ* 1998; **317:** 181.
2. Kaur J, *et al.* Dapsone-induced eosinophilic pneumonitis in a leprosy patient. *Indian J Lepr* 2005; **77:** 267–71.
3. Arunthathi S, Raju S. Dapsone induced pulmonary eosinophilia without cutaneous allergic manifestations—an unusual encounter—a case report. *Acta Leprol* 1998; **11:** 3–5.
4. Janier M, *et al.* Pulmonary eosinophilia associated with dapsone. *Lancet* 1994; **343:** 860–1.

Effects on mental state. Psychiatric adverse effects have been reported in leprosy patients receiving dapsone, but the role of dapsone in this effect is poorly defined.[1-4] Manic-depressive reactions have been reported in 2 patients[2,3] with skin disorders and psychosis[4] was reported in a patient being treated for leprosy. These reactions appeared to be idiosyncratic reactions to dapsone. In all cases symptoms resolved when dapsone was stopped.

1. Daneshmend T. Idiosyncratic dapsone induced manic depression. *BMJ* 1989; **299:** 324.
2. Carmichael AJ, Paul CJ. Idiosyncratic dapsone induced manic depression. *BMJ* 1989; **298:** 1524. Correction. *ibid.*; **299:** 56.
3. Gawkrodger D. Manic depression induced by dapsone in patient with dermatitis herpetiformis. *BMJ* 1989; **299:** 860.
4. Balkrishna, Bhatia MS. Dapsone-induced psychosis. *J Indian Med Assoc* 1989; **87:** 120–1.

Effects on the nervous system. A case review[1] of 21 patients who had dapsone-induced neuropathy reported that the median time to onset of symptoms was about 1 year; with a range of 11 days to 18 years. Symptoms occurred in patients taking doses varying from 25 to 800 mg/day and after a total cumulative dose of 4 to 1500 g. Most patients had either pure motor or mixed sensory-motor neuropathies, while pure sensory neuropathy was rarely reported. Patients generally recovered, either partially or completely, within one year of stopping dapsone. Progressive multifocal leukoencephalopathy has been reported in a patient with SLE treated with a dapsone-containing regimen, although it was unclear what role dapsone had played.[2]

1. Méry L, *et al.* Polynévrite sensitive induite par la dapsone (Disulone). *Ann Dermatol Venereol* 2003; **130:** 447–9.
2. Stahl NI. Progressive multifocal leukoencephalopathy in a minimally immunosuppressed patient with systemic lupus erythematosus treated with dapsone. *J Rheumatol* 2008; **35:** 725–7.

Effects on the pancreas. Acute pancreatitis has been associated with the use of dapsone to treat dermatitis herpetiformis in an 87-year-old man.[1] Symptoms resolved on stopping dapsone but recurred upon rechallenge.

1. Jha SH, *et al.* Dapsone-induced acute pancreatitis. *Ann Pharmacother* 2003; **37:** 1438–40.

Effects on taste. A persistent sweet taste and tingling of the face and lips was described in a patient receiving dapsone for ocular cicatricial pemphigoid.[1] The symptoms resolved when dapsone was stopped.

1. Stafanous SN, Morgan SJ. A previously unrecognised side effect of dapsone. *Br J Ophthalmol* 1997; **81:** 1113–14.

Hyperpigmentation. Hyperpigmented macules were reported in 32 of about 800 children given dapsone with pyrimethamine for 3 months or more for malaria prophylaxis.[1] The reaction was attributed to dapsone.

1. David KP, *et al.* Hyperpigmented dermal macules in children following the administration of Maloprim for malaria chemoprophylaxis. *Trans R Soc Trop Med Hyg* 1997; **91:** 204–8.

Hypersensitivity reactions. Dapsone syndrome is a rare idiosyncratic hypersensitivity reaction, although it has been suggested[1-3] that the incidence has increased since the introduction of multidrug therapy for leprosy. It usually occurs in the first 4 to 8 weeks of therapy, is not dose-related, and resolves within 14 days on stopping dapsone. Dapsone syndrome may also occur within 1 to 2 weeks of stopping the drug, due to its long elimination half-life and high protein binding.[4] Common clinical symptoms may include exanthematous skin rash, fever, hepatitis (cholestatic and hepatocellular injuries), eosinophilia, lymphadenopathy, and mononucleosis. The syndrome has occurred in leprosy patients,[5,6] in patients with skin disorders,[7] in patients with AIDS taking dapsone for prophylaxis of pneumocystis pneumonia,[4] and in patients taking weekly dapsone (with pyrimethamine) for malaria prophylaxis.[8] Fatalities have occurred.[9,10] Desensitisation has been successfully carried out in several patients with AIDS who exhibited hypersensitivity to dapsone.[11,12]

