SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
OFTAMYCIN 0.3% Eye Drops, Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Tobramycin 3 mg/mL
Excipients:
Benzalkonium chloride 0.1 mg/mL
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM
Eye drops, solution.
Clear and colorless solution. No particles should be observed.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
A topical antibiotic indicated in the treatment of external infections of the eye and its adnexa caused by susceptible bacteria.

4.2 Posology and method of administration
For ocular use.

Posology/frequency and duration of administration
Usage in adolescents and adults, including the elderly:
In mild to moderate diseases, 1 or 2 drops are instilled into the conjunctival sac of the affected eye(s) every 4 hours for 7 days.

In severe infections, 2 drops are instilled into the conjunctival sac of the affected eye(s) hourly until recovery is achieved. The dosage should be reduced prior to discontinuation of the treatment.

As with other antibiotics, the bacterial response to the treatment should be appropriately monitored.

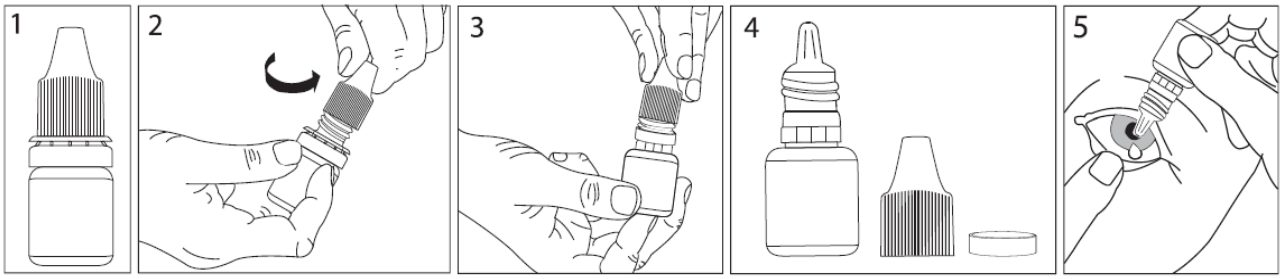
The treatment period is usually 7 to 10 days.

Method of administration
This medicine is for topical use only. It should not be injected or not be swallowed.

To prevent contamination of the dropper tip and solution, care should be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle.

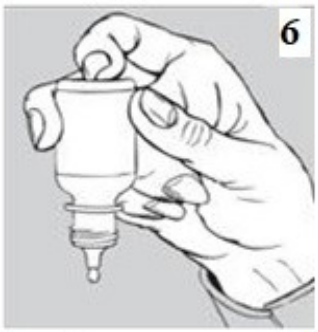
Closing of the eyelid after instilling or pressing gently on the nasolacrimal duct is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

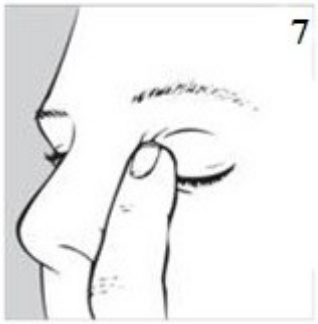
In case of concomitant therapy with other topical ocular medicines, an interval of 10-15 minutes should be allowed between two applications. Eye ointments should be applied last.



Administer OFTAMYCIN only to your eyes.

- Get the OFTAMYCIN bottle and a mirror.
- Wash your hands.
- Open the cap of the bottle (see Figure 2).
- Remove the ring under the cap (see Figure 3 and Figure 4).





- Hold the bottle, pointing down, between your thumb and middle finger.
- Tilt your head back. Pull down your lower eyelid with a clean finger until there is a pocket between your eyelid and your eye. The drop will go in here. (see Figure 5)
- Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
- Do not touch your eye, eyelid, surrounding areas or other surfaces with the dropper. Drops may be contaminated with germs.
- Gently press on the base of the bottle to release one drop from OFTAMYCIN at a time. (see Figure 6)
- After using OFTAMYCIN, release your eyelid, close your eye, place a finger on the inner corner of your eye and press it towards your nose. This prevents OFTAMYCIN from getting into the rest of the body. (see Figure 7)
- If you are using the drops in both eyes, repeat the same steps for your other eye.
- Close the bottle cap firmly immediately after use.

