py may predispose to toxicity (see Uses and Administration of Gentamicin Sulfate, p.284).

Tobramycin may be used as a 0.3% eye ointment or eye drops in the treatment of eye infections. It is also given by inhalation in patients with cystic fibrosis to control *Pseudomonas aeruginosa* infections in a dose of 300 mg every 12 hours for 28 days using a suitable nebuliser. Treatment is then stopped for 28 days before being resumed for another treatment period. This cycle may be repeated indefinitely.

◊ Reviews.

1. Cheer SM, *et al.* Inhaled tobramycin (TOBI): a review of its use in the management of pseudomonas aeruginosa infections in patients with cystic fibrosis. *Drugs* 2003; **63:** 2501–20.

Preparations

BP 2008: Tobramycin Injection;
USP 31: Tobramycin and Dexamethasone Ophthalmic Ointment; Tobramycin and Dexamethasone Ophthalmic Suspension; Tobramycin and Fluorometholone Acetate Ophthalmic Suspension; Tobramycin for Injection; Tobramycin Inhalation Solution; Tobramycin Injection; Tobramycin Ophthalmic Ointment; Tobramycin Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Bioptic; Fotex; Gotabiotic; Gotabiotic D; Klonamicin; Oftalbrax†; Radina; Tobi; Tobrabiotic; Tobradosa; Tobragan; Tobranet; Tobrex; Toflamixina; Tuberbut; Xao T; Xibrax; ***Austral.:*** Nebcin; Tobi; Tobrex; ***Austria:*** Brulamycin; Cromycin; Tobi; Tobrasix; Tobrex; ***Belg.:*** Obracin; Tobi; Tobrex; ***Braz.:*** Tobra-M†; Tobracin; Tobragan; Tobramina; Tobranom; Tobrex; Toflamixina†; ***Canad.:*** Nebcin†; Tobi; Tobrex; Tomycine†; ***Chile:*** Tobragan; Tobrex; Tobrin; Xolof; ***Cz.:*** Bramitob; Brulamycin; Tobi; Tobrex; ***Denm.:*** Nebcina; Tobi; Tobrex; ***Fin.:*** Nebcina†; Tobi; Tobrex; Tomycin; ***Fr.:*** Nebcine; Tobi; Tobrex; ***Ger.:*** Brulamycin†; Gernebcin; Tobi; Tobra-cell; Tobramaxin; ***Gr.:*** Colther; Eyebrex; Eyetobrin; Ikobel; Monobracin†; Monotobrin; Nebcin; Thilo-micine; Tobi; Tobrex; ***Hong Kong:*** Nebcin†; Tobrex; Toracin; ***Hung.:*** Brulamycin; Tobi; Tobrex; ***India:*** Ocutob; Tobacin; Tobazon; Tobraneg; ***Indon.:*** Bralifex; Dartobcin; Isotic Tobryne; Tobrex; Tobryne; ***Irl.:*** Nebcin†; Tobi; Tobralex†; ***Israel:*** Nebcin†; Tobi; Tobrex; ***Ital.:*** Bramicil; Bramitob; Nebicina; Tobi; Tobrabact; Tobral; Tobrastill; ***Malaysia:*** Tobrex; ***Mex.:*** Eyebrex; Micitrex; Obry; Tobra†; Tobrex; Trazil; Verbram; ***Neth.:*** Obracin; Tobi; Tobrabact; Tobrex; ***Norw.:*** Nebcina†; Tobi; Tobrex; ***NZ:*** Nebcin; Tobi†; Tobrex; ***Philipp.:*** Ramitop; Tobrex; ***Pol.:*** Tobi; Tobrex; Tobrosopt; ***Port.:*** Bramitob; Distobram†; Tobi; Tobra-Gobens; Tobrex; Tobrexan; Tobridavi; ***Rus.:*** Brulamycin (Бруламицин); Tobrex (Тобрекс); ***S.Afr.:*** Nebcin; Tobrex; ***Singapore:*** Tobrex; ***Spain:*** Tobi; Tobra Gobens; Tobrabact; Tobradistin†; Tobrex; Tobrexan; ***Swed.:*** Nebcina; Tobi; Tobrex; ***Switz.:*** Obracin; Tobi; Tobrex; ***Thai.:*** Tobrex; ***Turk.:*** Thilomaxine; Tobel; Tobrased; Tobrex; Tobsin; ***UK:*** Nebcin†; Tobi; ***USA:*** AkTob; Nebcin†; Tobi; Tobrasol; Tobrex; ***Venez.:*** Poentobral; Tobranax; Tobrasol; Tobrex; Trazil†.

