SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TOBREX 2X

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Tobrex 2X eye drops contains the active ingredient tobramycin 3 mg in 1 mL.

Excipient with known effect

Preservative: Benzododecinium bromide (BDAB)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Antibiotic for the treatment of superficial eye infections caused by bacteria sensitive to Tobramycin.

4.2. Dose and method of administration

The dose is one drop of TOBREX 2X eye drops into the conjunctival sac two times daily (morning and evening) for 7±1 days.

If severe disease: on the first day, four instillations while awake. Thereafter instill one drop in each eye twice a day, while awake, until completion of the 7±1 days-total treatment period.

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 of the bottle. Keep the bottle tightly closed when not in use.
After cap is removed, if the tamper evident snap collar is loose, remove before using the product.
In case of concomitant therapy with other topical ocular medicines, an interval of 5-10 minutes should be allowed between successive applications.

Use in elderly
No dosage adjustment in elderly patients is necessary.

Paediatric Population
TOBREX 2X eye drops may be used in children 1 year of age and older at the same dose as in adults. The safety and efficacy in children younger than 1 year of age have not been established, and no data are available.

Use in hepatic and renal impairment

Ocular application of tobramycin gives very little systemic exposure. In case of concomitantly administered systemic treatment with aminoglycoside antibiotics, care should be taken to monitor the total serum concentration in order to ensure that an appropriate therapeutic level is maintained.

4.3. Contraindications

- Hypersensitivity to the active substance or to other aminoglycosides, or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

FOR TOPICAL OPHTHALMIC USE ONLY. NOT FOR INJECTION INTO THE EYE.

Hypersensitivity

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 with this product, discontinue use and institute appropriate therapy.

If Tobrex 2X eye drops is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycosides therapy. Caution is advised when Tobrex 2X eye drops is used concomitantly with systemic aminoglycosides.

Caution should be exercised when prescribing Tobrex 2X 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.

General

As with any antibiotic, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Cross-sensitivity to other aminoglycoside antibiotics may occur. The possibility that patients that become sensitised to topical ocular tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered.

Ophthalmic solutions may retard corneal wound healing.

Renal, auditory, vestibular, or neuromuscular impairment

Patients receiving concomitant parenteral tobramycin (aminoglycoside) and topical tobramycin therapies should be monitored as clinically appropriate. Caution should be exercised with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction.

Contact lenses

Tobrex 2X eye drops should not be instilled while the patient is wearing contact lenses. Contact lens wear is not recommended during treatment of an ocular infection.

If patients continue to wear contact lenses while under treatment with Tobrex 2X eye drops, they should remove their lens(es) prior to instilling the drops in the affected eye(s). Lens(es) should not be inserted into the eye(s) until 15 minutes after instillation of the drops. Tobrex 2X eye drops contains benzododecinium bromide which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses.

4.5 Interactions with other medicinal products and other forms of interactions

If Tobrex 2X eye drops is 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 2X with other drugs with neurotoxic or ototoxic potential should be avoided.

Do not use Tobrex 2X simultaneously with a topical beta lactam type antibiotic as this is likely to result in inactivation of tobramycin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3.

There are no adequate, well-controlled studies using the topical administration of Tobrex 2X (tobramycin) eye drops in pregnant women.

A published retrospective assessment of women receiving parenteral aminoglycosides during pregnancy suggested no detectable teratogenic risk to the fetus. The number of women treated with parenteral tobramycin in this study was very small, 2 in the case group and 4 in the control group and so no firm specific conclusions with regard to tobramycin exposure can be drawn from this study. However, the study concluded that parenteral administration of gentamicin and oral neomycin during pregnancy presents no detectable terotogenic risk to the fetus, when restricted to structural developmental abnormalities. This conclusion can be extended to the class of aminoglycoside antibiotics as a whole.

There are no firm data concerning the detectable blood concentrations in mothers or tissue concentrations in the fetus. The systemic absorption of tobramycin after topical administration of Tobrex 2X is expected to be low.

Tobrex 2X should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus otherwise tobramycin is not recommended during pregnancy.

Refer to section 5.3 for pre-clinical reproductive studies on aminoglycosides.

Breast-feeding

There are no adequate, well-controlled studies using the topical administration of Tobrex 2X eye drops in women who are breast feeding. It is unknown whether tobramycin is excreted in human milk following topical ocular administration.

Tobramycin is excreted in human milk after systemic administration. Risk to the breast fed child cannot be excluded.

Tobrex 2X should be used only if the potential benefit for the mother justifies the potential risk to the infant.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of Tobrex 2X eye drops on human fertility.