1. Richardus JH, Smith TC. Increased incidence in leprosy of hypersensitivity reactions to dapsone after introduction of multidrug therapy. *Lepr Rev* 1989; **60:** 267–73.
2. Kumar RH, *et al.* Dapsone syndrome—a five year retrospective analysis. *Indian J Lepr* 1998; **70:** 271–6.
3. Rao PN, Lakshmi TSS. Increase in the incidence of dapsone hypersensitivity syndrome—an appraisal. *Lepr Rev* 2001; **72:** 57–62.
4. Lee KB, Nashed TB. Dapsone-induced sulfone syndrome. *Ann Pharmacother* 2003; **37:** 1044–6.
5. Alves-Rodrigues EN, *et al.* Dapsone syndrome with acute renal failure during leprosy treatment: case report. *Braz J Infect Dis* 2005; **9:** 84–6.
6. Bucaretchi F, *et al.* Dapsone hypersensitivity syndrome in an adolescent during treatment during [sic] of leprosy. *Rev Inst Med Trop Sao Paulo* 2004; **46:** 331–4.
7. Sener O, *et al.* Severe dapsone hypersensitivity syndrome. *J Investig Allergol Clin Immunol* 2006; **16:** 268–70.
8. Tee AKH, *et al.* Dapsone hypersensitivity syndrome masquerading as a viral exanthem: three cases and a mini-review. *Ann Acad Med Singapore* 2004; **33:** 375–8.
9. Frey HM, *et al.* Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; **94:** 777–9.
10. Agrawal S, Agarwalla A. Dapsone hypersensitivity syndrome: a clinico-epidemiological review. *J Dermatol* 2005; **32:** 883–9.
11. Metroka CE, *et al.* Desensitization to dapsone in HIV-positive patients. *JAMA* 1992; **267:** 512.
12. Cook DE, Kossey JL. Successful desensitization to dapsone for Pneumocystis carinii prophylaxis in an HIV-positive patient. *Ann Pharmacother* 1998; **32:** 1302–5.

Hypoalbuminaemia. Severe and often life-threatening hypoalbuminaemia has been reported rarely in patients taking dapsone for long periods for dermatitis herpetiformis.[1-3] Hypoalbuminaemia usually resolves rapidly once dapsone is withdrawn.

1. Kingham JGC, *et al.* Dapsone and severe hypoalbuminaemia. *Lancet* 1979; **ii:** 662–4 and 1018.
2. Foster PN, Swan CHJ. Dapsone and fatal hypoalbuminaemia. *Lancet* 1981; **ii:** 806–7.
3. Sinclair SA, *et al.* Life threatening hypoalbuminaemia associated with dapsone therapy. *Br J Dermatol* 1996; **135** (suppl 47): 45.

Photosensitivity. Photosensitivity has been reported in 6 patients who had taken dapsone for leprosy[1] and in a patient receiving dapsone for a bullous skin disease;[2] the topic has been reviewed.[3]

1. Dhanapaul S. DDS-induced photosensitivity with reference to six case reports. *Lepr Rev* 1989; **60:** 147–50.
2. Stockel S, *et al.* Dapsone-induced photodermatitis in a patient with linear IgA dermatosis. *Eur J Dermatol* 2001; **11:** 50–3.
3. De D, *et al.* Dapsone induced acute photosensitivity dermatitis; a case report and review of literature. *Lepr Rev* 2007; **78:** 401–4.

Treatment of Adverse Effects

In severe overdosage, repeated oral doses of activated charcoal should be given with the aim of preventing absorption of dapsone but also to aid the elimination of dapsone and its monoacetyl metabolite. Methaemoglobinaemia has been treated with slow intravenous injections of methylthioninium chloride 1 to 2 mg/kg repeated after 1 hour if necessary. Methylthioninium chloride should not be given to patients with G6PD deficiency since it will not be effective. Haemolysis has been treated by infusion of concentrated human red blood cells to replace the damaged cells. Supportive therapy includes giving oxygen and fluids.

Patients who develop dapsone syndrome (see Hypersensitivity Reactions, above) may require several weeks of corticosteroid therapy.

Overdosage. References.

1. Dawson AH, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989; **4:** 387–92.
2. Endre ZH, *et al.* Successful treatment of acute dapsone intoxication using charcoal hemoperfusion. *Aust N Z J Med* 1983; **13:** 509–12.
3. Hoetelmans RMW, *et al.* Combined dapsone and clofazimine intoxication. *Hum Exp Toxicol* 1996; **15:** 625–8.
4. Ferguson AJ, Lavery GG. Deliberate self-poisoning with dapsone: a case report and summary of relevant pharmacology and treatment. *Anaesthesia* 1997; **52:** 359–63.
5. Southgate HJ, Masterson R. Lessons to be learned: a case study approach: prolonged methaemoglobinaemia due to inadvertent dapsone poisoning; treatment with methylene blue and exchange transfusion. *J R Soc Health* 1999; **119:** 52–5.