Multi-ingredient: ***Arg.:*** Antibioptal; Bicrinol; Biocort; Bioptic DX; Decadron con Tobramicina; Fotadex; Gotabiotic F; Ingebrax; Klonamicin Compuesto; Larsen; Lotemicin; Polioftal; Radina Dex; Tobrabiotic D; Tobracort; Tobradex; Tobradiclo; Tobragan D; Tobratlas; Toflam; Toflamixina Plus; Xao-Dex†; Xibradex; ***Austria:*** Tobradex; ***Belg.:*** Ocubrax; Tobradex; ***Braz.:*** Tobracin D; Tobracort; Tobradex; ***Canad.:*** Tobradex; ***Chile:*** Poentobral Plus; Tobradex; Tobragan D; Tobrin-D; Todexona; Xolof D; ***Cz.:*** Tobradex; ***Fr.:*** Tobradex; ***Gr.:*** Dexamycin; Eyebrex-Dexa†; Lofoto; O-Biotic; Thilomicine Dex; Tobradex; Tobrafen; ***Hong Kong:*** Tobradex; ***Hung.:*** Ocubrax†; Tobradex; ***India:*** Obrasone; Ocutob-D; Tobazon DM; ***Indon.:*** Bralifex Plus; Isotic Tobrizon; Tobradex; ***Ital.:*** Tobradex; ***Malaysia:*** Tobradex; ***Mex.:*** Obrydex; Obrypre; Tobracort; Tobradex; Trazidex; Trazinac; ***Neth.:*** Tobradex; ***NZ:*** Tobradex; ***Philipp.:*** Tobradex; ***Pol.:*** Tobradex; ***Rus.:*** Tobradex (Тобрадекс); Tobrasone (Тобразон); ***S.Afr.:*** Tobradex; ***Singapore:*** Tobradex; ***Spain:*** Ocubrax; Tobradex; ***Switz.:*** Tobradex; Tobrafen; ***Thai.:*** Tobradex; ***Turk.:*** Ocubrax; ***UK:*** Tobradex; ***USA:*** Tobradex; ***Venez.:*** Poentobral Plus; Tobracort; Tobradex; Tobragan D; Todenac; Todex; Trazidex; Trazinac.

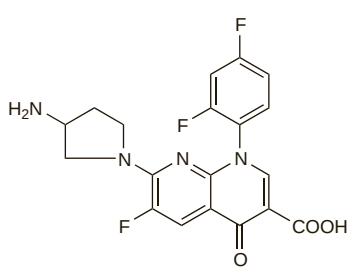
Tosufloxacin *(USAN, rINN)*

A-61827; Abbott-61827; Tosufloxacine; Tosufloxacino; Tosufloxacinum. (±)-7-(3-Amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

Тосуфлоксацин

$C_{19}H_{15}F_3N_4O_3$ = 404.3.

CAS — 100490-36-6 (anhydrous tosufloxacin); 108138-46-1 (anhydrous tosufloxacin); 107097-79-0 (tosufloxacin monohydrate).



Tosufloxacin Tosilate *(rINNM)*

A-64730; T-3262; Tosilato de tosufloxacino; Tosufloxacin Tosylate; Tosufloxacine, Tosilate de; Tosufloxacini Tosilas. Tosufloxacin toluene-4-sulphonate monohydrate.

Тосуфлоксацина Тозилат

$C_{19}H_{15}F_3N_4O_3.C_7H_8O_3S.H_2O$ = 594.6.

CAS — 115964-29-9; 144742-63-2.

Profile

Tosufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p.243). It is given orally as the tosilate in the treatment of susceptible infections in usual doses of 300 to 450 mg daily in 2 or 3 divided doses.

For blepharitis, conjunctivitis, corneal ulcers, and other eye infections caused by susceptible strains of bacteria, eye drops containing 0.3% of tosufloxacin tosilate are used.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Ozex.

Trimethoprim *(BAN, USAN, rINN)*

BW-56-72; NSC-106568; Triméthoprime; Trimethoprimum; Trimethoxyprim; Trimetopriimi; Trimetoprim; Trimetoprima; Trimetoprimas. 5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine.

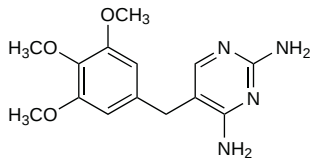
Триметоприм

$C_{14}H_{18}N_4O_3$ = 290.3.

CAS — 738-70-5.

ATC — J01EA01.

ATC Vet — QJ01EA01; QJ51EA01.



NOTE. Compounded preparations of trimethoprim may be represented by the following names:

- Co-trifamole (*BAN*)—trimethoprim 1 part and sulfamoxole 5 parts (see p.257)
- Co-trimazine (*BAN*)—trimethoprim 1 part and sulfadiazine 5 parts (see p.258)
- Co-trimoxazole (*BAN*)—trimethoprim 1 part and sulfamethoxazole 5 parts (see p.258)
- Co-trimoxazole (*PEN*)—trimethoprim and sulfamethoxazole.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*
Ph. Eur. 6.2 (Trimethoprim). A white or yellowish-white powder. Very slightly soluble in water; slightly soluble in alcohol.
USP 31 (Trimethoprim). White to cream-coloured, odourless crystals or crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in acetone; soluble in benzyl alcohol; practically insoluble in carbon tetrachloride and in ether; sparingly soluble in chloroform and in methyl alcohol. Store in airtight containers. Protect from light.