Additional information on special populations

Renal/Hepatic impairment

Ocular use of tobramycin results in minimal systemic exposure. If tobramycin is used concomitantly with aminoglycosides in systemic therapy, consideration should be given to monitoring the total serum concentration until it is ensured that an appropriate therapeutic level is achieved.

Pediatric population

The safety and efficacy of OFTAMYCIN is demonstrated in pediatric patients of 1 years and over at the same dose as adults (during 7-10 days for 2-3 times a day).

Efficacy and safety information is not available for children under 1 year of age.

Geriatric population

No special dosage adjustment is necessary in elderly patients.

4.3 Contraindications

It is contraindicated in patients with hypersensitivity to tobramycin or any of the other 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 pruritus, urticaria, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If hypersensitivity develops, treatment should be discontinued.

Cross-hypersensitivity with other aminoglycosides can occur. 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. If hypersensitivity develops with this product, the treatment should be discontinued and other drugs should be used (see section 4.8).

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Caution is advised when tobramycin is used concomitantly with systemic aminoglycosides and care should be taken to monitor total serum concentrations (see section 4.8).

Caution should be exercised when prescribing OFTAMYCIN 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 may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Patients should be advised not to wear contact lenses during ocular infection.

OFTAMYCIN contains benzalkonium chloride as preservative, which may cause eye irritation and is known to discolor soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of OFTAMYCIN and wait at least 15 minutes before reinsertion.

After application of OFTAMYCIN eye drops, following measures should be taken to reduce systemic absorption:
- Eyelid should be kept closed for 2 minutes,
- Lacrimal duct should be closed with the finger for 2 minutes.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with OFTAMYCIN. No clinically relevant interactions have been described with topical ocular dosing of OFTAMYCIN.

Interactions with tobramycin have been reported after systemic administration. However, any interaction risk of tobramycin with systemic absorption following topical application has been found to be minimal.

Concomitant and/or sequential use of an aminoglycoside (OFTAMYCIN) and other systemic, oral or topical drugs that have neurotoxic, ototoxic, or nephrotoxic effects may result in additive toxicity and should be avoided, whenever possible.

Topical corticosteroids, when used in combination with OFTAMYCIN, may mask the clinical signs

of bacterial, fungal, or viral infections and may suppress hypersensitivity reactions.

4.6 Fertility, pregnancy and lactation

General advice

Pregnancy category is B.

Women of childbearing potential/Birth control (Contraception)

No special measures have been defined for women who do not use any contraceptive method and have childbearing potential.

Pregnancy

There is no or limited data from the use of topical ocular tobramycin in pregnant women. Tobramycin does cross the placenta into the fetus after intravenous dosing in pregnant women. Tobramycin is not expected to cause ototoxicity from in utero exposure.

Studies in animals have shown reproductive toxicity after systemic exposure and at dosages considered sufficiently in excess of the maximal human dose in therapeutic use derived from tobramycin eye drops so as to have limited clinical relevance. Tobramycin has been proven not to cause teratogenicity in rats or rabbits (see section 5.3).

OFTAMYCIN should be used during pregnancy only if clearly needed.

Lactation

In systemic treatment, tobramycin passes to breast milk in amounts, which may have a significant risk to affect the child (after intravenous or intramuscular administration of up to 150 mg twice daily). It is not known whether tobramycin is excreted in human milk following topical ocular administration. Although the risk cannot be ignored in breastfed infant, systemic exposure is low when topically instilled and the risk in OFTAMYCIN usage is estimated as low. When this drug is prescribed to breastfeeding mothers, this fact should be taken into consideration.

Since most drugs are excreted in breast milk, a decision should be made whether to discontinue breastfeeding or discontinue/avoid the treatment, taking into consideration the benefit of breastfeeding for the child and the benefit of OFTAMYCIN treatment for the nursing mother.

Reproductive ability / Fertility

Studies have not been performed to evaluate the effect of topical ocular use of OFTAMYCIN on human fertility.

