SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EYETOBRIN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 3 mg tobramycin.

Excipient with known effect:
Each mL of solution contains 0.1 mg benzalkonium chloride (see section 4.4)
Each mL of solution contains 1 mg polysorbate 80 (see section 4.4)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear and colourless to slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EYETOBRIN is indicated for the treatment of external bacterial infections of the eye and its structures, such as conjunctivitis caused by tobramycin-sensitive bacteria in adults and children over 1 year of age.

4.2 Posology and method of administration

Posology

Use in adolescents and adults, including the elderly
In mild to moderate infections, the dose is one or two drops instilled in the conjunctival sac of the affected eye(s) every four hours.

For severe infection, the dose is one or two drops in the conjunctival sac of the affected eye(s) hourly. If there is improvement, frequency of administration may be decreased

Treatment is individualized according to the doctor's decision.

The usual duration of treatment is 7-10 days.

Paediatric population
EYETOBRIN may be used in children aged 1 year and older at the same dose as in adults. The maximum daily dose is 14 drops in children aged 1 to 2 years, and 46 drops in children aged 2 to 12 years. Available data is provided in section 5.1. Safety and efficacy in children under 1 year of age, have not been established and there is no data available.

Use in patients with hepatic and renal impairment
There are no studies conducted with EYETOBRIN in patients with hepatic or renal impairment. However, due to the low systemic absorption of tobramycin after topical administration of this product, no dosage adjustment is required.

Method of administration
Topical ocular use only. Not for injection into the eye.

Keep the bottle tightly closed when not in use. After cap is removed, if tamper evident snap collar is loose, remove before using product.

Gently closing the eyelid (s) and nasolacrimal occlusion after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic side effects.

In case of concomitant therapy with other topical ophthalmic medicinal products, an interval of 5 minutes should be allowed between successive applications. Eye ointments should be administered last. To prevent contamination of the dropper tip and suspension, care should be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle.

4.3 Contraindications

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

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, 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 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. Caution is advised when it is used concomitantly with other systemic aminoglycosides.

Caution should be exercised when prescribing EYETOBRIN to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinsons disease. Aminoglycosides may aggravate muscle weakness because of their potential effect on neuromuscular function.

As with any antibiotic, prolonged use of EYETOBRIN may result in overgrowth of non-susceptible microorganisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

As with any antibiotic, appropriate monitoring of the bacterial response to treatment should be performed.

This product contains 0.5 mg benzalkonium chloride in every 5 mL, which is equivalent to 0.1 mg/mL. Benzalkonium chloride which used as a preservative in EYETOBRIN may be absorbed by soft contact lenses and may change the colour of the contact lenses.
You should remove contact lenses before using this medicine and wait for at least 15 minutes before putting the lenses back.

Benzalkonium has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised.Patients should be monitored in case of prolonged use.

This product contains polysorbate 80. Polysorbates can cause allergic reactions.

4.5 Interactions with other medicinal products and other forms of interaction

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

Interactions with tobramycin after systemic administration have been reported. However, systemic absorption of tobramycin after topical ocular administration is so low that the risk of any interactions is minimal.

In case systemic treatment with aminoglycoside antibiotics is administered concomitantly, caution should be exercised to monitor the total serum concentration to ensure that an appropriate therapeutic level is maintained.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of use during pregnancy in humans has not been established. There are no or limited amount of data from the topical ocular use of tobramycin in pregnant women. Tobramycin does cross the placenta into the foetus after intravenous or intramuscular dosing in pregnant women. Tobramycin is not expected to cause ototoxicity from *in utero* exposure. A study with oral and parenteral aminoglycosides (including tobramycin) in pregnant women showed no detectable risk to the foetus.
Systemic treatment with animoglycosides has caused damage to the acoustic nerve and eventual deafness. Since systemic absorption after topical eye instillation is low, the risk is considered low when EYETOBRIN is used. Studies in animals have shown reproductive toxicity after systemic administration, at exposures considered sufficiently in excess of the maximum human ocular dosage delivered from EYETOBRIN, so they are of limited clinical significance. It has not been shown that tobramycin induces teratogenicity in rats or rabbits (section 5.3)

EYETOBRIN is not recommended during pregnancy as well as women of childbearing potential without contraception.

