

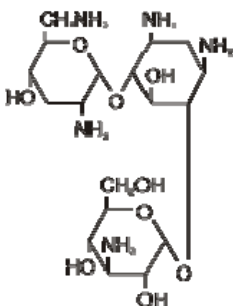
TOBEX®

Tobramycin Eye Drops 0.3%

Tobramycin Eye Ointment 0.3%

Name of the Medicine

TOBEX Eye Drops and TOBEX Eye Ointment (TOBEX) are sterile topical preparation containing tobramycin. Tobramycin is a water soluble aminoglycoside antibiotic active against a wide variety of ophthalmic bacterial pathogens. The chemical structure of tobramycin is represented as:



Empirical formula: C₁₈H₃₇N₅O₉

Molecular weight: 467.5

Chemical name: 4-O-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-6-O-(2,6-diamino-2,3,6-trideoxy-α-D-ribo-hexopyranosyl)-L-streptamine

CAS Registry Number: 32986-56-4

Description

TOBEX Eye Drops have been formulated as a sterile, preserved solution for topical application to the eye. TOBEX Eye Drops contain 3 mg/mL tobramycin, together with boric acid, sodium sulfate, sodium chloride, tyloxapol, sodium hydroxide and/or sulfuric acid (to adjust pH) and purified water. The solution is preserved with benzalkonium chloride (0.1 mg/mL).

TOBEX Eye Ointment has been formulated as a sterile, preserved ointment for topical application to the eye. TOBEX Eye Ointment contains 3 mg/g tobramycin, together with mineral oil and petroleum base. The ointment is preserved with chlorobutanol (5 mg/g).

Pharmacology

Actions

Tobramycin is a water soluble aminoglycoside antibiotic active against a variety of ophthalmic bacterial pathogens. *In vitro* studies have shown tobramycin to be active against susceptible strains of the following microorganisms:

Gram-positive:

Staphylococci, including methicillin-susceptible and -resistant *Staphylococcus aureus*, *S. epidermidis*, and other coagulase-negative species.

- Streptococcus species including *Streptococcus pneumoniae*.

Gram-negative:

- *Acinetobacter* spp.
- *Citrobacter* spp.
- *Enterobacter* spp.
- *Escherichia coli*

- *Haemophilus influenzae* (beta lactamase-negative and -positive)
- *Klebsiella pneumoniae*
- *Moraxella* spp.
- *Neisseria meningitidis*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Resistance development to the various aminoglycosides such as tobramycin or gentamicin is due to their close structural relationship. Resistance to one aminoglycosides generally confers resistance to several, but not all aminoglycosides. For instance, bacterial susceptibility studies demonstrate that in some cases bacteria resistant to gentamicin retain susceptibility to tobramycin. *In vitro* results, however, are not necessarily reliable predictors of clinical success in topical therapy.

Pharmacokinetics

Tobramycin and other aminoglycoside antibiotics exist in solution as highly polar cations and, therefore, do not readily penetrate external ocular tissues nor are they readily absorbed after oral administration. In rabbits, peak cornea tissue concentrations were similar for both TOBREX Eye Drops and Eye Ointment at 0.5 to 0.8 mcg/g. In humans, serum concentrations were less than 0.2 mcg/mL during a 36-hour treatment regimen with a 1.5% solution (cumulative topical ocular dose of 50 mg). In comparison, therapeutic intramuscular doses of 1 mg/kg every 8 hours gave peak plasma concentrations of 5 - 8 mcg/mL.

Tobramycin is excreted rapidly and extensively in the urine via glomerular filtration; primarily as unchanged drug. The plasma half-life has been reported to be 2.2 hours. Plasma protein binding is less than 10%.

Indications

Treatment of external infections of the eye and its adnexa caused by susceptible bacteria. Appropriate monitoring of bacterial response to topical antibiotic therapy should accompany the use of TOBREX.

Contraindications

Contraindicated in patients with known hypersensitivity to tobramycin or any other ingredients in this product.

Precautions

FOR TOPICAL USE ONLY. NOT FOR INJECTION INTO THE EYE

Hypersensitivity Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to TOBREX occurs, discontinue use. Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic tobramycin therapy. Although these effects have not been reported following topical ocular use of tobramycin, caution is advised when used concomitantly.

General As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Cross-sensitivity to other aminoglycoside antibiotics may occur.

Ophthalmic solutions and ointments may retard corneal wound healing.

Interactions with other medicines

Concurrent use of topical ocular tobramycin with a topical, β -lactam type antibiotic may result in inactivation of tobramycin.

If topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, the possibility of increased systemic toxicity cannot be excluded and care should be taken to monitor the total serum concentration. Prolonged levels above 12 mcg/mL should be avoided.

Aminoglycosides administered parenterally have been associated with neuromuscular and respiratory paralysis in cats. Despite the low systemic levels of tobramycin associated with ophthalmic administration, pulmonary status of anaesthetised patients should be monitored.

Peak and trough levels of parenterally administered aminoglycosides have been significantly elevated by the concomitant administration of indomethacin.

Concurrent and/or sequential use of TOBREX with other drugs with neurotoxic or ototoxic potential should be avoided. Antiemetics, such as dimenhydrinate, may mask the toxic effects of drugs causing ototoxicity.

Use in Pregnancy- Category B3

There are no adequate, well-controlled studies using the topical administration of TOBREX in pregnant women. A published retrospective assessment of women receiving parenteral aminoglycosides during pregnancy suggested no detectable teratogenic risk to the foetus. Studies in animals have shown evidence of an increased occurrence of foetal damage following systemic administration of aminoglycosides to pregnant mothers. There is evidence of selective uptake of aminoglycosides by the foetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following in utero exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the foetus. It should also be noted that therapeutic blood concentrations in the mother do not equate with safety for the foetus. Use of TOBREX by pregnant women is not likely to result in detectable blood concentrations in mothers or tissue concentrations in the foetus. TOBREX should not be used during pregnancy unless clearly needed, otherwise tobramycin is not recommended during pregnancy.