Trimethoprim Sulfate *(USAN, rINNM)*

BW-72U; Sulfato de trimetoprima; Trimethoprim Sulphate *(BANM)*; Triméthoprime, Sulfate de; Trimethoprimi Sulfas; Trimetoprim Sülfat.

Триметоприма Сульфат

$(C_{14}H_{18}N_4O_3)_2.H_2SO_4$ = 678.7.

CAS — 56585-33-2.

Pharmacopoeias. In *Viet.* and *US.*
USP 31 (Trimethoprim Sulfate). A white to off-white crystalline powder. Soluble in water, in alcohol, in dilute mineral acids, and in fixed alkalis. pH of a 0.05% solution in water is between 7.5 and 8.5. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Incompatibility. UK licensed product information states that trimethoprim injections (containing the lactate) should not be mixed with solutions of sulfonamides because of incompatibility. Although a former such preparation stated that it should not be diluted in chloride-containing infusion solutions, because of the risk of precipitating trimethoprim hydrochloride, others are stated to be compatible with sodium chloride 0.9% and some other chloride-containing solutions including Ringer's solution. Injections are considered compatible with glucose 5% and with sodium lactate.

Adverse Effects and Treatment

Trimethoprim is reasonably well tolerated in general, and the most frequent adverse effects at usual doses are pruritus and skin rash (in about 3 to 7% of patients) and mild gastrointestinal disturbances including nausea, vomiting, and glossitis.

Rarely, more severe effects have been reported. Sulfonamide-like skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Disturbances of liver enzyme values and cholestatic jaundice have been associated with trimethoprim. Rises in serum creatinine and blood-urea nitrogen have been reported although it is unclear whether this represents genuine renal dysfunction or inhibition of tubular secretion of creatinine. Photosensitivity has been reported. Fever is not uncommon but occasionally hypersensitivity reactions may be severe and anaphylaxis and angioedema have been reported. Cases of aseptic meningitis have also occurred.

Trimethoprim may cause a depression of haematopoiesis due to interference of the drug in the metabolism of folic acid, particularly when given over a prolonged period or in high doses. This may manifest as megaloblastic anaemia, or as thrombocytopenia and leucopenia; methaemoglobinaemia has also been seen. Calcium folinate 5 to 15 mg daily by mouth may be given to counter this effect. Trimethoprim is teratogenic in *animals*.

For further information on the adverse effects of trimethoprim when used with sulfamethoxazole, see Co-trimoxazole, p.258.

Effects on the eyes. There have been isolated reports of bilateral anterior uveitis associated with trimethoprim. In 2 such patients,[1,2] the reaction recurred upon rechallenge with trimethoprim. A third patient developed uveitis after co-trimoxazole, and subsequently uveitis with retinal haemorrhage following trimethoprim alone.[3]

1. Gilroy N, *et al.* Trimethoprim-induced aseptic meningitis and uveitis. *Lancet* 1997; **350:** 112.
2. Arola O, *et al.* Arthritis, uveitis, and Stevens-Johnson syndrome induced by trimethoprim. *Lancet* 1998; **351:** 1102.
3. Kristinsson JK, *et al.* Bilateral anterior uveitis and retinal haemorrhages after administration of trimethoprim. *Acta Ophthalmol Scand* 1997; **75:** 314–15.

Hyperkalaemia. Trimethoprim has been reported to induce hyperkalaemia,[1] particularly in HIV-infected patients being treated for pneumocystis pneumonia or in the elderly. The hyperkalaemia may be due to amiloride-like potassium-sparing properties of trimethoprim, and may be potentiated by ACE inhibitors.

1. Perazella MA. Trimethoprim-induced hyperkalaemia: clinical data, mechanism, prevention and management. *Drug Safety* 2000; **22:** 227–36.

Precautions

Trimethoprim should not be given to patients with a history of hypersensitivity to the drug, and it should be stopped if a skin rash appears. Care is necessary in giving trimethoprim to patients with renal impairment to avoid accumulation and toxicity: it should not be given in severe renal impairment unless blood concentrations can be monitored. It should be used with caution in patients with severe hepatic damage as changes may occur in the absorption and metabolism of trimethoprim.

It is suggested that regular haematological examination should be made during prolonged courses of treatment although the *BNF* considers evidence of their practical value to be unsatisfactory; patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. Trimethoprim should not usually be given to patients with serious haematological disorders and particularly not in megaloblastic anaemia secondary to folate depletion. Care should be taken in patients with actual, or possible, folate deficiency and use of folinic acid should be considered. Trimethoprim should be avoided during pregnancy. Elderly patients may be more susceptible to adverse effects and a lower dosage may be advisable.

Trimethoprim may interfere with some diagnostic tests, including serum-methotrexate assay where dihydrofolate reductase is used and the Jaffé reaction for creatinine.

For further information on precautions for trimethoprim given with sulfamethoxazole, see Co-trimoxazole, p.258.

Breast feeding. Trimethoprim appears in breast milk and the US licensed product information has stated that care is required when it is used in breast-feeding mothers.