Breastfeeding

Safety for use during human breastfeeding has not been established.

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. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from EYETOBRIN therapy taking into account the benefit of breastfeeding 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 EYETOBRIN on human fertility.

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may affect your ability to drive or operate machines. If blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile
In clinical studies, the most frequently reported adverse reactions were ocular hyperaemia and discomfort occurring in 1.4 and 1.2 % of patients.

Tabulated list of adverse reactions.
The following adverse reactions have been reported with EYETOBRIN during clinical trials or during post marketing experience and 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) and very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**Frequency**	**Adverse reaction**
Immune system disorders	Uncommon	hypersensitivity
	Not known	anaphylactic reaction
Nervous system disorders	Uncommon	headache
Eye disorders	Common	ocular discomfort, ocular hyperaemia, eye irritation
	Uncommon	punctate keratitis, keratitis, corneal epithelial damage, vision disorder, vision blurred, eye allergy, erythema of the eyelid, eye itching, conjunctival oedema, eyelid oedema, eye pain, eye pruritus, ocular excretion, eyelid disorder, lacrimation increased
	Not known	itching of the eyelid
Skin and subcutaneous tissue disorders	Uncommon	urticaria, dermatitis, blepharopathy, leukoderma, pruritus, dry skin
	Not known	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). Sensitivity to topically administered aminoglycosides may occur in some patients (see section 4.4).

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: ophthalmologicals, antimicrobials, antibiotics
ATC code: S01AA12

Mechanism of action

Tobramycin is a potent, broad-spectrum, fast 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 can occur via two main mechanisms: a) interference with the transport of tobramycin within the cell and b) inactivation of tobramycin by several aminoglycoside modifying enzymes, such as adenylating, phosphorylating and acetylating enzymes. Genetic information for the production of inactivation enzymes may be stored in the bacterial chromosome or in plasmids. Cross-resistance to other aminoglycosides may also occur.

Breakpoints

The breakpoints and the *in vitro* range, as mentioned below, are based on systemic tobramycin use. They might not be applicable to topical use of the product, as topical use results in higher concentrations and the physical/chemical conditions may affect the activity of the drug product at the site of administration.

The following breakpoints are defined for tobramycin by EUCAST

- *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
- Other species S ≤ 2 mg/L, R > 4 mg/L

Resistance against certain pathogens

The following information gives only an approximate guidance on probabilities whether bacteria will be susceptible to tobramycin in EYETOBRIN. Bacterial species that have recovered from external eye infections, like the ones observed in conjunctivitis, are listed below. *In vitro* studies have shown tobramycin to be active against most strains of microorganisms listed below also. The prevalence of 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 the agent in at least some types of infections is questionable.

USUALLY SENSITIVE SPECIES

Aerobic Gram-Positive Microorganisms

- *Corynobacterium* spp.
- *Stapylococcus aureus* (Methicillin-susceptible-MSSA)
- *Staphylococcus epidermidis* (Methicillin-susceptible)
- Other Coagulase-negative Staphylococci

Aerobic Gram-Negative Microorganisms

- *Acinetobacter calcoaceticus*
- *Enterobacter aerogenes*
- *Escherichia coli*
- *Haemophilus aegyptius*
- *Haemophilus influenzae*
- *Klebsiella pneumoniae*
- *Morganella morganii*
- *Moraxella lacunata*
- Certain species of Neisseria
- *Proteus mirabilis*

- Most strains of *Proteus vulgaris*
- *Pseudomonas aeruginosa*

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-Positive Microorganisms

- *Enterococcus* spp.
- *Staphylococcus aureus* (Methicillin-resistant-MRSA)
- *Staphylococcus epidermidis* (Methicillin-resistant)
- *Streptococcus pneumoniae*
- *Streptococcus* spp.

Aerobic Gram-Negative Microorganisms

- *Burkholderia cepacia*
- *Stenotrophomonas maltophilia*

Anaerobic microorganisms

- Strict anaerobic microorganisms

Others

- *Chlamydia* spp.
- *Mycoplasma* spp.
- *Rickettsia* spp.

