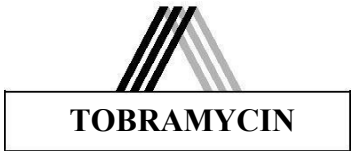
NOVARTIS



TOBREX®
3 mg / mL (0.3% w/v)
Sterile Ophthalmic Solution
Antibacterial

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Sterile Ophthalmic Solution.

Clear, colourless to pale yellow or brown solution.

Active substance(s)

Tobramycin (Tobrex®) Sterile Ophthalmic Solution:
One mL of solution contains 3 mg tobramycin

Excipients

Tobramycin (Tobrex®) Sterile Ophthalmic Solution:

Excipient with known effect: 1 mL of the eye drop solution contains 0.1 mg of benzalkonium chloride.

Other excipients: boric acid, tyloxapol, sodium chloride, sodium sulphate anhydrous, sulphuric acid and/or sodium hydroxide (to adjust pH), purified water.

INDICATIONS

Tobramycin (Tobrex®) 3 mg/mL (0.3% w/v) Sterile Ophthalmic Solution is a 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 Tobramycin (Tobrex®) 3 mg/mL (0.3% w/v) Sterile Ophthalmic Solution. Clinical studies have shown tobramycin to be safe and effective for use in children.

As with other antibiotics, appropriate monitoring of bacterial response to treatment should be performed.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

As indicated by physician:
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, following which treatment should be reduced prior to discontinuation.
Tobramycin (Tobrex®) 3 mg/g (0.3%) Sterile Ophthalmic Ointment may be used in conjunction with Tobramycin (Tobrex®) 3 mg/mL (0.3% w/v) Sterile Ophthalmic Solution.

Special populations

Renal and hepatic impairment

The safety and efficacy of Tobramycin (Tobrex®) Sterile Ophthalmic Solution in patients with renal and hepatic impairment has not been established.

Pediatric patients (below 1 year)

- Tobramycin (Tobrex®) Sterile Ophthalmic Solution can be used in pediatric patients (1 year of age and older) at the same dose as in adults. Limited information is available in pediatric patients younger than 1 year.
- Safety and effectiveness in pediatric patients below the age of 2 months has not been established.

Geriatric patients (65 years or above)

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

Method of administration

- For ocular use only.
- 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. *[Only applicable for eye drops containing a snap collar]*
- 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.
- 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.

CONTRAINDICATIONS

Hypersensitivity to the active substance, or to any of the excipients.

WARNINGS AND PRECAUTIONS

- 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, urticaria, 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 Tobramycin (Tobrex®) Sterile Ophthalmic Solution is used concomitantly with systemic aminoglycosides.
- Caution should be exercised when prescribing Tobramycin (Tobrex®) Sterile Ophthalmic Solution 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 Tobramycin (Tobrex®) Sterile Ophthalmic Solution may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.
- Contact lens wear is not recommended during treatment of an ocular infection.

Special excipients

Tobramycin (Tobrex®) Sterile Ophthalmic Solution contains benzalkonium chloride which may cause eye irritation and is known to discolor 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.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

System organ classification	Adverse drug reaction	Frequency category
Immune system disorders	Hypersensitivity	Uncommon
Nervous system disorders	Headache	Uncommon
Eye disorders	Ocular discomfort, ocular hyperaemia	Common
	Keratitis, corneal abrasion, visual impairment, vision blurred, eyelid oedema, erythema of eyelid, conjunctival oedema, dry eye, lacrimation increased, eye pain, eye pruritus, eye discharge	Uncommon
Skin and Subcutaneous disorders	Urticaria, dermatitis, madarosis, leukoderma, pruritus, dry skin	Uncommon

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Tobramycin (Tobrex®) Sterile Ophthalmic 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.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

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

INTERACTIONS

No clinically relevant interactions have been described with topical ocular dosing.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk.

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).

Tobramycin (Tobrex®) Sterile Ophthalmic Solution should be used during pregnancy only if clearly needed.

Data

Human data

Based on data from a paired case-control study, it was concluded that the risk of deafness in children born to mothers who had received gentamicin, neomycin and other aminoglycoside antibiotics during pregnancy cannot be excluded, but the magnitude is estimated to be small. Ototoxicity, which is known to occur after tobramycin therapy, has not been reported as an effect of *in utero* exposure. However, eighth cranial nerve toxicity in the fetus is well known following exposure to other aminoglycosides and may potentially occur with tobramycin.

Animal data

In embryo-fetal development studies in rats and rabbits, pregnant animals received subcutaneous tobramycin during the period of organogenesis at doses up to 100 and 40 mg/kg/day, respectively. There was no embryo-fetal toxicity in either species up to the maximum dose tested corresponding to 56 and 45 times the MROHD based on BSA, respectively.

In a peri- and postnatal development study in rats, subcutaneous administration of up to 100 mg/kg/day tobramycin during early gestation through the lactation period did not adversely affect the fertility index, gestational survival index, litter size, sex distribution, postpartum progeny survival index or weight of offspring. The ratio of the highest dose tested to the MROHD is 56 based on BSA.

