SUMMARY OF PRODUCT CHARACTERISTICS

NOVARTIS

Summary of Product Characteristics

NAME OF THE MEDICINAL PRODUCT

TOBREX® 0.3% sterile ophthalmic solution
(tobramycin)

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of solution contains 3 mg tobramycin.
Preservative: 1 mL of solution contains 0.1 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Sterile ophthalmic solution.
Clear, colourless to pale yellow or brown solution.

CLINICAL PARTICULARS

Therapeutic indications

TOBREX ophthalmic solution contains tobramycin, a water-soluble aminoglycoside antibiotic active against a wide variety of gram-negative and gram-positive ophthalmic pathogens.

TOBREX 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 TOBREX ophthalmic solution.
Clinical studies have shown tobramycin to be safe and effective for use in children (see section 4.2).

Posology and method of administration

Posology

As indicated by physician:
In mild to moderate disease, instil 1 or 2 drops into the affected eye(s) every 4 hours. In severe infections, instil 2 drops into the eye(s) hourly until improvement, following

which treatment should be reduced prior to discontinuation. The length of the treatment is dependent on the origin of the infection and may vary between 5 to 12 days.
TOBREX ophthalmic ointment may be used in conjunction with TOBREX ophthalmic solution.

Use in children
The safety and efficacy of TOBREX 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 TOBREX 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.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use.

Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the 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.

Contraindications

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

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, 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 TOBREX is used concomitantly with systemic aminoglycosides and care should be taken to monitor the total serum concentration.
- Caution should be exercised when prescribing TOBREX 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 TOBREX 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. 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.

Interaction with other medicinal products and other forms of interaction

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

Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of topical ocular tobramycin in pregnant women. Tobramycin does cross the placenta into the foetus after intravenous dosing in pregnant women. Tobramycin is not expected to cause ototoxicity from *in utero* exposure. Studies in animals have shown reproductive toxicity at dosages considered sufficiently in excess of the maximal human dose derived from tobramycin eye drops so as to have limited clinical relevance. Tobramycin has not been shown to induce teratogenicity in rats or rabbits (see section 5.3).

TOBREX ophthalmic solution should be used during pregnancy only if clearly needed.

Lactation
Tobramycin is excreted in human milk after systemic administration. It is unknown whether tobramycin is excreted in human milk following topical ocular 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 use of the product. However, a risk to the suckling child cannot be excluded.

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

Fertility
Studies have not been performed to evaluate the effect of topical ocular administration of TOBREX ophthalmic solution on human fertility.

Effects on ability to drive and use machines

TOBREX ophthalmic solution has no or negligible influence on the ability to drive and use machines.

However, 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.

Undesirable effects

Tabulated summary of adverse reactions
The following adverse reactions have been reported during clinical trials and identified from post-marketing surveillance. These are classified according to the subsequent convention: 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), very rare (<1/10,000) or not known (cannot be estimated from the available data; data from post-marketing surveillance). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Adverse reactions**
Immune system disorders	*Uncommon:* hypersensitivity *Not known:* anaphylactic reaction
Nervous system disorders	*Uncommon:* headache
Eye disorders	*Common:* ocular discomfort, ocular hyperaemia *Uncommon:* keratitis, corneal abrasion, visual impairment, vision blurred, erythema of eyelid, conjunctival

	oedema, eyelid oedema, eye pain, dry eye, eye discharge, eye pruritus, lacrimation increased *Not known:* eye allergy, eye irritation, eyelids pruritus
Skin and Subcutaneous Tissue Disorders	*Uncommon:* urticaria, dermatitis, madarosis, leukoderma, pruritus, dry skin *Not known:* Stevens Johnson's 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 (see section 4.4).
- If topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration (see section 4.4).

Overdose

An ocular overdose of TOBREX 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 TOBREX ophthalmic solution (punctate keratitis, erythema, increased lacrimation, oedema and lid itching) may be similar to adverse reaction effects seen in some patients.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Mechanism of action

Tobramycin is a potent, broad-spectrum, fast-working 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-haemolytic species, some non-haemolytic 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
Moraxella catarrhalis
Moraxella lacunata
Moraxella oslonensis
Morganella morganii
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.

PK/PD relationship
A specific PK/PD relationship has not been established for TOBREX. Published *in vitro* and *in vivo* studies have shown that tobramycin features a prolonged post-antibiotic effect, which effectively suppresses bacterial growth despite 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 minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC).

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

Pharmacokinetic properties

Absorption
Tobramycin is poorly absorbed across the cornea and conjunctiva with peak concentration of 3 micrograms/mL in aqueous humour 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.

Linearity/non-linearity pharmacokinetics
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.

Use in hepatic and renal impaired patients
Tobramycin pharmacokinetics with eye drops has not been studied in these patient populations.

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

Preclinical safety data

Non-clinical data revealed no special hazard for humans from topical ocular exposure to tobramycin based on conventional repeated-dose topical ocular toxicity studies, genotoxicity or carcinogenicity studies. Effects in non-clinical reproductive and developmental studies with tobramycin were observed only at exposures considered sufficiently in excess of the maximum human ocular dosage indicating little relevance to clinical use.

PHARMACEUTICAL PARTICULARS

List of excipients
Benzalkonium chloride, boric acid, tyloxapol, sodium chloride, sodium sulfate anhydrous, sulfuric acid and/or sodium hydroxide (to adjust pH), purified water.

Incompatibilities
Not applicable.

Other information

Shelf Life

Do not use this medicine after the expiry date which is stated on the packaging.
Discard 4 weeks after first opening.
Keep this medicine out of the sight and reach of children.

Storage

Do not store above 30°C.

Instruction for handling

To avoid contamination, the tip of dropper bottle or eye ointment tube must not come into contact with the eyelids, the area around the eye or other surfaces. Close the bottle or tube tightly when not in use.

Swissmedic number

44538, 45508, 56825

Pack sizes

Eye drops: 5 ml dropper bottle
Eye ointment: 3.5 g tube
Eye gel: 5 ml dropper bottle

Nature and contents of container

DROP-TAINER® dispenser containing 5 mL.

Special precautions for disposal

No special requirements.

Market Authorization Holder

Novartis Pharma Schweiz AG, 6343 Risch, Switzerland

Manufactured by:

ALCON-COUVREUR
B-2870 Puurs (Belgium) for Novartis Pharma AG, Basel, Switzerland