1. NAME OF THE MEDICINAL PRODUCT

TOBREX® (tobramycin 0.3%) Ophthalmic Solution
TOBREX® (tobramycin 0.3%) Ophthalmic Ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution:
Active: tobramycin 0.3% (3 mg/ml)
Preservative: benzalkonium chloride 0.01% (0.1 mg/ml)
Excipients: See section 6.1

Ointment:
Active: 0.3% tobramycin (3 mg / g)
Preservative: 0.5% chlorobutanol (5 mg / g)
Inactive: mineral oil, solid petrolatum

3. PHARMACEUTICAL FORM

Eye drops, solution.
Ophthalmic Ointemnt

4. CLINICAL PARTICULARS

4.1 *Therapeutic indications*

TOBREX® 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®.

4.2 Posology and method of administration

Solution: In mild to moderate cases, instill one or two drops in the affected eye or eyes every four hours. In severe infections, instill two drops in the eye and affected eyes every hour until an improvement is observed. From that moment, the treatment must be reduced before its suspension.
Ointment: In mild to moderate cases, apply 1 to 1.5 centimeters of the ointment in the affected eye or eyes two or three times per day.

In severe conditions apply 1 to 1.5 centimeters of ointment in the affected eye or eyes every three or four hours until you notice improvement. From that moment, the treatment must be reduced before its suspension. After the application of the ointment, look down before closing the eyelids. TOBREX® ointment can be used concomitantly with TOBREX® solution.

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, remove before using product.
- 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.
- 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.

4.3 *Contraindications*

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

4.4 *Special warnings and precautions for use*

- 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 tobramycin therapy and caution is advised when used concomitantly.
- Caution should be exercised when prescribing TOBREX® 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® 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® contains benzalkonium chloride / benzododecinium bromide 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*

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

4.6 *Fertility, pregnancy and lactation*

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

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® should be used during pregnancy only if clearly needed.

Breast-feeding
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 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 at application, the patient must wait until the vision clears before driving or using machinery.

4.8 *Undesirable effects*

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
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
Skin and Subcutaneous Tissue Disorders	*Uncommon:* urticaria, dermatitis, madarosis, leukoderma, pruritus, dry skin

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Class	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

4.9 *Overdose*

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 contents of one bottle or tube.

5 PHARMACOLOGICAL PROPERTIES

5.1 *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.

Elderly population

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

5.2 *Pharmacokinetic properties*

Absorption

Tobramycin is poorly absorbed across the cornea and conjunctiva with peak concentration of 3 µg/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 µg/ml tobramycin in human tears after a single dose. Ocular surface concentration generally exceeds the MIC of the most resistant isolates (MICs > 64 µg/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.

Use in pediatrics:

Aminoglycosides including tobramycin has been commonly used among children, infants and neonates to treat serious Gram-negative infections. Tobrex (0.3% ophthalmic tobramycin) is approved for use in children. Clinical pharmacology of tobramycin in children has been described after systemic administration.

5.3 *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.

6 PHARMACEUTICAL PARTICULARS

6.1 *List of excipients*

Ointment:
Chlorobutanol
Solid Vaseline
Mineral oil

Eye Drops:
Benzalkonium chloride
Boric acid
Tyloxapol
Sodium chloride sodium
Sulphate anhydrous
Sulphuric acid and/or sodium hydroxide (to adjust pH), purified water

6.2 ***Incompatibilities***

Not applicable.

6.3 ***Special precautions for storage***

Ointment:
Store at 2° - 8°C
Do not use this medicine after the expiry date, which is stated on the packaging.
Discard 4 weeks after first opening.

Eye Drops:
Store at 2° - 25°C (36° - 77°F).
Do not use this medicine after the expiry date, which is stated on the packaging.
Discard 4 weeks after first opening.

6.4 ***Nature and contents of container***

Ointment:
Tube with 3.5g

Eye Drops:
DROPTAINER dispenser containing 5 ml, 10ml.

6.5 ***Special precautions for disposal***

No special requirements.

Manufactured by:

Alcon Laboratories Inc.
Fort Worth, Texas 76134, USA
S.A. Alcon-Couvreur N.V.,
Rijksweg 14, B-2870 Puurs (Bélgica)

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