effect on tolerability and may be associated with a higher rate of therapeutic failure (see HIV Infection and AIDS, p.1944).

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 18/05/05)
2. 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 04/04/05)
3. 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 04/04/05) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5412a10.htm (accessed 13/06/05)
4. Ioannidis JPA, *et al*. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Arch Intern Med* 1996; **156:** 177–88.
5. El-Sadr WM, *et al*. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. *Clin Infect Dis* 1999; **29:** 775–83.
6. Wormser GP, *et al*. Low-dose intermittent trimethoprim-sulfamethoxazole for prevention of Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *Arch Intern Med* 1991; **151:** 688–92.
7. Stein DS, *et al*. Use of low-dose trimethoprim-sulfamethoxazole thrice weekly for primary and secondary prophylaxis of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1991; **35:** 1705–9.
8. Ruskin J, LaRiviere M. Low-dose co-trimoxazole for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus disease. *Lancet* 1991; **337:** 468–71.
9. Bozzette SA, *et al*. The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. *Am J Med* 1995; **98:** 177–82.
10. 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.

Toxoplasmosis. There is some evidence that giving co-trimoxazole for prophylaxis of pneumocystis pneumonia produces an additional benefit in acting prophylactically against toxoplasmic encephalitis in persons with HIV infection or AIDS,[1-5] but the evidence (as for other drugs) has been largely anecdotal or from small retrospective studies. In the USA, the CDC recommends[1] that co-trimoxazole 960 mg daily (as for *Pneumocystis carinii* pneumonia prophylaxis, above) be given to HIV-infected patients who are seropositive for *Toxoplasma* and have a CD4+ count below 100 cells/microlitre.

Co-trimoxazole has also produced promising results in preliminary studies for the treatment of toxoplasmic encephalitis in patients with AIDS,[6] and a systematic review[7] considered it an effective treatment, particularly in resource-poor settings where alternatives such as pyrimethamine with sulfadiazine might not be available.

For a discussion of toxoplasmosis and its management, see p.826.

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.
2. Zangerle R, Allerberger F. Effect of prophylaxis against Pneumocystis carinii on toxoplasma encephalitis. *Lancet* 1991; **337:** 1232.
3. Carr A, *et al*. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1992; **117:** 106–11.
4. Beaman MH, *et al*. Prophylaxis for toxoplasmosis in AIDS. *Ann Intern Med* 1992: **117:** 163–4.
5. 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.
6. Torre D, *et al*. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1998; **42:** 1346–9.
7. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/07/08).