Bacterial susceptibility studies show that microorganisms resistant to gentamicin retain their sensitivity to tobramycin, in some cases.

Clinical trials data

Summary of safety data from clinical trials are presented in section 4.8

Elderly

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

Pediatric population

Over 600 pediatric patients were participated in 10 clinical trials with ocular drops or ocular ointment of tobramycin for the treatment of bacterial conjunctivitis or blepharitis. The patients ranged in age from 1 to 18 years. Overall, the safety profile in pediatric patients was comparable to that of adult patients. For children under 1 year of age, there are no dosage recommendations due to lack of data.

5.2 Pharmacokinetic properties

Absorption

Tobramycin is poorly absorbed through the cornea and conjunctiva when administered by topical ocular route. After topical administration of tobramycin 0.3% w/v, a peak concentration of 3 µg/ mL is reached in the aqueous humour after 2 hours, followed by a rapid decline. In addition, systemic absorption of tobramycin in humans is low after topical administration. However, a single dose of tobramycin 0.3 % w/v releases 527± 428 µg/mL of tobramycin to human tears after ocular administration. Ocular surface concentration generally exceeds the minimum inhibitory concentration (MIC) of most resistant strains isolated (MIC > 64 µg/mL).

Distribution

The systemic volume of distribution is 0.26 L/kg in humans. Tobramycin has a low binding affinity to plasma proteins, at a percentage of 0-30%.

Biotransformation

Tobramycin is primarily excreted unchanged in the urine.

Elimination

Tobramycin is excreted rapidly and extensively in the urine, through glomerular filtration, as an unmodified drug. Systemic clearance of tobramycin was 1.45 ± 0.19 mL/min×kg in patients of normal weight following intravenous administration and its systemic clearance decreased proportionally to renal function. The elimination half-life of tobramycin is approximately 2 hours.

Linear/Non-linear pharmacokinetics

Ophthalmic or systemic absorption with increasing administration concentrations after topical administration of tobramycin has not been evaluated. Therefore, the linearity of exposure to topical ocular dose cannot be established.

Pharmacokinetics/Pharmacodynamics

There is no specified relation of pharmacokinetics/pharmacodynamics for the product EYETOBRIN. Published *in vitro* and *in vivo* studies have shown that tobramycin has a prolonged effect after administration, which suppresses the bacterial growth, despite low concentrations in plasma. Studies of systemic administration of tobramycin have reported higher concentrations in single dose system than in multiple dose system. However, based on current indications, systemic administration of a single daily dose is just as effective as administering multiple daily doses. Tobramycin has concentration-dependent antimicrobial activity. By increasing antibiotic levels above the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC), greater efficacy is achieved.

Use in patients with hepatic and renal impairment

The pharmacokinetics of tobramycin using eye drops have not been studied in these patient groups.

Effect of age in pharmacokinetics

There is no change in pharmacokinetics of tobramycin in elderly people compared to younger adults.

Pediatric population

Aminoglycosides, including tobramycin, have often been administered in children, infants and neonates to treat severe Gram-negative infections. EYETOBRIN has been approved for administration in children. Clinical pharmacology of tobramycin in children has been described after systemic administration. Total clearance increased and distribution volume decreased with age, while lower C_{max} values were found compared to adults.

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 for low-dose short-term courses of therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid
Sodium chloride
Sodium sulfate Anhydrous
Polysorbate 80
Benzalkonium chloride
Water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Any remaining solution should be discarded 28 days after first opening.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

The product is available in 5 mL plastic LDPE vial with a LDPE dropper tip and a white screw cap.

6.6 Instructions for use/handling

Any unused medicinal product or waste material should be disposed in accordance with local regulations in force.

7. MANUFACTURER

COOPER S.A. Pharmaceuticals
64 Aristovoulou St.
118 53 Athens
GREECE

8. MARKETING AUTHORISATION HOLDER

Medomie Pharma Ltd., POB 742, Givatayim 5358305

9. MARKETING AUTHORISATION NUMBER

179-19-37677-99

Approved in July 2025.