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.

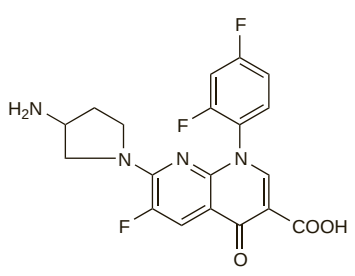
Tosufloxacin *(USAN, rINN)*

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.

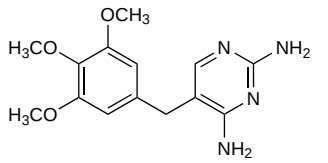
Триметоприм

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