

1. NAME OF THE MEDICINAL PRODUCT
TOBRALIN (TOBRAMYCIN OPHTHALMIC SOLUTION USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Label Claim:
Tobramycin Sulphate USP
Equivalent to Tobramycin0.3 % W/V
Benzalkonium Chloride Solution NF0.005%W/V
(As Preservative)
Sterile Isotonic Aqueous BaseQ.S.

3. PHARMACEUTICAL FORM

Ophthalmic (Eye Drop)

4. Clinical particulars

4.1 Therapeutic indications

Topical antibiotic 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 Tobralin Ophthalmic Solution. Clinical studies have shown tobramycin to be safe and effective for use in children.

4.2 Posology and method of administration

Posology

As indicated by physician:

In mild to moderate disease, instill 1 to 2 drops into the affected eye(s) every 4 hours. In severe infections, instill 2 drops into the eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation.

Use in children

The safety and efficacy of Tobralin ophthalmic solution in children younger than 1 year of age have not been established.

Use in patients with hepatic or renal impairment

The safety and efficacy of Tobralin ophthalmic solution in patients with hepatic or renal impairment have not been established.

Use in elderly population

No overall clinical differences in safety or efficacy have been observed between the elderly and other adult populations.

Method of administration

For ocular use.

Keep the bottle tightly closed when not in use. After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product. To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.

Either nasolacrimal occlusion or gently closing the eyelid(s) after administration is recommended. This may reduce the systemic absorption of medicinal products administered via ocular route and result in a decrease in systemic adverse reactions. If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

NOT FOR INJECTION INTO THE EYE.

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 during use of this medicine, treatment should be discontinued.

Cross-hypersensitivity to other aminoglycosides can occur, and the possibility that patients who become sensitized to topical ocular tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Caution is advised when Tobralin Eye Drops are used concomitantly with systemic aminoglycosides, and care should be taken to monitor the total serum concentration.

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

As with other antibiotic preparations, prolonged use of Tobrex ophthalmic solution may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Contact lens wear is not recommended during treatment of an ocular infection. Tobrex ophthalmic solution contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of this product and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

If Tobralin (topical tobramycin) Eye Drops are used while the patient is on a systemic aminoglycoside antibiotic, the patient's total serum aminoglycoside concentration should be monitored. Caution is advised when used concomitantly with any products with potential neurotoxic, ototoxic or nephrotoxic effects. Do not use Tobrex simultaneously with a topical beta lactam type antibiotic as this is likely to result in inactivation of tobramycin.

4.6 Pregnancy and Lactation

Fertility

There are no data regarding the effects of topical ocular administration of Tobralin ophthalmic solution on human fertility. Tobramycin did not impair fertility in rats (see Section 5.3 Preclinical safety data).

Pregnancy

There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. Tobramycin does cross the placenta into the fetus after intravenous dosing in pregnant women. Reproductive studies with tobramycin in rats and rabbits have not shown evidence of harm to the fetus following subcutaneous administration at dose levels greater than 45-fold the maximum recommended ocular human dose (MROHD) of 0.288 mg/kg/day based on body surface area (BSA) (see Animal data). Tobralin ophthalmic solution should be used during pregnancy only if clearly needed.

Lactation

It is not known if tobramycin is transferred into human milk following topical ocular administration. Limited published data in lactating women indicate that tobramycin is transferred into human milk following intramuscular administration. It is not likely that the amount of tobramycin would be detectable in human milk or be capable of producing clinical effects in the infant following topical ocular use of the product. However, a risk to the breast-fed child cannot be excluded.

A decision should be made whether to discontinue breast-feeding or to discontinue or abstain from Tobralin ophthalmic solution therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

Tabulated summary of adverse reactions

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

System Organ Class	Adverse reactions
Immune system disorders	<i>Uncommon</i> : hypersensitivity
Nervous system disorders	<i>Uncommon</i> : headache

Eye disorders	<i>Common:</i> ocular discomfort, ocular hyperaemia <i>Uncommon:</i> keratitis, corneal abrasion, visual impairment, vision blurred, eyelid oedema, erythema of eyelid, conjunctival oedema, dry eye, lacrimation increased, eye pain, eye pruritus, eye discharge
Skin and Subcutaneous Tissue Disorders	<i>Uncommon:</i> urticaria, dermatitis, madarosis, leukoderma, pruritus, dry skin

The following adverse drug reactions have been derived from post-marketing experience with Tobrex Eye drops, solution via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

System organ classification	Adverse reactions
Immune system disorders	anaphylactic reaction
Eye disorder	eye allergy, eye irritation, eyelids pruritus
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome, erythema multiforme, rash

Description of selected adverse reactions

- Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic tobramycin therapy

4.9 Overdose

An ocular overdose of Tobralin Ophthalmic Solution may be flushed from the eye(s) with lukewarm water. Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, or in the event of accidental ingestion of the content of one bottle. Clinically apparent signs and symptoms of an overdose of Tobralin Ophthalmic Solution (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: anti-infectives – antibiotics. ATC code: S01AA12.

