AUSTRALIAN PRODUCT INFORMATION –

TOBREX (tobramycin) Eye Drops

TOBREX (tobramycin) Eye Ointment

1 NAME OF THE MEDICINE

Tobramycin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of TOBREX Eye Drops contains tobramycin 0.3% (3mg).

Each gram of TOBREX Eye Ointment contains tobramycin 0.3% (3mg).

May contain traces of potential allergens such as soya beans from the manufacturing process.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

TOBREX (tobramycin) 0.3% Eye Drops and TOBREX (tobramycin) 0.3% Eye Ointment (TOBREX) are sterile topical antibiotic formulations prepared specifically for topical therapy of bacterial eye infections. TOBREX Eye Drops has a pH range between 7.0 and 8.0.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TOBREX (tobramycin) Eye Drops and TOBREX (tobramycin) Eye Ointment are topical antibiotics indicated in the 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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

TOBREX Eye Drops

In mild to moderate disease, instill one or two drops into the affected eye(s) every four hours. In severe infections, instill two drops into the eye(s) hourly until improvement.

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 infections, apply a 1 - 1.5 cm ribbon every three to four hours until improvement.

Treatment with TOBREX should be reduced prior to discontinuation. The usual duration of treatment is 7-10 days.

4.3 CONTRAINDICATIONS

TOBREX (tobramycin) Eye Drops and Eye Ointment are contraindicated in patients with known hypersensitivity to tobramycin or to other aminoglycosides or any other ingredients in this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

FOR TOPICAL OPHTHALMIC USE ONLY. NOT FOR INJECTION INTO THE EYE.

Hypersensitivity

Sensitivity to topically administered aminoglycosides may occur in some patients. Severity of hypersensitivity reactions may vary from local effects to generalized reactions such as erythema, itching, urticarial, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

If TOBREX (topical tobramycin) Eye Drops or Eye Ointment are administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Although these effects have not been reported following topical ocular use of tobramycin, caution is advised when using TOBREX Eye Drops or TOBREX Eye Ointment concomitantly with systemic aminoglycosides.

General

As with any antibiotic, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Cross-sensitivity to other aminoglycoside antibiotics may occur. The possibility that patients that become sensitised to topical ocular tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered.

Ophthalmic solutions and ointments may retard corneal wound healing

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.

Caution should be exercised when prescribing TOBREX (tobramycin) Eye Drops or Eye Ointment to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson's disease. Aminglycosides may aggravate muscle weakness because of their potential effect on neuromuscular function.

Contact lenses

Neither TOBREX (tobramycin) Eye Drops nor 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. Avoid contact with 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.

Use in hepatic and renal impairment

TOBREX (tobramycin) Eye Drops or Eye Ointment have 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.

Use in the elderly

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

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

If TOBREX (topical tobramycin) Eye Drops or Eye Ointment are used while the patient is on a systemic aminoglycoside antibiotic, the patient's total serum aminoglycoside concentration should be monitored.

Concurrent and/or sequential use of TOBREX with other drugs with neurotoxic or ototoxic potential should be avoided.

Do not use TOBREX simultaneously with a topical beta lactam type antibiotic as this is likely to result in inactivation of tobramycin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies have not been performed to evaluate the effect of topical ocular administration of TOBREX (tobramycin) Eye Drops or Eye Ointment on human fertility.

Use in pregnancy – Pregnancy Category B3

There are no adequate, well-controlled studies using the topical administration of TOBREX (tobramycin) Eye Drops or Eye Ointment in pregnant women.

A published retrospective assessment of women receiving parenteral aminoglycosides during pregnancy suggested no detectable teratogenic risk to the foetus. The number of women treated

with parenteral tobramycin in this study was very small, 2 in the case group and 4 in the control group and so no firm specific conclusions with regard to tobramycin exposure can be drawn from this study. However, the study concluded that parenteral administration of gentamicin and oral neomycin during pregnancy presents no detectable teratotogenic risk to the foetus, when restricted to structural developmental abnormalities. This conclusion can be extended to the class of aminoglycoside antibiotics as a whole.

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.

There is no firm data concerning the detectable blood concentrations in mothers or tissue concentrations in the foetus. The systemic absorption of tobramycin after topical administration of TOBREX is expected to be low.

TOBREX should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the foetus otherwise tobramycin is not recommended during pregnancy.

Use in lactation

There are no adequate, well-controlled studies using the topical administration of TOBREX (tobramycin) Eye Drops or Eye Ointment in women who are breast feeding. It is unknown whether tobramycin is excreted in human milk following topical ocular administration. Tobramycin is excreted in human milk after systemic administration. Risk to the breastfed child cannot be excluded. TOBREX should be used only if the potential benefit for the mother justifies the potential risk to the infant.

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

The most frequent adverse reactions to TOBREX (tobramycin) Eye Drops and 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 post-marketing 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.

Not Known: anaphylactic reaction.

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: Stevens-Johnson syndrome, erythema multiforme, 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.

4.9 OVERDOSE

Clinically apparent signs and symptoms of TOBREX (tobramycin) Eye Drops or Eye Ointment 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tobramycin is actively transported across the bacterial cell membrane, and binds to a specific receptor protein on the 30 S subunit of bacterial ribosomes and interferes with an initiation complex between messenger RNA (mRNA) and the 30 S subunit, thus inhibiting protein synthesis.

Microbiology

In vitro data

In vitro studies have demonstrated tobramycin is active against susceptible strains of the following microorganisms:

- Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.
- Streptococci, including some of the group A - beta-haemolytic species, some non-haemolytic species, and some Streptococcus pneumoniae.
- *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis* (indole-negative) and indole-positive *Proteus* species.

Bacterial resistance may develop upon prolonged use.

Tobramycin is not effective against most strains of group D Streptococci.

5.2 PHARMACOKINETIC PROPERTIES

No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In vitro and *in vivo* studies with tobramycin did not reveal a mutagenic potential.

Carcinogenicity

No studies have been conducted to evaluate the carcinogenic potential of tobramycin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TOBREX (tobramycin) Eye Drops contain boric acid, sodium sulfate, sodium chloride, tyloxapol, sodium hydroxide and/or sulphuric acid (to adjust pH) and purified water. Each mL of TOBREX Eye Drops contains benzalkonium chloride 0.01% (0.1 mg) as preservative.

TOBREX (tobramycin) Eye Ointment contains mineral oil and petroleum base. Each gram of TOBREX Eye Ointment contains chlorobutanol 0.5% (5 mg) as preservative.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Discard container 4 weeks after opening.

6.5 NATURE AND CONTENTS OF CONTAINER

TOBREX (tobramycin) Eye Drops
5 mL LDPE bottle with PP closure.

TOBREX (tobramycin) Eye Ointment
3.5 g aluminium tubes with HDPE and/or LDPE nozzle.

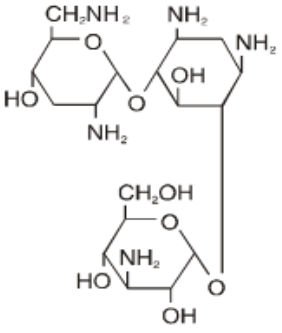
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structure of tobramycin is represented as:



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

Empirical formula:
$C_{18}H_{37}N_5O_9$

Molecular weight:
467.5

CAS number

32986-56-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
Macquarie Park NSW 2113
Telephone: 1800 671 203
Web site: www.novartis.com.au

® = Registered Trademark

9 DATE OF FIRST APPROVAL

12 September 2006

10 DATE OF REVISION

20 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.5	Remove DROP-TAINER* and route of administration and include container materials

Internal document code: tox201123i