The American Academy of Pediatrics considers trimethoprim, when given with sulfamethoxazole, to be compatible with breast feeding.[1]

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 28/05/04)

Fragile X syndrome. A warning that trimethoprim and other folate antagonists should be avoided in children with the fragile X chromosome which is associated with mental retardation and is folate sensitive.[1]

1. Hecht F, Glover TW. Antibiotics containing trimethoprim and the fragile X chromosome. *N Engl J Med* 1983; **308:** 285–6.

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

Interactions

Trimethoprim may increase serum concentrations and potentiate the effect of a number of drugs, including phenytoin, digoxin, procainamide, rosiglitazone, and repaglinide. The effect may be due to competitive inhibition of renal excretion, decreased metabolism, or both. It has been suggested that trimethoprim may potentiate the effects of warfarin. Trimethoprim has been reported to reduce the renal excretion and increase blood concentrations of zidovudine, zalcitabine, and lamivudine. Trimethoprim and dapsone increase each other's serum concentrations, whereas rifampicin may decrease trimethoprim concentrations.

An increased risk of nephrotoxicity has been reported with the use of trimethoprim or co-trimoxazole and ciclosporin. Intravenous use of trimethoprim and sulfonamides may reduce ciclosporin concentrations in blood. Hyponatraemia has been reported in patients given trimethoprim with diuretics. An increased risk of thrombocytopenia has been seen in elderly patients given co-trimoxazole with diuretics, although it is unclear which component of the antibacterial is responsible.

Use of trimethoprim with other depressants of bone marrow function may increase the likelihood of myelosuppression, and there may be a particular risk of megaloblastic anaemia if it is given with other folate inhibitors, such as pyrimethamine or methotrexate.

Severe hyperkalaemia has been noted in patients given trimethoprim (or co-trimoxazole) together with an ACE inhibitor.

Antimicrobial Action

Trimethoprim is a dihydrofolate reductase inhibitor. It inhibits the conversion of bacterial dihydrofolic acid to tetrahydrofolic acid which is necessary for the synthesis of certain amino acids, purines, thymidine, and ultimately DNA. It acts in the same metabolic pathway as the sulfonamides. It exerts its selective action because of a far greater affinity for the bacterial than the mammalian enzyme. Trimethoprim may be bacteriostatic or bactericidal depending on growth conditions; pus, for example, may inhibit the action of trimethoprim because of the presence of thymine and thymidine.

Spectrum of activity. Trimethoprim is active against many Gram-negative and Gram-positive aerobes, as well as some protozoa. The following species are usually susceptible (but see also Resistance, below).

Many Gram-positive cocci are sensitive, including *Staphylococcus aureus*, streptococci including *Streptococcus pyogenes*, *Str. pneumoniae*, and the viridans streptococci, and to a variable extent enterococci, although their sensitivity is reduced in the presence of folate.

Other sensitive Gram-positive organisms include strains of *Listeria*, *Corynebacterium diphtheriae*, and the Gram-positive bacilli.

Among the Gram-negative organisms, most of the Enterobacteriaceae are susceptible, or moderately so, including *Citrobacter*, *Enterobacter*, *Escherichia coli*, *Hafnia*, *Klebsiella*, *Proteus mirabilis*, *Providencia*, *Salmonella*, some *Serratia*, *Shigella*, and *Yersinia*. *Legionella* and *Vibrio* are also sensitive, and so are *Haemophilus influenzae* and *H. ducreyi*.

Anaerobic species are usually resistant, and so, to varying degrees are *Brucella*, *Neisseria*, and *Nocardia*. *Mycobacterium tuberculosis* is resistant although *M. marinum* may not be. *Pseudomonas aeruginosa* is resistant, and so are the Chlamydiaceae, Mycoplasma spp., and Rickettsia spp., as well as the spirochaetes.

Trimethoprim has some activity against *Pneumocystis jirovecii* and against some protozoa such as *Naegleria*, *Plasmodium*, and *Toxoplasma*.

Activity with other antimicrobials. Because their modes of action are complementary, affecting different stages in folate metabolism, a potent synergistic effect exists between trimethoprim and sulfonamides against many organisms *in vitro*.

Fixed-dose combinations of trimethoprim with various sulfonamides are available, of which co-trimoxazole (trimethoprim with sulfamethoxazole in a 1:5 mixture) is the most widely used. For further details on the antimicrobial action of co-trimoxazole, see p.259.

Synergy has also been reported with rifampicin, and with the polymyxins.

Resistance. Resistance to trimethoprim may be due to several mechanisms. Clinical resistance is often due to plasmid-mediated dihydrofolate reductases that are resistant to trimethoprim: such genes may become incorporated into the chromosome via transposons. Resistance may also be due to overproduction of dihydrofolate reductase, changes in cell permeability, or bacterial mutants which are intrinsically resistant to trimethoprim because they depend on exogenous thymine and thymidine for growth. Despite fears of a rapid increase in resistance if trimethoprim was used alone there is little evidence that this has been any worse than in areas where it has been used in combination with sulfonamides. Nonetheless, trimethoprim resistance has been reported in many species, and very high frequencies of resistance have been seen in some developing countries, particularly among the Enterobacteriaceae.