Tobrex Eye drops has a boron containing excipient. In animal studies, boron has been shown to cause reduced fertility and embryofoetal development effects, and this appears to be dose related. The relevance of this to humans is uncertain. When used as directed (see section 4.2), the use of this medicine is unlikely to exceed the safety threshold for maximum daily boron exposure.

4.7 Effects on ability to drive or use machines

As with other ophthalmic medications, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs upon application, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

The most frequent adverse reactions to Tobrex 2X eye drops are localised ocular toxicity and hypersensitivity, including punctate keratitis, eye and lid itching, lid swelling, ocular hyperaemia, conjunctival erythema and lacrimation. These reactions occur in approximately 3% of patients treated with Tobrex 2X.

Other adverse reactions associated with ophthalmic tobramycin are burning and stinging of the eyes.

A summary of treatment emergent adverse events based on literature and postmarketing experience and their estimate of frequencies (very common, common, uncommon, rare, very rare, and not known) in accordance with preferred term and system organ classes (SOC) of any severity are listed below.

Within each frequency-grouping, undesirable effects are presented in decreasing order of seriousness. These adverse reactions were observed following ophthalmic use of Tobramycin:

Immune system disorders

Uncommon (> 0.1% to ≤ 1%): hypersensitivity.

Not known: anaphylactic reaction.

Nervous system disorders

Uncommon (> 0.1% to ≤ 1%): headache.

Eye disorders

Common (> 1% to < 10%): ocular discomfort, ocular hyperaemia.

Uncommon (> 0.1% to ≤ 1%): keratitis, corneal abrasion, conjunctival disorder, visual impairment, vision blurred, erythema of eyelid, conjunctival oedema, eyelid oedema, eyelid disorder, eye pain, dry eye, eye discharge, eye pruritus, foreign body sensation in eyes, lacrimation increased.

Not known: eye allergy, eye irritation, eyelids pruritus.

Skin and subcutaneous tissue disorders

Uncommon (> 0.1% to ≤ 1%): urticaria, dermatitis, madarosis, leukoderma, pruritus, dry skin.

Not known: Stevens-Johnson syndrome, erythema multiforme, rash.

If topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, the possibility of increased systemic toxicity cannot be excluded and care should be taken to monitor the total serum concentration. Prolonged levels above 12 micrograms/mL should be avoided.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

4.9 Overdose

Clinically apparent signs and symptoms of Tobrex 2X eye drops overdose are not expected when used as above nor in the event of accidental ingestion of the contents of one bottle. However, excessive local reactions may occur. In such cases treatment should be discontinued and appropriate treatment instituted.

A topical overdose of Tobrex 2X may be flushed from the eye(s) with lukewarm water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensory organ; ophthalmologicals; antibiotics ATC Code SO1AA12.

Mechanism of action

Tobramycin is actively transported across the bacterial cell membrane, and binds to a specific receptor protein on the 30 S subunit of bacterial ribosomes and interferes with an initiation complex between messenger RNA (mRNA) and the 30 S subunit, thus inhibiting protein synthesis.

Pharmacodynamic effects

Microbiology

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 - beta-haemolytic species, some non- haemolytic species, and some *Streptococcus pneumoniae*.
- *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis* (indole-negative) and indole-positive *Proteus* species.

Bacterial resistance may develop upon prolonged use.

Tobramycin is not effective against most strains of group D *Streptococci.*

5.2 Pharmacokinetic properties

Not available.

5.3 Preclinical safety data

Pregnancy

Studies in animals have shown evidence of an increased occurrence of foetal damage following systemic administration of aminoglycosides to pregnant mothers. There is evidence of selective uptake of aminoglycosides by the foetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following *in utero* exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus. It should also be noted that therapeutic blood concentrations in the mother do not equate with safety for the fetus.

Carcinogenicity

No studies have been conducted to evaluate the carcinogenic potential of tobramycin.

Mutagenicity

In vitro and in vivo studies with tobramycin did not reveal a mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol, trometamol, xanthan gum, boric acid, polysorbate 80, benzododecinium bromide (BDAB), sulphuric acid and/or sodium hydroxide, purified water.

6.2 Incompatibilities

Unknown

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store Tobrex 2X eye drops below 30°C. Contents should be discarded 28 days after opening.

6.5 Nature and contents of container

Tobrex 2X eye drops come in a 5 mL opaque, Droptainer bottle consisting of a low density polyethylene bottle with a low density polyethylene plug and polypropylene cap.

6.6 Special precautions for disposal

No special requirements for disposal.

8. LICENSE HOLDER ,IMPORTER AND IT'S ADDRESS

NOVARTIS ISRAEL LTD

P.O.B 7126, Tel Aviv

9.REGISTRATION NUMBER

136 70 31413

Revised in January 2022 according to MoH guidelines.