4.7 Effects on ability to drive and use machines

OFTAMYCIN has no or negligible influence on the ability to drive and use machines. As with any other eye preparation, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If temporary blurred vision occurs at application, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile:

In clinical trials, the most frequently reported adverse reactions were ocular hyperemia and ocular discomfort, occurring in approximately 1.4% and 1.2% of patients.

Adverse reactions are classified as follows: 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). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions were obtained from clinical trials and post-marketing spontaneous reports. The following adverse reactions were observed following ophthalmic use of OFTAMYCIN eye drops and/or ointment:

Immune system disorders
Uncommon: Hypersensitivity
Not known: Anaphylactic reaction

Nervous system disorders
Uncommon: Headache

Eye disorders
Common: Ocular discomfort, ocular hyperemia, eye allergy, eyelid pruritus
Uncommon: Keratitis, corneal abrasion, visual impairment, blurred vision, erythema of the eyelids, conjunctival edema, eye irritation, eye pain, dry eye, eye discharge, increased lacrimation, eye pruritus
Not known: Eye allergy, eyelid pruritus

Skin and subcutaneous tissue disorders
Uncommon: Urticaria, dermatitis, madarosis (eyelash loss), leukoderma (vitiligo), pruritus, dry skin
Not known: Stevens-Johnson syndrome, rash, erythema multiform, erythema

Additional information on special populations:
Hypersensitivity to topically applied aminoglycosides may occur in some patients (see section 4.4).

If tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration (see section 4.4).

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic tobramycin therapy (see section 4.4).

Pediatric population:
The frequency, type and severity of adverse reactions in children are expected to be the same as in adults. OFTAMYCIN 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 (see section 4.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose
Due to the characteristics of this product, no toxic systemic effects are to be expected with its ophthalmic use or in the event of accidental ingestion of the contents of one bottle.

Clinically symptoms of an overdose of OFTAMYCIN (punctate keratitis, erythema, increased lacrimation, edema and eyelid itching) may be similar to adverse effects seen in some patients.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologics, anti-infectives, antibiotics.
ATC code: S01AA12

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 adenylating, 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 i*n vitro* spectrum as mentioned as follows 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 > 4mg/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 as follows 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 accolens*,
- *Corynebacterium bovis*,
- *Corynebacterium macginleyi*,

- *Corynebacterium pseudodiphtheriticum*,
- *Kocuria kristinae*,
- *Staphylococcus aureus* (methicillin susceptible -MSSA),
- *Staphylococcus haemolyticus* (methicillin susceptible - MSSH),
- *Staphylococcus epidermidis* (coagulase-positive and -negative),
- Streptococci (including some of the group A beta-hemolytic species, some non-hemolytic species, and some *Streptococcus pneumonia*).

Aerobic Gram-negative microorganisms:
- *Acinetobacter junii*,
- *Acinetobacter ursingii*,
- *Citrobacter koseri*,
- *Escherichiacoli*,
- *Klebsiella oxytoca*,
- *Klebsiella pneumoniae*,
- *Moraxella catarrhalis*,
- *Moraxellaoslonensis*,
- *Morganella morganii*,
- *Neisseria perflava*
- *Proteus mirabilis*,
- *Pseudomonas aeruginosa*,
- *Serratia liquifaciens*.
- *Acinetobacter calcoaceticus*,
- *Enterobacter aerogenes*,
- *H. aegyptius*,
- *Haemophilus influenzae*,
- *Moraxella lacunata*,
- Most *Proteus vulgaris* strains,

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 haemolyticus* (methicillin resistant - MRSH);
- Staphylococcus, other coagulase-negative spp.;
- *Serratia marcescens*.

INHERENTLY RESISTANT ORGANISMS:
Aerobic Gram-positive microorganisms:
- *Enterococcifaecalis*,
- *Staphylococcus aureus* (methicillin resistant - MRSA),
- *Streptococcus mitis*,
- *Streptococcus pneumoniae*,
- *Streptococcus pyogenes*,
- *Streptococcus sanguis*.

Aerobic Gram-negative microorganisms:
- *Chryseobacterium indologenes*,
- *Haemophilus influenzae*,
- *Stenotrophomonas maltophilia*,
- *Burkholderia cepacia*.

Anaerobic bacteria:
- *Propionibacterium acnes*.