◊ References.

1. Huovinen P, *et al.* Trimethoprim and sulfonamide resistance. *Antimicrob Agents Chemother* 1995; **39:** 279–89.

Pharmacokinetics

Trimethoprim is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations in the circulation occur about 1 to 4 hours after an oral dose; peak plasma concentrations of about 1 microgram/mL have been reported after a single dose of 100 mg. About 45% is bound to plasma proteins. Trimethoprim is widely distributed to various tissues and fluids including kidneys, liver, lung and bronchial secretions, saliva, aqueous humour, prostatic tissue and fluid, and vaginal secretions; concentrations in many of these tissues are reported to be higher than serum concentrations but concentrations in the CSF are about one-quarter to one-half of those in serum. Trimethoprim readily crosses the placenta and it appears in breast milk. The half-life is about 8 to 10 hours in adults and somewhat less in children, but is prolonged in severe renal impairment and in neonates, whose renal function is immature.

Trimethoprim is excreted primarily by the kidneys through glomerular filtration and tubular secretion. About 10 to 20% of trimethoprim is metabolised in the liver and small amounts are excreted in the faeces via the bile, but most, about 40 to 60% of a dose, is excreted in urine, predominantly as unchanged drug, within 24 hours. Trimethoprim is removed from the blood by haemodialysis to some extent.

Uses and Administration

Trimethoprim is a diaminopyrimidine antibacterial that is used for the treatment of infections due to sensitive organisms, including gastro-enteritis and respiratory-tract infections, and in particular for the treatment and prophylaxis of urinary-tract infections. For details of these infections and their treatment, see Choice of Antibacterial, p.162.

Trimethoprim is also used with sulfonamides. The most common combination is co-trimoxazole (trimethoprim with sulfamethoxazole) (p.258). Other combinations are co-trimazine (with sulfadiazine) and co-trifamole (with sulfamoxole); trimethoprim has also been used with sulfamerazine, sulfametopyrazine, sulfametrole, and sulfamethoxypyridazine, and, in veterinary practice, with sulfadoxine, sulfaquinoxaline, sulfatroxazole, sulfadimethoxine, sulfadimidine, or sulfafurazole.

Trimethoprim with sulfamethoxazole (co-trimoxazole) or with dapsone is used in the management of pneumocystis pneumonia (p.521).

The usual adult oral dose of trimethoprim in acute infection is 100 or 200 mg twice daily; doses of 200 or 300 mg daily as a single dose are also used. For the dosage of trimethoprim when given with sulfamethoxazole, see under Co-trimoxazole, p.259. Up to 20 mg/kg daily may be given in combination with dapsone for the treatment of pneumocystis pneumonia.

Children may be given 6 to 8 mg/kg daily of trimethoprim in 2 divided doses: regimens for children are, 6 to 12 years, 100 mg twice daily; 6 months to 5 years, 50 mg twice daily; 6 weeks to 5 months, 25 mg twice daily.

For long-term prophylaxis the usual dose is 100 mg at night for adults; children aged 6 to 12 years may be given 50 mg at night and those aged 6 months to 5 years, 25 mg at night. Alternatively, children may be given a dose of 1 to 2 mg/kg at night.

Trimethoprim is also given intravenously by injection or infusion as the lactate although doses are in terms of the base. The usual dose is 200 mg every 12 hours in adults; children may be given 8 mg/kg daily in 2 or 3 divided doses. Initial doses may be higher or given more frequently in severely ill patients.

Care should be taken in patients with moderate to severe renal impairment and doses generally should be reduced (see below).

Trimethoprim with polymyxin B has been used topically in the treatment and prophylaxis of eye infections. Trimethoprim sulfate and trimethoprim hydrochloride are also used.

Administration. ***SINGLE-DOSE THERAPY.*** Although there are obvious advantages to a single-dose regimen, one study[1] found that there was about a 1 in 4 risk of recurrence of urinary-tract infection within 10 days in 50 children given, according to age, a single dose of 75 to 450 mg of trimethoprim. The problems with a single-dose regimen were confirmed by others[2] in a study involving 344 evaluated cases of cystitis in 306 women. Only 122 of 173 cases treated with trimethoprim 320 mg as a single dose were evaluated as cured after 5 weeks, compared with 149 of 171 given 160 mg twice daily for 1 week (71 versus 87%). Again, these results suggest that about 1 patient in 4 would have to be re-treated.

1. Nolan T, *et al.* Single dose trimethoprim for urinary tract infection. *Arch Dis Child* 1989; **64:** 581–6.
2. Österberg E, *et al.* Efficacy of single-dose versus seven-day trimethoprim treatment of cystitis in women: a randomized double-blind study. *J Infect Dis* 1990; **161:** 942–7.

Administration in renal impairment. Doses of trimethoprim should generally be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC):

- CC 15 to 27 mL/minute: normal dose for 3 days reduced to one-half thereafter
- CC below 15 mL/minute: half the normal dose from the start of treatment

Plasma concentrations should be monitored in patients with severe renal impairment.

