SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OFTAMYCIN-DX 0.3%+0.1% Sterile Eye Ointment
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g of eye ointment contains:
Active substance:
Tobramycin 3 mg
Dexamethasone 1 mg
Excipient(s) with known effect:
For a 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

It is indicated in adults and in children aged 2 years and older for the treatment of ocular infection and ocular inflammatory conditions at risk of ocular infection, for which a corticosteroid is indicated.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
According to the prescription, apply a small amount (about 1 cm of ointment) to the conjunctival sac 3 to 4 times a day.

Method of administration:
For ocular use only. Not suitable for injection or oral use.
The tip of the tube should not touch the eye.
Nasolacrimal occlusion and eye closure are recommended after application. This may reduce the systemic absorption of the ophthalmic medicinal product and result in reduced systemic side effects. If more than one topical eye medicine is being used, at least 5 minutes should be waited between each application. Eye ointment should be used last.

Additional information on special populations:
Renal / Hepatic impairment:
OFTAMYCIN-DX has not been studied in these patient populations.

Pediatric population:
OFTAMYCIN-DX can be used in children aged 2 years and older at the same doses as adults. The currently available data are described in section 5. Efficacy and safety in children under 2 years of age are not yet known and there are no available data on this issue.
OFTAMYCIN-DX is not recommended for use in infants and young children unless absolutely necessary.

Geriatric population:
No special dose adjustment is required in the elderly.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Herpes Simplex Keratitis
- Smallpox vaccination, chickenpox or other viral infections of the cornea and conjunctiva
- Fungal disease or untreated parasitic infections of the eye.
- Mycobacterial infections of the eye caused by acid-fast bacilli such as, but not limited to, *Mycobacterium tuberculosis*, *Mycobacterium leprae* or *Mycobacterium avium*.
- Ocular hypertension
- Acute purulent endophthalmitis, purulent conjunctivitis, and purulent and herpetic blepharitis that may be masked or aggravated by corticosteroids
- Stye

4.4 Special warnings and precautions for use

- Some patients may develop sensitivity to topically applied aminoglycoside antibiotics. 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 the use of the medicinal product, treatment should be stopped.
- 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 aminoglycoside therapy. Caution should be exercised when OFTAMYCIN-DX is administered concomitantly with systemic aminoglycoside therapy.
- Prolonged use of corticosteroids via the topical ophthalmic route can lead to ocular hypertension and/or glaucoma with damage to the optic nerve, reduced visual acuity and visual field damage, and posterior subcapsular cataract formation. Intraocular pressure should be monitored regularly and frequently in patients on long-term corticosteroid ophthalmic therapy. This is particularly important in pediatric patients treated with dexamethasone-containing products, as the risk of corticosteroid-induced ocular hypertension may be greater in children under six years of age and may occur earlier than the response to steroids in adults. The frequency and duration of treatment should be carefully assessed and intraocular pressure (IOP) should be monitored from the start of treatment. There is a higher risk of corticosteroid-induced increase in IOP occurring earlier in pediatric patients. The risk of high intraocular pressure is increased in predisposed patients (e.g. diabetic patients) due to corticosteroids and/or cataract formation.
- Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ophthalmic dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). In these cases, treatment should be discontinued progressively.
- Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections.
- Corticosteroids can reduce resistance to and enhance the development of bacterial, viral, fungal or parasitic infections and mask clinical signs of infection.
- The possibility of fungal infection should be considered in persistent corneal ulcers where corticosteroid therapy is used. If a fungal infection develops, corticosteroid treatment should be stopped.

- Prolonged use of tobramycin may result in overgrowth of organisms that are not sensitive to treatment, including fungi. If superinfection occurs, appropriate treatment should be initiated immediately.
- Perforation is known to occur with the use of topical corticosteroids in diseases that cause thinning of the cornea or sclera.
- Topical ophthalmic corticosteroids may slow corneal wound healing. Topical NSAIDs are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems (see section 4.5).
- It is recommended not to wear contact lenses during treatment of inflammation or eye infection.
- Contact with soft contact lenses should be avoided.