Precautions

Dapsone should not be used in patients with severe anaemia. It is recommended that regular blood counts be performed during treatment. Patients deficient in G6PD or methaemoglobin reductase, or with haemoglobin M are more susceptible to the haemolytic effects of dapsone.

Where possible, liver function should be monitored during treatment.

It is now generally considered that the benefits of dapsone in the treatment of leprosy during pregnancy outweigh any potential risks to the pregnant patient or fetus. Some recommend folic acid 5 mg daily for leprosy patients receiving dapsone during pregnancy.

Breast feeding. Dapsone is distributed into breast milk and the American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, use of dapsone in a breast-feeding mother has resulted in sulfonamide detected in the infant's urine.[2] There has also been a report of haemolytic anaemia in a breast-fed infant (see Effects on the Blood, under Adverse Effects, above). A study in 3 lactating women who were given a single dose of dapsone 100 mg plus pyrimethamine and chloroquine estimated that if their infants were breast fed they would receive 4.6, 10, or 14.3%, respectively, of the maternal dose in the 9-day period after it was given.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)
2. Dreisbach JA. Sulphone levels in breast milk of mothers on sulphone therapy. *Lepr Rev* 1952; **23:** 101–6.
3. Edstein MD, *et al.* Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; **22:** 733–5.

Porphyria. Dapsone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. References.

1. Brabin BJ, *et al.* Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Safety* 2004; **27:** 633–48.

Interactions

Serum concentrations of dapsone are increased, with a consequent increased risk of adverse effects, when given with probenecid, probably as a result of reduced renal excretion of dapsone. Increased dapsone and trimethoprim concentrations have also been reported in patients receiving both drugs, who may similarly be at greater risk of dapsone toxicity. Rifampicin reduces serum concentrations of dapsone to a level that may compromise efficacy in infections other than leprosy. Rifampicin concentrations are generally unaffected. Dapsone may reduce the anti-inflammatory effects of clofazimine (p.255).

Cimetidine. Cimetidine has been reported to increase the area under the curve for dapsone, but to decrease the area under the curve for the metabolite dapsone hydroxylamine. Haematotoxicity is thought to be related to production of this metabolite (see Effects on the Blood, above).

Pyrimethamine. Although some licensed product information has warned that dapsone-induced haematotoxicity could be potentiated by folic acid antagonists such as pyrimethamine, the tolerability of dapsone plus pyrimethamine was similar to dapsone alone when each treatment was given on a once-weekly basis to patients with HIV infection.[1] Dapsone concentrations were not significantly higher in patients receiving dapsone plus pyrimethamine than in those receiving dapsone alone.

1. Falloon J, *et al.* Pharmacokinetics and safety of weekly dapsone and dapsone plus pyrimethamine for prevention of pneumocystis pneumonia. *Antimicrob Agents Chemother* 1994; **38:** 1580–7.

Trimethoprim. In a study of AIDS patients with pneumocystis pneumonia, the mean peak serum concentrations of dapsone after 7 days were 1.5 micrograms/mL after 100 mg daily and 2.1 micrograms/mL after the same dose with trimethoprim 20 mg/kg daily; concentrations of trimethoprim were also increased.[1] Elevated dapsone concentrations may contribute to the toxicity and the efficacy of this combination.

1. Lee BL, *et al.* Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of Pneumocystis pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1989; **110:** 606–11.

Antimicrobial Action

Dapsone is a sulfone active against a wide range of bacteria and some protozoa, but it is mainly used for its action against *Mycobacterium leprae*. Like the sulfonamides it may inhibit folic acid synthesis in susceptible organisms although this is not considered to be the mechanism of action in *M. leprae*. It is usually considered to be bacteriostatic against *M. leprae*, although it may also possess weak bactericidal activity. It is also active against *Plasmodium* and *Pneumocystis jirovecii*.

As with the sulfonamides, antibacterial activity is inhibited by *p*-aminobenzoic acid.

Secondary (acquired) dapsone resistance of *M. leprae* is mainly associated with dapsone being used on its own. Primary dapsone resistance has also been reported with increasing frequency in areas with secondary resistance. Resistance of *M. leprae* to dapsone should be suspected whenever a patient relapses clinically and bacteriologically.