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; Trimethoprim Oral Suspension; Trimethoprim Tablets;
USP 31: Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution; Sul-

famethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets; Trimethoprim Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Alprim; Triprim; ***Austria:*** Motrim; Solotrim; Triprim; Wellcoprim; ***Canad.:*** Proloprim†; ***Cz.:*** Infecto Trimet†; Triprim; ***Denm.:*** Monotrim; Trimopan; ***Fin.:*** Trimetin; Trimex; Trimopan; ***Fr.:*** Wellcoprim†; ***Ger.:*** Infecto Trimet; TMP†; ***Irl.:*** Ipral†; Monotrim†; ***Malaysia:*** Alprim; ***Neth.:*** Monotrim; Wellcoprim†; ***NZ:*** TMP; Triprim†; ***Pol.:*** Trimesan; Urotrim; ***S.Afr.:*** Purium; Triprim†; ***Singapore:*** Alprim; ***Spain:*** Tediprima; ***Swed.:*** Idotrim; ***Switz.:*** Monotrim†; ***Thai.:*** Utisept; ***UAE:*** Trimol-A; ***UK:*** Monotrim; Trimopan; ***USA:*** Primsol; Proloprim; Trimpex.

Multi-ingredient: ***Arg.:*** Adrenol; Bacti-Uril; Bacticel; Bactrim; Bactrim Balsamico; Cotrizol-G; Danferane; Diocla†; Dosulfin Bronquial; Dosulfin Fuerte; Enterobacticel; Neoftalm; Neoftalm Dexa; Neolag; Netocur; Netocur Balsamico; Neumobacticel; Novidrine; Rifaprim; Ritroprim†; Sulfagrand; Trimepol; Trimepol D; Tritenk; Urisept NF; Uro-Bactrim†; ***Austral.:*** Bactrim; Cosig†; Resprim; Septrin; Trimoxazole; ***Austria:*** Bactrim; Cotribene; Eusaprim; Lidaprim; Oecotrim; Polytrim; Trimetho comp; ***Belg.:*** Bactrim; Cotrim; Eusaprim; Ophtalmotrim†; Polytrim; Steroprim†; ***Braz.:*** Assepium; Assepium Balsamico; Bac-Sulfitrin; Bacfar; Bacprotin; Bacris†; Bacteracin; Bactrim; Bactrisan; Bactrizol; Bactropin; Batrox; Baxapril†; Benectrin; Benectrin Balsamico; Binoctrin†; Clotrizol†; Diazol; Dientrin; Dispeptrin; Duoctrin†; Ectrin; Ectrin Balsamico; Espectrin†; Espectroprima†; Gamactrin; Imuneprim; Infectrin; Lifactrin†; Linurin†; Lupectrim†; Metoprin; Metoprin Balsamico; Neotrin; Pulkrin; Qiftrin†; Quimio-Ped†; Roytrin†; Selectrin; Selectrin Balsamico; Septiolan†; Teutrin; Tricban; Triglobe; Trimexazol; Trimezol†; Uro-Baxapril†; Urоctrin; Uropol; ***Canad.:*** Apo-Sulfatrim; Coptin; Novo-Trimel; Nu-Cotrimox; PMS-Polytrimethoprim; Polytrim; Septra; ***Chile:*** Bacterol; Bactrimel; Entero Micinovo; Introcin†; Septrin; Trelibec; Uro-Micinovo; ***Cz.:*** Apo-Sulfatrim†; Berlocid†; Biseptol; Bismoral; Nopil†; Oriprim†; Primotren; Sumetrolim; Supracombin†; ***Denm.:*** Sulfotrim†; ***Fin.:*** Cotrim; Ditrim; Trimetin Duplo; ***Fr.:*** Bactrim; Eusaprim†; ***Ger.:*** Bactoreduct†; Berlocid; Berlocombin†; Cotrim; Cotrim-Diolan; CotrimHefa; Cotrimhexal; Cotrimox-Wolff; Cotrimstada; Drylin; Eusaprim; Kepinol; Microtrim†; Sigaprim†; Supracombin†; TMS; ***Gr.:*** Bactrimel; Bioprim†; Lidaprim; Septrin; ***Hong Kong:*** Chemitrim†; Chemoprim; Cotrim; Dhatrin; Letus; Lidaprim; Septrin; ***Hung.:*** Cotripharm; Oftalmotrim†; Potesept†; Sumetrolim; ***India:*** Aubril; 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†; Lidaprim†; ***Jpn:*** Bactramin; ***Malaysia:*** Bacin; Balin; Baserin†; Beaglobe; Chemix; Cotrim; Oftalmotrim; Resprim; Triglobe†; Trimexazole; Trisulprim†; Trizine; Virin†; ***Mex.:*** Andoprim; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric; Bactide; Bactilen; Bactiver; Bactrim; Bactrim Compositum; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Brogamax; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Guayaprin; Kaltrim; Kelfiprim†; Maxtrim; Metoxiprim; Microbactim†; Mixange; Octex; Octiban; Pisatrina; Polibatrin; Pribac; Protaxol; Protrim; Rifaprim; Sadocin; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultiprim†; Syraprim†; Thriazol; Tribakin; Trime/Sulfa†; Trimetoger; Trimetox; Trimexazol; Trimexole; Trimexole Compositum; Trimzol; Trinelax†; Trisufin†; Vanadyl; ***Neth.:*** Bactrimel; Eusaprim†; Lidatrim; Polytrim; 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; Triglobe; Trim-S; Trimephar; Trimocom; Trimoxis; Triphimox; Trizine; Trizole; Xanazole; Zamboprim; Zolmed; ***Pol.:*** Bactrim; Biseptol; Groseptol†; Septrin; Two-Septol; ***Port.:*** Bactrim; Cotrim†; Metomide†; Microcetim; Oftalmotrim; Septrin; ***Rus.:*** Biseptol (Бисептол); Lidaprim (Лидаприм); Oriprim (Ориприм); Rancotrim (Ранкотрим); ***S.Afr.:*** Acuco; Bactrim; Bencole; Casicot; Cocydal; Cozole; Durobac; Fabubac†; Lagatrim; Meditrim; Mezenol†; Polytrim†; Purbac; Septran; Spectrim; Supristol†; Trimethox; Trimzol; Xerazole; Xeroprim†; ***Singapore:*** Apo-Sulfatrim; Bacin; Balin; BS†; Chemix; Chemoprim; Co-Trimexazole; Dhatrin; Septrin†; Suprim; Trimaxazole; Trimezole†; ***Spain:*** Bactopumon; Balsoprim; Bronco Aseptilex Fuerte; Broncomega†; Broncovir; Bronquicisteina; Bronquidiazina CR; Bronquimar; Bronquimucil†; Busetal†; Cotrazol; Eduprim Mucolitico; Eduprim†; Gobens Trim; Momentol; Neumopectolina†; Oftalmotrim; Oftalmotrim Dexa†; Otix; Pulmo Menal†; Pulmosterin Duo; Septrin; Soltrim; ***Swed.:*** Bactrim; Eusaprim; Trimin sulfa†; ***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; Lidaprim†; M-Trim; Mano-Trim; Med-Sultrim†; Mega-Prim; Metrim; Metxaprim; Mycosamthong; Po-Trim; Primoptic†; Pulvicin†; Septrin†; Spectrim; Sulbacta; Sulfometh; Suntrim; Tampo†; Toprim†; Trimexazole; Triprim; Trixzol; Zoleprim†; ***Turk.:*** Bactrim; Bakton; Kemoprim; Metoprim; Mikrosid; Oftalmotrim; Polycilline; Polytrim; Septrin; Sulfatrim; Trifen; Trimoks; ***UAE:*** Trimol; ***UK:*** Fectrim; Polytrim†; Septrin; ***USA:*** Bactrim; Cotrim; Polytrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.:*** Bactrimel; Bactron†; Co-Sultrin; Forcrim; Trimecor; Trimetoprim Sulfa†; Tripur.

