NOVARTIS

## 1. NAME OF THE MEDICINAL PRODUCT

**TOBREX**® 3 mg/mL Tobramycin sterile eye drops, solution

## 2. 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.

## 3. PHARMACEUTICAL FORM

Sterile ophthalmic solution.

Clear, colourless to pale yellow or brown solution.

## 4. CLINICAL PARTICULARS

### 4.1 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.

### 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.

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.

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 Tobrex® 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 Tobrex® 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 Tobrex® (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 Fertility, pregnancy and lactation**

**Fertility**

There are no data regarding the effects of topical ocular administration of Tobrex® 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). Tobrex® 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**

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 Tobrex® 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**

**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 (≥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).

| **System Organ Class** | **Adverse reactions** |
|---|---|
| Immune system disorders | *Uncommon:* hypersensitivity |
| Nervous system disorders | *Uncommon:* headache |

| | |
|---|---|
| Eye disorders | *Common:* ocular discomfort, ocular hyperaemia<br><br>*Uncommon:* 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 | *Uncommon:* 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 (see section 4.4).

### 4.9 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, 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, rapid-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

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*

**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 $MIC_{90}$ 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.

**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.

**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).

**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 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, 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 Shelf life
24 Months

### 6.4 Special precautions for storage
Do not store above 30°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
Plastic bottle dispenser containing 5 mL.

### 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

(Information issued: May 2021.SIN)

**Novartis Pharma AG, Basel, Switzerland**