Mode of Action:

Tobramycin is a potent, broad-spectrum, rapid-acting bactericidal aminoglycoside antibiotic. It exerts its primary effect on bacterial cells by inhibiting polypeptide assembly and synthesis on the ribosome.

Resistance:

Resistance to tobramycin occurs by several different mechanisms including (1) alterations of the ribosomal subunit within the bacterial cell; (2) interference with the transport of tobramycin into the cell, and (3) inactivation of tobramycin by an array of adenylating, phosphorylating, and acetylating enzymes. Genetic information for production of inactivating enzymes may be carried on the bacterial chromosome or on plasmids. Cross resistance to other aminoglycosides may occur.

Susceptibility Testing Breakpoints

The breakpoints and the in vitro spectrum as mentioned below are based on systemic use. These breakpoints might not be applicable on topical ocular use of the medicinal product as higher concentrations are obtained locally and the local physical/chemical circumstances can influence the activity of the product on the site of administration. In accordance with EUCAST, the following breakpoints are defined for tobramycin:

Enterobacteriaceae	S ≤ 2 mg/L, R > 4 mg/L
Pseudomonasspp.	S ≤ 4 mg/L, R > 4 mg/L
Acinetobacterspp.	S ≤ 4 mg/L, R > 4 mg/L
Staphylococcusspp.	S ≤ 1 mg/L, R > 1 mg/L
Notspecies-related	S ≤ 2 mg/L, R > 4 mg/L

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of moxifloxacin in at least some types of infections is questionable.

The information listed below gives only an approximate guidance on probabilities whether microorganisms will be susceptible to tobramycin in this medicine. Bacterial species that have been recovered from external infections of the eye such as observed in conjunctivitis are presented here. The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of tobramycin in at least some types of infections is questionable.

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-hemolytic species, some non-hemolytic species, and some *Streptococcus pneumoniae*. *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis* (indole-negative) and indole-positive *Proteus* species, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata*, and *Acinetobacter calcoaceticus* (*Herellea vaginacola*) and some *Neisseria* species. Bacterial susceptibility studies demonstrate that in some cases, microorganisms resistant to gentamicin retain susceptibility to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

Species for which acquired resistance might be a problem:

Acinetobacter baumannii
Bacillus cereus
Bacillus thuringiensis
Kocuria rhizophila
Staphylococcus aureus (*methicillin resistant – MRSA*)
Staphylococcus haemolyticus (*methicillin resistant –MRSH*)
Staphylococcus, *other coagulase-negative spp.*
Serratia marcescens

Inherently resistant organisms:

Aerobic Gram-positive microorganisms:

Enterococcus faecalis
Streptococcus mitis
Streptococcus pneumoniae
Streptococcus sanguis
Chryseobacterium indologenes

Aerobic Gram-negative

microorganisms: Haemophilus influenzae
Stenotrophomonas maltophilia

Anaerobic bacteria:

Propionibacteriumacnes

Data from clinical studies

Cumulative safety data from pharmacodynamics clinical trials are presented in section 4.8.

5.2 Pharmacokinetic properties

Ocular Pharmacokinetics

The tobramycin MIC90 for ocular isolates commonly involved in superficial ocular bacterial infection is 16µg/mL. Following a single administration of Tobrex ophthalmic solution, the mean duration of time that tobramycin remained above MIC90 value was 25.1 minutes in the tear film of the human eye.

Absorption

Tobramycin is poorly absorbed across the cornea and conjunctiva with peak concentration of 3 micrograms/mL in aqueous humor after 2 hours followed by a rapid decline after topical administration of 0.3% tobramycin. Additionally, systemic absorption

of tobramycin in human is poor after topical ocular administration of tobramycin. However, topical ocular tobramycin 0.3% delivers 527 ± 428 micrograms/mL tobramycin in human tears after a single dose. Ocular surface concentration generally exceeds the MIC of the most resistant isolates (MICs > 64 micrograms/ml).

Distribution

The systemic volume of distribution is 0.26 L/kg in man. Human plasma protein binding of tobramycin is low at less than 10%.

Biotransformation

Tobramycin is excreted in the urine primarily as unchanged drug.

Excretion

Tobramycin is excreted rapidly and extensively in the urine via glomerular filtration, primarily as unchanged drug. Systemic clearance was 1.43 ± 0.34 mL/min/kg for normal weight patients after intravenous administration and its systemic clearance decreased proportionally to renal function. The plasma half-life is approximately two hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeated-dose toxicity and genotoxicity studies. For information on developmental toxicity studies, see Section 4.6 Fertility, pregnancy and lactation. In fertility studies, subcutaneous administration of tobramycin did not impair fertility in rats up to 100 mg/kg/day corresponding to 56 times, the MROHD based on BSA.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium Chloride solution
Boric acid
Sodium Chloride
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months for the date of manufacturing.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

1 x 5 ml

6.6 Special precautions for disposal <and other handling>

There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

7 <APPLICANT/MANUFACTURER>

Stallion laboratories Pvt. Ltd.

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