Drug resistance. Monotherapy with dapsone was the standard of treatment for all forms of leprosy until the 1980's, when concerns about dapsone resistance led WHO to introduce a multidrug treatment (MDT) regimen consisting of dapsone, rifampicin, and clofazimine. Long-term follow-up studies[1,2] designed to evaluate the efficacy of WHO MDT regimen reported relapse rates of 1.1 to 9% after a minimum of 2 years treatment. Drug sensitivity analyses were reported for 15 of these patients; no resistance to clofazimine or rifampicin was reported, while isolates from 3 patients showed dapsone resistance.[1] An evaluation of drug resistance after the introduction of WHO MDT regimen in Nepal[3] concluded that secondary resistance to dapsone does not develop under this regimen. Strains of *Mycobacterium leprae* with multiple resistance to rifampicin, ofloxacin, and dapsone have been isolated from a patient who had previously received dapsone monotherapy followed by treatment with rifampicin plus ofloxacin for 28 days.[4]

1. Cellona RV, *et al.* Long-term efficacy of 2 year WHO multiple drug therapy (MDT) in multibacillary (MB) leprosy patients. *Int J Lepr Other Mycobact Dis* 2003; **71:** 308–19.
2. Norman G, *et al.* Relapses in multibacillary patients treated with multi-drug therapy until smear negativity: findings after twenty years. *Int J Lepr Other Mycobact Dis* 2004; **72:** 1–7.
3. Roche PW, *et al.* Dapsone drug resistance in the MDT era. *Int J Lepr Other Mycobact Dis* 2000; **68:** 323–5.
4. Cambau E, *et al.* Multidrug-resistance to dapsone, rifampicin, and ofloxacin in Mycobacterium leprae. *Lancet* 1997; **349:** 103–4.

Pharmacokinetics

Dapsone is almost completely absorbed from the gastrointestinal tract with peak plasma concentrations occurring 2 to 8 hours after a dose. Steady-state concentrations are not attained until after at least 8 days of daily dosage; doses of 100 mg daily provide trough concentrations of 500 nanograms/mL, which are well in excess of the MIC for *M. leprae*. About 70 to 90% of dapsone in the circulation is bound to plasma proteins and nearly 100% of its monoacetylated metabolite is bound.

Dapsone undergoes enterohepatic recycling. It is widely distributed; it is present in saliva and breast milk and crosses the placenta. The half-life ranges from 10 to 50 hours; with a mean of 20 to 30 hours.

Dapsone is acetylated to monoacetyldapsone, the major metabolite, and other mono and diacetyl derivatives. Acetylation exhibits genetic polymorphism. Hydroxylation is the other major metabolic pathway resulting in hydroxylamine dapsone, which may be responsible for dapsone-associated methaemoglobinaemia and haemolysis.

Dapsone is mainly excreted in the urine, only 20% of a dose as unchanged drug.

◊ References.

1. Zuidema J, *et al.* Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet* 1986; **11:** 299–315.
2. May DG, *et al.* The disposition of dapsone in cirrhosis. *Clin Pharmacol Ther* 1992; **51:** 689–700.
3. Mirochnick M, *et al.* Pharmacokinetics of dapsone in children. *J Pediatr* 1993; **122:** 806–9.
4. Opravil M, *et al.* Levels of dapsone and pyrimethamine in serum during once-weekly dosing for prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis. *Antimicrob Agents Chemother* 1994; **38:** 1197–9.
5. Gatti G, *et al.* Penetration of dapsone into cerebrospinal fluid of patients with AIDS. *J Antimicrob Chemother* 1997; **40:** 113–15.
6. Mirochnick M, *et al.* Pharmacokinetics of dapsone administered daily and weekly in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 1999; **43:** 2586–91.
7. Mirochnick M, *et al.* Population pharmacokinetics of dapsone in children with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2001; **70:** 24–32.
8. Thiboutot DM, *et al.* Pharmacokinetics of dapsone gel, 5% for the treatment of acne vulgaris. *Clin Pharmacokinet* 2007; **46:** 697–712.

Metabolism. Measurement of the relative activity of the two main routes of dapsone metabolism (acetylation and hydroxylation) suggests that the risk of adverse effects is greater in individuals in whom the *N*-hydroxylation route predominates.[1] This is consistent with the hypothesis that the toxicity of dapsone is related to production of an active metabolite. See also Effects on the Blood, above.

1. Bluhm RE, *et al.* Development of dapsone toxicity in patients with inflammatory dermatoses: activity of acetylation and hydroxylation of dapsone as risk factors. *Clin Pharmacol Ther* 1999; **65:** 598–605.

Uses and Administration

Dapsone is used as part of multidrug regimens in the treatment of all forms of leprosy (p.176). It has also been used in the prophylaxis of leprosy and in the management of household contacts of leprosy patients. Dapsone is used as an alternative to co-trimoxazole or pentamidine for the treatment and prophylaxis of pneumocystis pneumonia (below), and has been used with pyrimethamine for the prophylaxis of malaria (see under Pyrimethamine, p.611). It is also used in dermatitis herpetiformis and other dermatoses (see Skin Disorders, below). It has been tried for the prophylaxis of toxoplasmosis (p.826) and for the treatment of cutaneous leishmaniasis (p.824) and actinomycetoma (see Mycetoma, p.180).

