1. NAME OF THE MEDICINAL PRODUCT

Tobrex® **0.3%** sterile ophthalmic ointment
(Tobramycin)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of ointment contains 3 mg tobramycin.
Preservative: 1 g of ointment contains 5 mg chlorobutanol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile ophthalmic ointment.
White to off-white homogeneous ointment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Tobrex® ophthalmic ointment 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 ointment.
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, apply a 1.5 centimetre ribbon into the affected eye(s) 2 or 3 times per day.
In severe infections, instil a 1.5 centimetre ribbon into the eye(s) every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation.
Tobrex ophthalmic ointment may be used in conjunction with Tobrex ophthalmic solution.

<u>Use in children</u>

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

<u>Use in patients with hepatic or renal impairment</u>

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

<u>Use in elderly population</u>

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

Method of administration

For ocular use.

To prevent contamination of the tube tip and ointment, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the tube tip. Keep the tube 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.

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 applied 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 Tobrex Eye Ointment are used concomitantly with systemic aminoglycosides, and care should be taken to monitor the total serum concentration.
- Caution should be exercised when prescribing Tobrex Eye Ointment 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 ointment may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.
- Ophthalmic ointments may retard corneal wound healing.
- Contact lens wear is not recommended during treatment of an ocular infection

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Pregnancy :
There are no or limited amount of data from the use of topical ocular tobramycin studies in pregnant women. Tobramycin does cross the placenta into the fetus after intravenous dosing in pregnant women. Topical ocular 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 Tobrex Eye Ointment 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 ointment 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 ointment 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

Tabulated summary of adverse reactions
The following adverse reactions have been identified during clinical trials with Tobrex Eye Drops and/or Tobrex Eye Ointment] and are classified according to 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) 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 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 (see section 4.4).

4.9 Overdose

An ocular overdose of Tobrex ophthalmic ointment 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 tube.

Clinically apparent signs and symptoms of an overdose of Tobrex Ophthalmic Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-infectives – antibiotics.

ATC code: S01AA12.

Mechanism of action

Tobramycin is a potent, broad-spectrum, rapidly 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

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 - betahemolytic 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 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

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 MIC or minimum bactericidal concentration (MBC).

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 ointment, the mean duration of time that tobramycin remained above MIC_{90} value 44.4 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.

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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional repeated-dose toxicity and genotoxicity studies.

Effects in non-clinical reproductive and developmental studies with Tobramycin were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorobutanol, liquid paraffin, white soft paraffin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Do not store above 27° C.
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.

6.5 Nature and contents of container

Tube containing 3.5 g

6.6 Instructions for use and handling and disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 Manufacturer

See folding box

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Novartis Pharma AG, Basel, Switzerland