Preparations

BP 2008: Co-trimoxazole Intravenous Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets; ***USP 31:*** Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Adrenol; Bacticel; Bactrim; Cotrizol-G; Danferane; Diocla†; Dosulfin Fuerte; Netocur; Novidrine; Sulfagrand; Tritenk; Urisept NF; ***Austral.:*** Bactrim; Cosig†; Resprim; Septrin; Trimoxazole; ***Austria:*** Bactrim; Cotribene; Eusaprim; Oecotrim; Trimetho comp; ***Belg.:*** Bactrim; Cotrim; Eusaprim; Steroprim†; ***Braz.:*** Assepium; Bac-Sulfitrin; Bacfar; Bacprotin; Bactris†; Bacteracin; Bactrim; Bactrisan; Bactrizol; Bactropin; Batrox; Baxapril†; Benectrin; Binoctrin†; Clotrizol†; Dientrin; Duoctrin†; Ectrin; Espectrin†; Espectroprima†; Gamactrin; Imuneprim; Infectrin; Lifactrin†; Linurin†; Lupectrim†; Metoprin; Neotrin; Pulkrin; Qiftrin†; Quimio-Ped†; Roytrin†; Selectrin; Septiolan†; Teutrin; Tricban; Trimexazol; Trimezol†; Uropol; ***Canad.:*** Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; Septra; ***Chile:*** Bacterol; Bactrimel; Introcin†; Septrin; Trelibec; ***Cz.:*** Apo-Sulfatrim†; Berlocid†; Biseptol; Bismoral; Nopil†; Oriprim†; Primotren; Sumetrolim; Supracombin†; ***Denm.:*** Sulfotrim†; ***Fin.:*** Cotrim; ***Fr.:*** Bactrim; Eusaprim†; ***Ger.:*** Bactoreduct†; Berlocid; Cotrim; Cotrim-Diolan; CotrimHefa; Cotrimhexal; Cotrimox-Wolff; Cotrimstada; Drylin; Eusaprim; Kepinol; Microtrim†; Sigaprim†; Supracombin†; TMS; ***Gr.:*** Bactrimel; Bioprim†; Septrin; ***Hong Kong:*** Chemitrim†; Chemoprim; Cotrim; Dhatrin; Letus; Septrin; ***Hung.:*** Sumetrolim; ***India:*** Bactrim; Ciplin; Colizole; Cotrimol†; Oriprim; Sepmax; Septran; Tabrol; Trisulfose; ***Indon.:*** Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim; Cotrimol; Dumotrim; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim; Meprotrin; Nufaprim; Ottoprim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim; Sultrimmix; Trimezol; Triminex; Trimoxsul; Trixzol; Trizole; Ulfaprim; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.:*** Duobact†; Septrin; ***Israel:*** Diseptyl; Resprim; Septrin; ***Ital.:*** Abacin†; Bactrim; Chemitrim; Eusaprim; Gantrim†; ***Jpn:*** Bactramin; ***Malaysia:*** Bacin; Baserin†; Chemix; Cotrim; Resprim; Trimexazole; Virin†; ***Mex.:*** Andoprim; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric; Bactide; Bactilen; Bactiver; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Kaltrim; Maxtrim; Metoxiprim; Microbactim†; Mixange; Octiban; Pisatrina; Polibatrin; Pribac; Protaxol; Protrim; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultiprim†; Syraprim†; Thriazol; Tribakin; Trime/Sulfa†; Trimetoger; Trimetox; Trimexazol; Trimexole; Trimzol; Trinelax†; Trisufin†; Vanadyl; ***Neth.:*** Bactrimel; Eusaprim†; Sulfotrim; ***Norw.:*** Bactrim; Trimetoprim-Sulfa†; ***NZ:*** Apo-Sulfatrim; Trisul; ***Philipp.:*** Bacidal; Bactille; Bactrim; Bacxal; Baczole; Bantizol; Chromo-Z; Combi-Methoxan; Costazole; Cozole; Drilozole; Fedimed; Forteprim; Globaxol; Ivatrim; Kassemox; Lictora; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Synermed; Triforam; Trim-S; Trimephar; Trimocom; Trimoxis; Triphimox; Trizole; Xanazole; Zamboprim; Zolmed; ***Pol.:*** Bactrim; Biseptol; Groseptol†; Septrin; Two-Septol; ***Port.:*** Bactrim; Cotrim†; Metomide†; Microcetim; Septrin; ***Rus.:*** Biseptol (Бисептол); Oriprim (Ориприм); Rancotrim (Ранкотрим); ***S.Afr.:*** Acuco; Bactrim; Bencole; Casicot; Cocydal; Cozole; Durobac; Fabubac†; Lagatrim; Meditrim; Mezenol†; Purbac; Septran; Spectrim; Trimethox; Trimzol; Xerazole; Xeroprim†; ***Singapore:*** Apo-Sulfatrim; Bacin; BS†; Chemix; Chemoprim; Dhatrin; Septrin†; Suprim; Trimezole†; ***Spain:*** Broncomega†; Busetal†; Eduprim†; Gobens Trim; Momentol; Septrin; ***Swed.:*** Bactrim; Eusaprim; ***Switz.:*** Agoprim†; Bactrim; Cotrim; Escoprim; Groprim; Lagatrim; Mediprim; Nopil; Sigaprim†; Supracombin†; ***Thai.:*** Actin; Bacin; Bacta†; Bactrim; Baczole; Chemoprim†; Co-Tasian; Co-Trimed; Conprim; Cotamox; Ko-Cap; Ko-Kure; Ladar; Lastrim; Letus; M-Trim; Mano-Trim; Med-Sultrim†; Mega-Prim; Metrim; Metxaprim; Mycosamthong; Po-Trim; Pulvicin†; Septrin†; Spectrim; Sulbacta; Sulfometh; Suntrim; Tampo†; Toprim†; Trimexazole; Triprim; Trixzol; Zoleprim†; ***Turk.:*** Bactrim; Bakton; Kemoprim; Metoprim; Mikrosid; Septrin; Trifen; Trimoks; ***UAE:*** Trimol; ***UK:*** Fectrim; Septrin; ***USA:*** Bactrim; Cotrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.:*** Bactrimel; Bactron†; Co-Sultrin; Forcrim; Trimecor; Trimetoprim Sulfa†; Tripur.