Dapsone is usually given orally. There are some reports of it being given by intramuscular injection, but such injections can be painful and cause abscess formation.

The most common regimens for **leprosy** are those recommended by WHO. For multibacillary leprosy, rifampicin 600 mg and clofazimine 300 mg are both given *once a month* with dapsone 100 mg and clofazimine 50 mg both *daily* for 12 months. Adults weighing less than 35 kg receive reduced doses of rifampicin and dapsone, and in such patients the dapsone dose is 50 mg or 1 to 2 mg/kg daily.

The WHO regimen for paucibacillary leprosy consists of rifampicin 600 mg once a month and dapsone 100 mg daily; both are given for 6 months. Doses are reduced in low-weight patients as for multibacillary leprosy.

The doses of dapsone used for the prophylaxis and treatment of **pneumocystis pneumonia** are discussed in more detail under pneumocystis pneumonia, below.

The dose needed to treat **dermatitis herpetiformis** has to be titrated for individual patients, but it is usual to start with an oral dose of 50 mg daily, gradually increased to 300 mg daily or more if required. This dose should be reduced to a minimum as soon as possible. Maintenance dosage can often be reduced in patients receiving a gluten-free diet.

In the treatment of **acne**, dapsone is applied topically as a 5% gel twice daily.

For details of doses in infants, children, and adolescents, see below.

Administration in children. For the treatment of multibacillary leprosy in children WHO recommends that children aged 10 to 14 years may be given oral dapsone 50 mg plus rifampicin 450 mg and clofazimine 150 mg *once a month*, together with dapsone 50 mg *daily* and clofazimine 50 mg on *alternate days*; both are given for 12 months. For paucibacillary leprosy WHO recommends oral dapsone 50 mg plus rifampicin 450 mg *once a month*, together with dapsone 50 mg *daily*; both are given for 6 months. For children less than 10 years of age the dose should be adjusted according to body weight.

For details of doses for the treatment of pneumocystis pneumonia in infants, children, and adolescents, see below.

Connective tissue disorders. Relapsing polychondritis (p.1510) has responded to dapsone, as has Behçet's syndrome (p.1499) and SLE. Vasculitic syndromes such as hypersensitivity vasculitis (p.1505) have also improved following dapsone.

Idiopathic thrombocytopenic purpura. Dapsone has been reported[1-4] to be of benefit in some patients, including children, with refractory idiopathic thrombocytopenic purpura (p.1505).

1. Radaelli F, *et al.* Adult refractory chronic idiopathic thrombocytopenic purpura: can dapsone be proposed as second-line therapy? *Br J Haematol* 1999; **104:** 641–2.
2. Dutta TK, *et al.* Dapsone in treatment of chronic idiopathic thrombocytopenic purpura in adults. *J Assoc Physicians India* 2001; **49:** 421–5.
3. Meeker ND, *et al.* Dapsone therapy for children with immune thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2003; **25:** 173–5.
4. Damodar S, *et al.* Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults—a report on 90 patients. *Eur J Haematol* 2005; **75:** 328–31.

Pneumocystis pneumonia. Dapsone is used alone or with pyrimethamine[1] for *primary and secondary prophylaxis* of pneumocystis pneumonia (p.521) in patients unable to tolerate co-trimoxazole. In adults a dose of dapsone 100 mg daily in one or two doses is commonly used and has been reported to have similar efficacy to co-trimoxazole.[2] Dapsone has also been given with pyrimethamine in various regimens including:

- dapsone 50 mg daily with pyrimethamine 50 mg once weekly[3]
- dapsone 100 mg plus pyrimethamine 50 mg both given twice weekly[4]
- dapsone 200 mg plus pyrimethamine 75 mg both given once weekly[5]

In children from 1 month to 18 years of age the recommended dose of dapsone is 2 mg/kg daily (to a maximum of 100 mg daily) or 4 mg/kg weekly (to a maximum of 200 mg weekly).[1]

For *treatment* of adults and adolescents, dapsone 100 mg once daily with trimethoprim 5 mg/kg three times daily, for 21 days, has been suggested for mild to moderate disease in patients unable to tolerate co-trimoxazole.[6] Infants and children under 13 years of age may be given a dose of dapsone of 2 mg/kg once daily (to a maximum of 100 mg daily) plus trimethoprim 5 mg/kg three times daily.[7]

1. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5108.pdf (accessed 03/10/07)
2. Bozzette SA, *et al.* A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; **332:** 693–9.
3. Girard P-M, *et al.* Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; **328:** 1514–20.
4. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.
5. 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.
6. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 03/10/07) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5412.pdf (accessed 05/10/07)
7. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-14): 1–63. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5314.pdf (accessed 03/10/07)

Skin disorders. Dapsone is used for the suppression of skin lesions in dermatitis herpetiformis (p.1578). The mechanism of action is unknown but is unrelated to its antimicrobial activity. Reports, generally involving small numbers of patients, suggest that dapsone may also be beneficial for bullous or mucous membrane pemphigoid (p.1582), pyoderma gangrenosum (p.1583), recurrent erythema multiforme (p.1580), and urticaria (p.1584). Topical dapsone is available in the USA for the treatment of acne.