Troleandomycin *(BAN, USAN, rINN)*

NSC-108166; Triacetyloleandomycin; Troleandomicina; Troleandomisin; Troléandomycine; Troleandomycinum; Troleandomysiini. The triacetyl ester of oleandomycin .

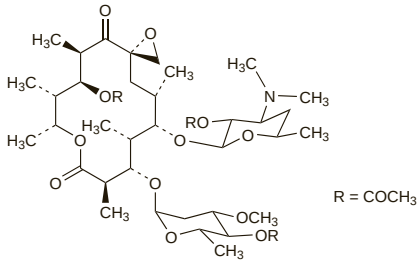
Тролеандомицин

$C_{41}H_{67}NO_{15}$ = 814.0.

CAS — 2751-09-9.

ATC — J01FA08.

ATC Vet — QJ01FA08.



Pharmacopoeias. In *Fr.* and *US*.

USP 31 (Troleandomycin). A white, odourless, crystalline powder. It contains the equivalent of not less than 750 micrograms of oleandomycin per mg. Slightly soluble in water and in ether; freely soluble in alcohol; soluble in chloroform. A 10% solution in alcohol and water (1:1) has a pH of 7.0 to 8.5. Store in airtight containers.

Profile

Troleandomycin is a prodrug of the macrolide antibacterial oleandomycin that has actions similar to those of erythromycin (p.269). It has been given orally in the treatment of susceptible infections although more effective antibacterials are generally preferred.

Preparations

USP 31: Troleandomycin Capsules.

Proprietary Preparations (details are given in Part 3)
Ital.: Triocetin†; ***Turk.:*** Tekmisin; ***USA:*** TAO†.