Bacterial susceptibility studies demonstrate that in some cases, microorganisms resistant to gentamicin retain susceptibility to tobramycin.

Pediatric population:
Over 600 pediatric patients were enrolled in 10 clinical studies with tobramycin eye drops or eye ointment for the treatment of bacterial conjunctivitis, blepharitis or blepharoconjunctivitis. These patients ranged in age from 1 year to 18 years. Overall, the safety profile in pediatric patients was comparable to that of adult patients. For children younger than age 1, no recommendation on a posology can be made due to a lack of data.

Pharmacokinetics / Pharmacodynamics relationship:
A specific pharmacokinetic/pharmacodynamic relationship has not been established for OFTAMYCIN. 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).

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

5.2 Pharmacokinetic properties
General Properties
Absorption:
Tobramycin is poorly absorbed across rabbit cornea and conjunctiva, and minimal amounts are absorbed into the eye after topical administration of tobramycin.

Additionally, systemic absorption of tobramycin is poor clinically after topical ocular administration of tobramycin products with similar concentration to OFTAMYCIN (0.3%). The high concentration of tobramycin in OFTAMYCIN delivers tobramycin at the site of infection (ocular surface) at a concentration generally much higher than the concentration of the most resistant isolates (MICs > 64 mcg/mL; tobramycin concentration in human eye after a single dose of OFTAMYCIN is 848 ± 674 mcg/mL, 1 minute after dosing).

Tobramycin concentration in healthy human tears remains over MIC_{90} (16 mcg/mL as described for ocular isolates) at least up to 44 minutes post dosing of a treatment with OFTAMYCIN.

Distribution:
The 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.

Elimination:
Tobramycin is excreted rapidly and extensively in the urine via glomerular filtration, primarily as unchanged drug. The plasma half-life is approximately two hours. The reported systemic clearance in adult subjects with normal renal function ranged from of 0.05 - 0.1 L/hr/kg and decreased with decreased renal function.

Linearity/non-linearity:
Ocular or systemic absorption with increasing dosing concentrations after topical ocular administration has not been tested. Therefore, the linearity of exposure with ocular dose could not be established.

Use in hepatic and renal impairment:
OFTAMYCIN eye drops and eye ointment have not been studied in these patient populations. However, due to low systemic absorption of tobramycin after topical administration of this product, dose adjustment is not necessary.

Use in pediatrics:
OFTAMYCIN may be used in pediatric patients (1 year of age and older) at the same dose as in adults. However, limited information is available in pediatric patients younger than 1 year of age.

5.3 Preclinical safety data
Tobramycin is very poorly absorbed from the gastrointestinal tract. High parenterally administered doses of tobramycin have been reported to cause renal toxicity in rats and dogs, and ototoxicity in cats.

Preclinical studies have shown high systemic doses of tobramycin were administered using the intra-peritoneal (IP) route at 30 and 60 mg/kg to rats during periods of major organogenesis; which caused increases in glomerular density and the loss of cortical area within the kidney in the fetuses and in newborn rats. Similarly in other laboratory animals, aminoglycoside antibiotics are considered to be ototoxic.

Prolonged systemic treatment of tobramycin in cats administered using the subcutaneous route at 20, 40 and 80 mg/kg/day for 30 weeks resulted in dose-dependent degeneration of hair cells and supporting sensory structures in the ear. However, the human ear is now perceived as being anatomically more protected and thereby, less vulnerable to aminoglycoside-induced injury than with the animal models.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Benzalkonium chloride

Tyloxapol
Sodium chloride
Anhydrous sodium sulphate
Boric acid
Sodium hydroxide
Sulfuric acid
Water for injection

6.2 Incompatibilities
There is no known pharmaceutical incompatibility.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 25°C at room temperature.
Once the bottle is opened, this product should be used within 4 weeks (28 days). During this period, the product can be stored below 25°C at room temperature.

6.5 Nature and contents of container
An opaque white, low-density polyethylene bottle (LDPE), containing 5 mL eye drops, with LDPE dropper tip and orange HDPE screw cap is used as the packaging material. Each cardboard box contains one bottle and one package leaflet.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece - İSTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER
2015/93

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 07.02.2015
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT
16.08.2023