Spider bites. As discussed on p.2239, necrotic araneism resulting from the bite of spiders of the genus *Loxosceles* is usually treated conservatively with surgical repair of any persistent defect. A prospective clinical study[1] of 31 patients with brown recluse spider bites indicated that treatment with dapsone 100 mg daily for 14 days followed by delayed surgical intervention if necessary reduced the incidence of wound complications and residual scarring compared with treatment by immediate surgical excision. A dose of 100 mg twice daily has also been given for 14 days.[2] An evaluation[3] of the management of brown recluse spider bites found that common treatments did not reduce healing time or scarring; dapsone was associated with slower healing rate and an increased risk of scarring.

1. Rees RS, *et al.* Brown recluse spider bites: a comparison of early surgical excision versus dapsone and delayed surgical excision. *Ann Surg* 1985; **202:** 659–63.
2. King LE, Rees RS. Dapsone treatment of a brown recluse bite. *JAMA* 1983; **250:** 648.
3. Mold JW, Thompson DM. Management of brown recluse spider bites in primary care. *J Am Board Fam Pract* 2004; **17:** 347–52.

Preparations

BP 2008: Dapsone Tablets;
USP 31: Dapsone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Daps; ***Canad.:*** Aczone; ***Israel:*** Avlosulfon†; ***Mex.:*** Dapsoderm-X; Novasulfon†; ***Philipp.:*** Lepravir; ***Port.:*** Sulfona; ***Spain:*** Sulfona; ***Thai.:*** Dopsan; Servidapsone†; ***USA:*** Aczone.

Multi-ingredient: ***Austral.:*** Maloprim; ***Austria:*** Isoprodian; ***Fr.:*** Disulone; ***Ger.:*** Isoprodian†; ***Irl.:*** Maloprim†; ***S.Afr.:*** Maloprim†; ***Singapore:*** Pyrisone.

Daptomycin *(BAN, USAN, rINN)*

Daptomicina; Daptomycine; Daptomycinum; LY-146032. *N*-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine 1.13-3.4-lactone.

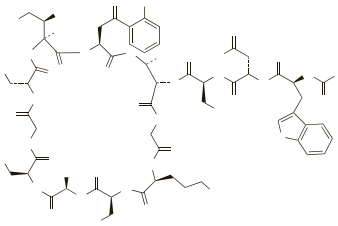
Даптомицин

$C_{72}H_{101}N_{17}O_{26}$ = 1620.7.

CAS — 103060-53-3.

ATC — J01XX09.

ATC Vet — QJ01XX09.



Adverse Effects and Precautions

The most common adverse effects associated with daptomycin are gastrointestinal effects including nausea and vomiting, constipation, diarrhoea, and dyspepsia. Headache, insomnia, dizziness, and fever may occur. Injection site reactions have occurred. Effects on the skin have included rash and pruritus. Abnormal liver function tests and jaundice have been reported. Other reported adverse effects include hypertension or hypotension, renal failure, dyspnoea, and anaemia. There have been rare cases of hypersensitivity, anaphylaxis, and infusion reactions.

Elevated plasma creatine phosphokinase (CPK) concentrations during daptomycin therapy may be associated with muscle pain and/or weakness, myositis, myopathy, and rarely rhabdomyolysis; patients with renal impairment or taking other drugs known to cause myopathy (see Interactions, below) may be at increased risk. All patients should be monitored for the development of muscle pain or weakness, and plasma CPK concentrations measured once weekly. More frequent measurements should be performed in those with an increased risk of myopathy, or with a baseline CPK concentration greater than 5 times the upper limit of normal (ULN), or who develop signs of myopathy. Daptomycin should be stopped in patients with signs of myopathy and CPK concentrations greater than 5 times the ULN, or in those without reported signs of myopathy but with CPK concentrations greater than 10 times the ULN.

Daptomycin should be given with caution and in reduced dosage to patients with renal impairment; clinical response and renal function should be monitored closely.

Consideration should be given to stopping daptomycin therapy in patients who develop signs or symptoms of peripheral neuropathy.