Trospectomycin Sulfate *(USAN, rINNM)*

Sulfato de trospectomicina; Trospectomycin Sulphate *(BANM)*; Trospectomycine, Sulfate de; Trospectomycini Sulfas; U-63366 (trospectomycin); U-63366F. (2*R*,4a*R*,5a*R*,6*S*,7*S*,8*R*,9*S*,9a*R*,10a*S*)-2-Butyl-4a,7,9-trihydroxy-6,8-bis(methylamino)perhydropyrano[2,3-*b*][1,4]benzodioxin-4-one sulphate pentahydrate.

Троспектомицина Сульфат

$C_{17}H_{30}N_2O_7.H_2SO_4.5H_2O$ = 562.6.

CAS — 88669-04-9 (trospectomycin); 88851-61-0 (trospectomycin sulfate).

Profile

Trospectomycin is a water-soluble derivative of spectinomycin (p.332) but is more active against Gram-positive organisms, *Haemophilus influenzae*, and *Chlamydia trachomatis* as well as *Neisseria*. It has been investigated in various infections and given as the sulfate intravenously or intramuscularly. Reported adverse effects include perioral paraesthesia, pain at the injection site, nausea, and dizziness.

Trovafloxacin Mesilate *(rINNM)*

CP-99219-27; CP-99219 (trovafloxacin); Mesilato de trovafloxacino; Trovafloxacin Mesylate *(USAN)*; Trovafloxacine, Mésilate de; Trovafloxacini Mesilas. 7-[(1*R*,5*S*,6*S*)-6-Amino-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulphonate.

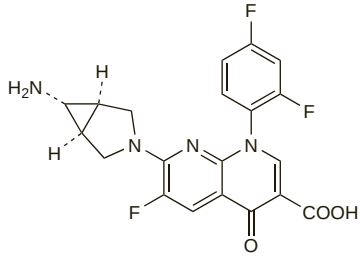
Тровафлоксацина Мезилат

$C_{20}H_{15}F_3N_4O_3.CH_4O_3S$ = 512.5.

CAS — 147059-72-1 (trovafloxacin); 147059-75-4 (trovafloxacin mesilate).

ATC — J01MA13.

ATC Vet — QJ01MA13.



(trovafloxacin)

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Dizziness was the most common adverse effect reported with trovafloxacin.

Trovafloxacin preparations have been withdrawn worldwide after reports of unpredictable severe hepatic adverse effects, including some fatalities. Symptomatic pancreatitis was also reported.

Antimicrobial Action

As for Ciprofloxacin, p.246. It is more active against pneumococci.

Pharmacokinetics

Trovafloxacin is readily absorbed from the gastrointestinal tract after an oral dose, peak plasma concentrations occurring after about 1 to 2 hours. After intravenous use, alatrofloxacin is rapidly converted to trovafloxacin. Oral bioavailability is 88%. Trovafloxacin is widely distributed into body tissues and is about 76% bound to plasma proteins. It appears in breast milk.

The serum half-life of trovafloxacin ranges from about 9 to 12 hours. Trovafloxacin is metabolised by conjugation, 13% of a dose appearing in the urine as the glucuronide and 9% in the faeces as the *N*-acetyl metabolite; other metabolites appear in both the urine and faeces in minor amounts, but about 50% of an oral dose is excreted unchanged, mainly in the faeces but also in the urine.

Uses and Administration

Trovafloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247). It was given orally as the mesilate for the treatment of susceptible infections. The prodrug alatrofloxacin (p.200) was used as the mesilate for intravenous infusion.

Trovafloxacin and alatrofloxacin preparations have been withdrawn worldwide after reports of unpredictable severe hepatic adverse effects, including some fatalities.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Trovan†; ***Gr.:*** Trovan†; ***Mex.:*** Trovan†; ***USA:*** Trovan†.

Tulathromycin *(USAN, rINN)*

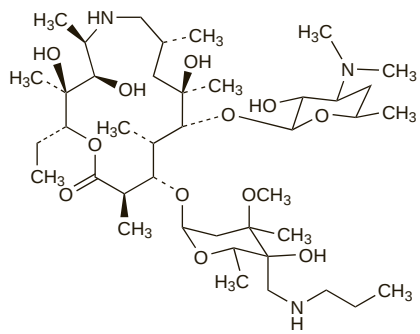
CP-472295 (component A); CP-547272 (component B); Tulathromycine; Tulathromycinum; Tulatromicina.

Тулатромицин

$C_{41}H_{79}N_3O_{12}$ = 806.1.

CAS — 217500-96-4 (component A); 280755-12-6 (component B).

ATC Vet — QJ01FA94.



(tulathromycin A)

Profile

Tulathromycin is a macrolide antibacterial used in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Tylosin *(BAN, rINN)*

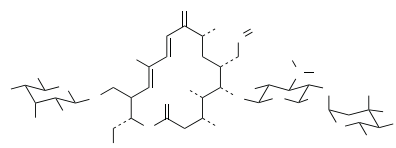
Tilosina; Tilozin; Tylosiini; Tylosine; Tylosinum; Tylozyna.

Тилозин

$C_{46}H_{77}NO_{17}$ = 916.1.

CAS — 1401-69-0.

ATC Vet — QJ01FA90; QJ51FA90.



(tylosin A)