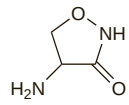
Multi-ingredient: ***Arg.:*** Bacti-Uril; Bactrim Balsamico; Dosulfin Bronquial; Enterobacticel; Netocur Balsamico; Neumobacticel; Uro-Bactrim†; ***Braz.:*** Assepium Balsamico; Benectrin Balsamico; Diazol; Dispeptrin; Ectrin Balsamico; Metoprin Balsamico; Selectrin Balsamico; Uro-Baxapril†; Urectrin; ***Chile:*** Entero Micinovo; Uro-Micinovo; ***Hung.:*** Cotripharm; ***Mex.:*** Bactrim Compositum; Brogamax; Guayaprin; Octex; Sadocin; Trimexole Compositum; ***Singapore:*** Co-Trimexazole; Trimaxazole; ***Spain:*** Bactopumon; Balsoprim; Bronco Aseptilex Fuerte; Broncovir; Bronquicisteina; Bronquidiazina CR; Bronquimar; Bronquimucil†; Cotrazol; Eduprim Mucolitico; Neumopectolina†; Pulmo Menal†; Pulmosterin Duo.

Cycloserine *(BAN, rINN)*

Cicloserina; D-Cycloserin; Cyclosérine; D-Cycloserine; Cycloserinum; Cykloserin; SC-49088; Sikloserin; Sykloseriini. (+)-(*R*)-4-Aminoisoxazolidin-3-one.

Циклосерин

$C_3H_6N_2O_2$ = 102.1.
CAS — 68-41-7.
ATC — J04AB01.
ATC Vet — QJ04AB01.



Description. Cycloserine is an antimicrobial substance produced by the growth of certain strains of *Streptomyces orchidaceus* or *S. garyphalus*, or obtained by synthesis.

Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Cycloserine). A white to pale yellow, crystalline powder, odourless or has a faint odour. It is hygroscopic and deteriorates upon absorbing water. Freely soluble in water. pH of a 10% solution in water is between 5.5 and 6.5. Store in airtight containers.

Adverse Effects and Treatment

The most frequent adverse effects with cycloserine involve the CNS and include anxiety, confusion, disorientation, depression, psychoses possibly with suicidal tendencies, aggression, irritability, and paranoia. Vertigo, headache, drowsiness, speech difficulties, tremor, paresis, hyperreflexia, dysarthria, paraesthesia, coma, and convulsions may also occur. Neurological reactions are dose related and may be reduced by keeping plasma concentrations below 30 micrograms/mL. It has been reported that up to 30% of patients have experienced adverse effects. These reactions usually subside when cycloserine is stopped or the dosage is reduced. Pyridoxine has been used in an attempt to treat or prevent neurological reactions but its value is unproven.

Hypersensitivity reactions including skin reactions and photosensitivity occur rarely. Serum aminotransferase values may be raised, especially in patients with a history of liver disease. Folate and vitamin B_{12} deficiency, megaloblastic anaemia, and sideroblastic anaemia have been reported occasionally when cycloserine has been used with other antituberculous drugs. Heart failure has occurred in patients receiving daily doses of 1 g or more.

Precautions

Cycloserine is contra-indicated in patients with epilepsy, depression, psychosis, severe anxiety, severe renal impairment, or in those who misuse alcohol. Cycloserine should be stopped, or the dose reduced, if skin reactions or symptoms of CNS toxicity develop.