Effects on the lungs. Bronchiolitis obliterans organising pneumonia with eosinophilic infiltration has been reported in an 84-year-old man after 4 weeks of daptomycin therapy;[1] clinical improvement occurred after the drug was stopped. The mechanism of toxicity was unknown and the authors suggested that it might be associated with epithelial injury caused by daptomycin accumulating in the alveolar spaces.

A 60-year-old man receiving daptomycin developed eosinophilic pneumonia resulting in respiratory failure that required mechanical ventilation;[2] he improved after stopping the drug and starting corticosteroid therapy.

1. Cobb E, *et al.* Organizing pneumonia and pulmonary eosinophilic infiltration associated with daptomycin. *Ann Pharmacother* 2007; **41:** 696–701.
2. Hayes D, *et al.* Eosinophilic pneumonia induced by daptomycin. *J Infect* 2007; **54:** e211–e213.

Pregnancy. Intravenous daptomycin, 4 mg/kg daily for 14 days, was successfully used to treat pyelonephritis associated with vancomycin-resistant enterococci (VRE) in a 27-week pregnant woman; no neonatal abnormalities were reported.[1]

1. Shea K, *et al.* Successful treatment of vancomycin-resistant Enterococcus faecium pyelonephritis with daptomycin during pregnancy. *Ann Pharmacother* 2008; **42:** 722–5.

Interactions

There may be an increased risk of myopathy if daptomycin is given with other drugs also known to have this adverse effect, such as statins, fibrates, and ciclosporin. Licensed product information recommends stopping the latter if possible; otherwise, plasma creatine phosphokinase concentrations should be measured more than once weekly in addition to the usual precautions (see Adverse Effects and Precautions, above).

Daptomycin is mainly excreted by renal filtration and caution is advised if given with drugs that reduce renal filtration, such as NSAIDs and selective inhibitors of cyclo-oxygenase-2, since plasma concentrations of daptomycin may be increased.

Daptomycin has been reported to interact with a particular reagent used in some assays of PT-INR resulting in apparent prolongation of PT and elevation of INR.

Antimicrobial Action

Daptomycin is a lipopeptide antibacterial that is reported to have a spectrum of antibacterial activity similar to that of vancomycin (p.359) and greater potency against most Gram-positive bacterial strains *in vitro*; it is inactive against Gram-negative bacteria. Daptomycin disrupts the bacterial cell membrane potential by binding to the cell membranes in a calcium-dependent process, but without entering the cytoplasm, thus inhibiting the synthesis of protein, DNA, and RNA.

Daptomycin has shown activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci.

It is reported to show antimicrobial synergy *in vitro* with aminoglycosides, beta lactams, and rifampicin against *Staph. aureus* (including meticillin-resistant strains) and enterococci (including vancomycin-resistant strains).

Resistance to daptomycin has been shown in clinical studies but only rarely; the mechanism of resistance has not been identified.

◊ Reviews.

1. Boucher HW, Sakoulas G. Perspectives on daptomycin resistance, with emphasis on resistance in Staphylococcus aureus. *Clin Infect Dis* 2007; **45:** 601–8.

Pharmacokinetics

Daptomycin is not absorbed to any significant extent after oral doses. The pharmacokinetics of daptomycin are generally linear at intravenous doses ranging from 4 to 12 mg/kg once daily. Peak plasma concentrations are achieved within 0.5 to 0.8 hours. It is distributed mainly into the extracellular space with a volume of distribution of about 0.1 litres/kg. Daptomycin crosses the blood-brain barrier and the placenta. It is about 90% bound to plasma proteins, mainly serum albumin.

In-vitro studies indicate that daptomycin is not metabolised by, and does not affect, the cytochrome P450 isoenzyme system. Little or no metabolism is thought to take place although 4 minor metabolites have been detected in the urine.

Daptomycin is excreted mainly via renal filtration with about 78% and 6% of a dose recovered in the urine and faeces, respectively. It has an elimination half-life of about 8 hours after an intravenous dose of 4 mg/kg once daily for 7 days and is prolonged in patients with renal impairment; a two- to threefold increase has been reported in those with severe impairment or end-stage renal disease.

Daptomycin is removed by haemodialysis or peritoneal dialysis.

◊ References.

1. Dvorchik B, *et al.* Population pharmacokinetics of daptomycin. *Antimicrob Agents Chemother* 2004; **48:** 2799–2807.

Uses and Administration

Daptomycin is given by intravenous infusion over 30 minutes for the treatment of complicated Gram-positive infections of the skin and soft tissues, and *Staphylococcus aureus* bacteraemia, including right-sided endocarditis, caused by meticillin-susceptible and meticillin-resistant strains.

For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

For the treatment of skin and soft-tissue infections, daptomycin is given in a dose of 4 mg/kg once daily for 7 to 14 days. A higher dose of 6 mg/kg once daily is given for 2 to 6 weeks in the treatment of bacteraemia.

For details of dosage modification in patients with renal impairment, see below.