Use in Lactation

In systemic treatment, tobramycin passes over to human milk in such amounts that there is a risk of affecting the child. As systemic absorption when instilled topically in the eye is low, the risk is judged to be low when using TOBREX but this should be considered when prescribing TOBREX to nursing mothers. TOBREX should be used only if the potential benefit for the mother justifies the potential risk to the infant.

Paediatric Use

Safety and effectiveness in children below the age of 1 year have not been established.

Use in Elderly

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

Renal, Auditory, Vestibular, or Neuromuscular Impairment

Patients receiving concomitant parenteral tobramycin (aminoglycoside) and topical tobramycin therapies should be monitored as clinically appropriate. Caution should be exercised with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction.

Renal & Hepatic Impairment

TOBREX has not been studied in these patient populations. However, due to low systemic absorption of tobramycin after topical administration of this product, dose adjustment is not necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the carcinogenic potential of tobramycin. *In vitro* and *in vivo* studies with tobramycin did not reveal a mutagenic potential

Contact Lenses

Neither TOBREX Eye Drops or Eye Ointment should be instilled while the patient is wearing contact lenses. Contact lens wear is not recommended during treatment of an ocular infection.

If patients continue to wear contact lenses while under treatment with TOBREX Eye Drops, they should remove their lens(es) prior to instilling the drops in the affected eye(s). Lens(es) should not be inserted into the eye(s) until 15 minutes after instillation of the drops. TOBREX Eye Drops contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses.

Due to the nature of the ointment base, patients should be advised not to wear their contact lenses while they are being treated with TOBREX Eye Ointment.

Effects on ability to drive and use machines

As with other ophthalmic medications, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs upon application, the patient must wait until the vision clears before driving or using machinery.

Adverse Effects

The most frequent adverse reactions to TOBREX Eye Drops and TOBREX Eye Ointment are localised ocular toxicity and hypersensitivity, including punctate keratitis, eye and lid itching, lid swelling, ocular hyperaemia, conjunctival erythema and lacrimation. These reactions occur in approximately 3% of patients treated with TOBREX.

Other adverse reactions associated with ophthalmic tobramycin are burning and stinging of the eyes. For ophthalmic ointment dosage form: blurred vision.

A summary of treatment emergent adverse events based on literature and postmarketing experience and their estimate of frequencies (very common, common, uncommon, rare, very rare, and not known) in accordance with preferred term and system organ classes (SOC) of any severity are listed below.

Within each frequency-grouping, undesirable effects are presented in decreasing order of seriousness. These adverse reactions were observed following ophthalmic use of Tobramycin Eye Drops and/or Eye Ointment:

Immune system disorders:

Uncommon (> 0.1% to ≤ 1%): hypersensitivity

Nervous system disorders:

Uncommon (> 0.1% to ≤ 1%): headache

Eye disorders:

Common (> 1% to < 10%): ocular discomfort, ocular hyperaemia

Uncommon (> 0.1% to ≤ 1%): keratitis, corneal abrasion, conjunctival disorder, visual impairment, vision blurred, erythema of eyelid, conjunctival oedema, eyelid oedema, eyelid disorder, eye pain, dry eye, eye discharge, eye pruritus, foreign body sensation in eyes, lacrimation increased

Not known: eye allergy, eye irritation, eyelids pruritus

Skin and subcutaneous tissue disorders:

Uncommon (> 0.1% to ≤ 1%): urticaria, dermatitis, madarosis, leukoderma, pruritus, dry skin

Not Known: rash

If topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, the possibility of increased systemic toxicity cannot be excluded and care should be taken to monitor the total serum concentration. Prolonged levels above 12 mcg/mL should be avoided.

Dosage and Administration

TOBREX Eye Drops

In mild to moderate disease, instil one or two drops into the affected eye(s) every four hours.

In severe infections, instil two drops into the eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation.

The usual duration of treatment is 7 to 10 days.

TOBREX Eye Ointment

In mild to moderate disease, apply a 1 - 1.5 cm ribbon into the affected eye(s) two or three times per day.

In severe infection, instil a 1 – 1.5 cm ribbon into the affected eye(s) every three to four hours until improvement, following which treatment should be reduced prior to discontinuation.

The usual duration of treatment is 7 to 10 days.

Overdosage

Clinically apparent signs and symptoms of TOBREX overdose are not expected when used as above nor in the event of accidental ingestion of the contents of one bottle or tube.. However, excessive local reactions may occur. In such cases treatment should be discontinued and appropriate treatment instituted.

A topical overdose of TOBREX may be flushed from the eye(s) with lukewarm water.

Poison Schedule of the Medicine

Prescription Only Medicine.

Presentation and Storage Conditions

TOBREX Eye Drops

5 mL DROP-TAINER® dispenser, containing tobramycin 0.3% (3 mg/mL).

TOBREX Eye Ointment

3.5 g ophthalmic tubes containing tobramycin 0.3% (3 mg/g).

Storage

Store below 25°C. Discard contents within 4 weeks of opening.

Name and Address of Sponsor

This product is made in Belgium and supplied in Australia by:

Alcon Laboratories (Australia) Pty Ltd
25 Frenchs Forest Road East
Frenchs Forest NSW 2086

Distributed in New Zealand by:

Alcon New Zealand Limited
c/o Pharmaco (NZ) Limited
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