Lactation

Risk summary

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 must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Females and males of reproductive potential

Infertility

There are no data regarding the effects of topical ocular administration of Tobramycin (Tobrex®) Sterile Ophthalmic Solution on human fertility. Tobramycin did not impair fertility in rats (see Section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, nor in the event of accidental ingestion of the content of one bottle or tube.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

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

Mechanism of 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 adenylylating, 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.

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
- *Pseudomonas spp*. S ≤4 mg/L, R >4 mg/L
- *Acinetobacter spp*. S ≤4 mg/L, R >4 mg/L
- *Staphylococcus spp*. S ≤1 mg/L, R >1 mg/L
- *Not species-related* S ≤2 mg/L, R >4 mg/L

Clinical efficacy against specific pathogens

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.

Commonly susceptible species

Aerobic Gram-positive microorganisms:

- Bacillus megaterium
- Bacillus pumilus
- Corynebacterium macginleyi
- Corynebacterium pseudodiphtheriticum
- Kocuria kristinae
- Staphylococcus aureus (methicillin susceptible – MSSA)
- Staphylococcus epidermidis (coagulase-positive and –negative)
- Staphylococcus haemolyticus (methicillin susceptible – MSSH)
- Streptococci (inlcuding some of the group A beta-hemolytic species, some nonhemolytic species, and some Streptococcus pneumoniae)

Aerobic Gram-negative microorganisms:

- Acinetobacter calcoaceticus
- Acinetobacter junii
- Acinetobacter ursingii
- Citrobacter koseri
- Enterobacter aerogenes
- Escherichia coli
- H. aegyptius
- Haemophilus influenzae
- Klebsiella oxytoca
- Klebsiella pneumoniae
- Morganella morganii
- Moraxella catarrhalis
- Moraxella lacunata
- Moraxella oslonensis
- Some Neisseria species
- Proteus mirabilis

- Most Proteus vulgaris strains
- Pseudomonas aeruginosa
- Serratia liquifaciens

Anti-bacterial activity against other relevant pathogens

Species for which acquired resistance might be a problem:

- Acinetobacter baumanii
- 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:

- Propionibacterium acnes

Bacterial susceptibility studies demonstrate that in some cases, microorganisms resistant to gentamicin retain susceptibility to tobramycin.

Pharmacokinetics (PK)

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.

Elimination

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.

Linearity/non-linearity

Ocular or systemic absorption with increasing dosing concentrations after topical ocular administration has not been evaluated. Therefore, the linearity of exposure with topical ocular dose could not be established.

PK/PD relationship

A specific PK/PD relationship has not been established for Tobramycin (Tobrex®) Sterile Ophthalmic Solution. Published *in vitro* and *in vivo* studies have shown that tobramycin features a prolonged post-antibiotic effect, which effectively suppresses bacterial growthdespite low serum concentrations.

Systemic administration studies have reported higher maximum concentrations with once daily compared to multiple daily dosing regimens. However, the weight of current evidence suggests that once daily systemic dosing is equally as efficacious as multiple-daily dosing. Tobramycin exhibits a concentration-dependent antimicrobial kill and greater efficacy with increasing levels of antibiotic above the MIC or minimum bactericidal concentration (MBC).

Special populations

Pediatric patients (below 18 years)

Aminoglycosides including tobramycin has been commonly used among children, infants and neonates to treat serious Gram-negative infections. Tobramycin (Tobrex®) 3 mg/mL (0.3% w/v) Sterile Ophthalmic Solution is approved for use in children. Clinical pharmacology of tobramycin in children has been described after systemic administration.

Geriatric patients (65 years of age or above)

There is no change in tobramycin pharmacokinetics with older patients when compared to younger adults.

Renal impairment

Tobramycin pharmacokinetics with eye drops has not been studied in this patient population.

Hepatic impairment

Tobramycin pharmacokinetics with eye drops has not been studied in this patient population.

CLINICAL STUDIES

Tobramycin (Tobrex®) Sterile Ophthalmic Solution is a well-established product.

NON-CLINICAL SAFETY DATA

Non-clinical data revealed no special hazard for humans from topical ocular exposure to tobramycin based on repeated-dose topical ocular toxicity studies, genotoxicity or carcinogenicity studies. For information on developmental toxicity studies, see Section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

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.

INCOMPATIBILITIES

Not applicable

STORAGE

Store at temperatures not exceeding 25°C.
Keep container tightly closed.
Tobramycin (Tobrex®) Sterile Ophthalmic Solution should not be used after the date marked "EXP" on the pack.
Discard 4 weeks after first opening.
Tobramycin (Tobrex®) Sterile Ophthalmic Solution must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

AVAILABILITY

Sterile solution in 5 mL DROPTAINER® Dispenser containing Tobramycin 0.3 % (TOBREX®) Ophthalmic Solution.

CAUTION:

Food, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

Registration Number/Date of Renewal of Authorization:
Tobramycin (TOBREX®) Sterile Ophthalmic Solution: DR-XY7060 / 13 November 2019

Information issued: May 2021

Manufactured by:
ALCON-COUVREUR NV
Rijksweg 14, Puurs, B-2870, Belgium

Imported by:
NOVARTIS HEALTHCARE PHILIPPINES, INC.
5th and 6th Floors Ayala North Exchange Building, Tower 1, Ayala Avenue corner Salcedo & Amorsolo Sts., Brgy. San Lorenzo, Makati, Metro Manila