Cycloserine has a low therapeutic index, and dosage should be adjusted according to plasma concentrations, which should be monitored at least weekly in patients with renal impairment, in those taking doses greater than 500 mg daily, and in patients showing signs of neurotoxicity. Plasma concentrations should be maintained below 30 micrograms/mL. Haematological, renal, and hepatic function should be monitored. Patients with mild to moderate renal impairment require lower doses.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cycloserine,[1] and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Morton RF, *et al*. Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; **3:** 169–72.
2. 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)

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

Interactions

Patients receiving cycloserine and taking alcohol are at increased risk of convulsions; for reference to increased blood-alcohol concentrations in patients receiving cycloserine, see p.1627.

Neurotoxic effects may be potentiated by use of cycloserine with ethionamide, and concurrent use of cycloserine and isoniazid may result in increased CNS toxicity, such as dizziness and drowsiness.

Antimicrobial Action

Cycloserine interferes with bacterial cell wall synthesis by competing with D-alanine for incorporation into the cell wall. It has variable activity against Gram-positive and Gram-negative bacteria including *Escherichia coli* and *Staphylococcus aureus*.

Cycloserine is active against *Mycobacterium tuberculosis* and some other mycobacteria. Resistance develops if cycloserine is used alone.

Pharmacokinetics

Cycloserine is readily and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations of 10 micrograms/mL have been obtained 3 to 4 hours after a dose of 250 mg, rising to 20 to 30 micrograms/mL on repeating the dose every 12 hours. The plasma half-life is about 10 hours and is prolonged in patients with renal impairment.

Cycloserine is widely distributed into body tissues and fluids, including the CSF, placenta, and breast milk, producing fetal blood concentrations approaching those in maternal serum.

Cycloserine is excreted largely unchanged by glomerular filtration. About 50% of a single 250-mg dose is excreted unchanged in the urine within 12 hours and about 70% is excreted within 72 hours. As negligible amounts of cycloserine appear in the faeces, it is assumed that the remainder of a dose is metabolised to unidentified metabolites. It is removed by haemodialysis.

Pregnancy and breast feeding. Cycloserine has been shown to pass to the fetus, into amniotic fluid,[1] and into breast milk.[2] Concentrations in breast milk after 250 mg four times daily have been reported to range from 6 to 19 micrograms/mL.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
2. Morton RF, *et al*. Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; **3:** 169–72.

Uses and Administration

Cycloserine is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p.196) as part of a multidrug regimen when resistance to primary drugs has developed. It has been used in urinary-tract infections, although less toxic drugs are preferred.

The usual adult oral dose in tuberculosis is 250 mg twice daily for 2 weeks, followed by 0.5 to 1 g daily in divided doses. Dosage in patients with mild to moderate renal impairment should be reduced and doses for all patients should be adjusted by monitoring plasma concentrations (see Precautions, above).

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

Cycloserine has been tried for the adjunctive treatment of schizophrenia. L-Cycloserine has been investigated for the treatment of Gaucher disease (p.2249).

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.

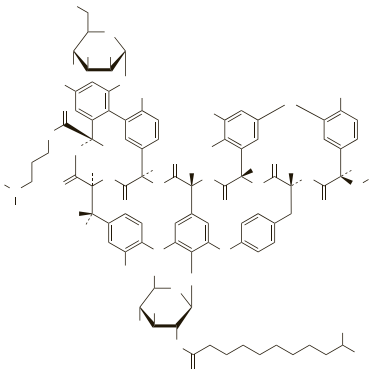
Dalbavancin *(BAN, USAN, rINN)*

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.

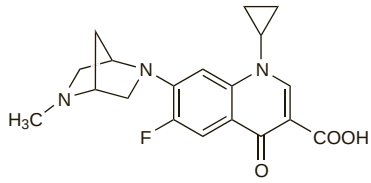
Danofloxacin Mesilate *(BANM, rINNM)*

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.

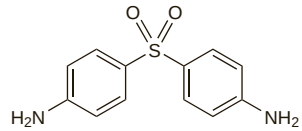
Дапсон

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

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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.

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