Daptomycin has also been investigated for the treatment of vancomycin-resistant enterococcal infections, complicated urinary-tract infections, and community-acquired pneumonia.

◊ References.

1. Fenton C, *et al.* Daptomycin. *Drugs* 2004; **64:** 445–55.
2. Steenbergen JN, *et al.* Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 2005; **55:** 283–8.
3. Schriever CA, *et al.* Daptomycin: a novel cyclic lipopeptide antimicrobial. *Am J Health-Syst Pharm* 2005; **62:** 1145–58.
4. French GL. Bactericidal agents in the treatment of MRSA infections—the potential role of daptomycin. *J Antimicrob Chemother* 2006; **58:** 1107–17.
5. Hair PI, Keam SJ. Daptomycin: a review of its use in the management of complicated skin and soft-tissue infections and *Staphylococcus aureus* bacteraemia. *Drugs* 2007; **67:** 1483–1512.
6. Enoch DA, *et al.* Daptomycin. *J Infect* 2007; **55:** 205–13.
7. Weis F, *et al.* Daptomycin, a lipopeptide antibiotic in clinical practice. *Curr Opin Investig Drugs* 2008; **9:** 879–84.
8. Forrest GN, *et al.* Clinical experience with daptomycin for the treatment of patients with documented gram-positive septic arthritis. *Ann Pharmacother* 2008; **42:** 213–17.

Administration in renal impairment. In patients with a creatinine clearance of less than 30 mL/minute, including those receiving dialysis, the intravenous dosage of daptomycin should be modified to 4 mg/kg once every 48 hours in the treatment of skin and soft-tissue infections, and to 6 mg/kg once every 48 hours in the treatment of bacteraemia.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Cubicin; ***Gr.:*** Cubicin; ***Israel:*** Cubicin; ***Port.:*** Cubicin; ***UK:*** Cubicin; ***USA:*** Cubicin.

Demeclocycline *(BAN, rINN)*

Demeclociclina; Déméclocycline; Demeclocyclinum; Demeklocyklin; Demeklosykliini; Demethylchlortetracycline. (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyltetracycline.

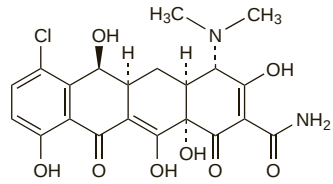
Демеклоциклин

$C_{21}H_{21}ClN_2O_8$ = 464.9.

CAS — 127-33-3 (demeclocycline); 13215-10-6 (demeclocycline sesquihydrate).

ATC — D06AA01; J01AA01.

ATC Vet — QD06AA01; QJ01AA01.



Pharmacopoeias. In *US.*

USP 31 (Demeclocycline). A yellow, odourless crystalline powder. Sparingly soluble in water; soluble 1 in 200 of alcohol and 1 in 40 of methyl alcohol; dissolves readily in 3N hydrochloric acid and in alkaline solutions. pH of a 1% solution in water is between 4.0 and 5.5. Store in airtight containers. Protect from light.

Demeclocycline Hydrochloride *(BANM, rINNM)*

Déméclocycline, chlorhydrate de; Demeclocyclini hydrochloridum; Demeklociklin-hidroklorid; Demeklociklino hidrochloridas; Demeklocyklin-hydrochlorid; Demeklocyklinhydroklorid; Demeklocykliny chlorowodorek; Demeklosiklin Hidroklorür; Demeklosykliinihydrokloridi; Demethylchlortetracycline Hydrochloride; Hidrocloruro de demeclociclina.

Демеклоциклина Гидрохлорид

$C_{21}H_{21}ClN_2O_8$,HCl = 501.3.

CAS — 64-73-3.

ATC — D06AA01; J01AA01.

ATC Vet — QD06AA01; QJ01AA01.

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

Ph. Eur. 6.2 (Demeclocycline Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Soluble or sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

USP 31 (Demeclocycline Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 60 of water and 1 in 50 of methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone and in chloroform; sparingly soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Tetracycline, p.347.

Phototoxic reactions occur more frequently with demeclocycline than with other tetracyclines and patients should avoid direct exposure to sunlight or artificial ultraviolet light.

Reversible nephrogenic diabetes insipidus with polyuria, polydipsia, and weakness may occur in patients treated with demeclocycline, particularly with prolonged treatment and/or high doses. Plasma creatinine should be monitored in patients receiving demeclocycline for long periods for the treatment of inappropriate secretion of antidiuretic hormone, since tetracycline-induced renal impairment may not otherwise be apparent in the absence of oliguria. For a comment that the usefulness of demeclocycline for this indication may be limited by nephrotoxicity in patients with cardiac or hepatic disease, see Syndrome of Inappropriate ADH Secretion under Uses and Administration, below.