Wearing contact lenses during treatment of ocular infection or inflammation is not recommended. If patients are allowed to wear contact lenses, they should be asked to remove them before OFTAMYCIN-DX is administered and to wait at least 15 minutes before reinsertion.

Caution should be exercised when prescribing to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson's disease. Aminoglycosides may increase muscle weakness due to their potential effects on neuromuscular function.

Visual disturbances
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes, which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

4.5 Interaction with other medicinal products and other forms of interaction
The concomitant use of topical NSAIDs and topical corticosteroids can potentially increase wound healing problems. In patients treated with ritonavir, plasma concentrations of dexamethasone may increase (see section 4.4).

CYP3A4 inhibitors (including ritonavir and cobicistat) may reduce dexamethasone clearance, resulting in increased effects and adrenal suppression/Cushing's syndrome. The combination should be avoided unless the benefit outweighs the risk of systemic side effects of corticosteroids, in which case patients should be monitored for systemic effects of corticosteroids.

Additional information on special populations:
No data are available.

Pediatric population:
No data are available.

4.6 Pregnancy and lactation
General advice
Pregnancy category is C.

Women with childbearing potential / Contraception
No studies have been conducted to evaluate the effect of topical tobramycin/dexamethasone administration on fertility.

Pregnancy
There are insufficient data on the use of tobramycin/dexamethasone in pregnant women.
Animal studies are insufficient for effects on pregnancy and/or embryonal/fetal development and/or delivery and/or postnatal development (see section 5.3). The potential risk for humans is unknown. OFTAMYCIN-DX should not be used during pregnancy unless necessary.
Tobramycin crosses the placenta to the fetus after intravenous administration in pregnant women. Tobramycin is not expected to cause ototoxicity following exposure in utero. Prolonged or repeated use of corticoids during pregnancy has been associated with an increased risk of intrauterine growth retardation. Children born to mothers who received high doses of corticosteroids during pregnancy should be carefully observed to detect any signs of hypoadrenalism. Animal studies have shown reproductive toxicity following systemic administration of tobramycin and dexamethasone. These effects were observed at doses considered to be adequate above the maximum dosage for ocular use administered to the mother. Tobramycin has not been observed to cause teratogenicity in rats and rabbits. Administration of 0.1% dexamethasone caused fetal abnormalities in rabbits (see section 5.3).
OFTAMYCIN-DX should be used in pregnancy only if the potential maternal benefits outweigh the potential fetal risks.

Breastfeeding
It is not known whether tobramycin or dexamethasone for topical ophthalmic use is excreted in breast milk. Tobramycin is excreted in breast milk after systemic administration. There are no data on whether dexamethasone passes into human milk. It is unlikely that tobramycin and dexamethasone will be present in breast milk in amounts that can be measured or that may affect children after the medicine has been applied topically. However, the risk to babies cannot be ignored. OFTAMYCIN-DX should not be used during breastfeeding unless the potential benefits outweigh the potential risk.

Fertility
No studies have been conducted to evaluate the effects of topical ocular tobramycin on human and animal fertility. Clinical data to assess the effect of topical ocular dexamethasone on male or female fertility is limited. Dexamethasone had no adverse effect on fertility in a rat model with prior chorionic gonadotropin administration.

4.7 Effects on ability to drive and use machines
OFTAMYCIN-DX has no significant effect on driving and using machines. However, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after application of the medicine, 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 involving more than 1,600 patients, tobramycin/dexamethasone was administered up to six times daily. No serious ophthalmic or systemic adverse reactions related to tobramycin/dexamethasone or components of the combination have been reported in clinical studies. The most commonly reported adverse reactions with tobramycin/dexamethasone were eye pain, increased intraocular pressure, eye irritation (burning after instillation) and itching in less than 1% of patients.

The adverse reactions listed in the table below were reported during clinical trials with the tobramycin/dexamethasone combination and are classified into the following groups: very common (/1/10), common (≥1/100, <1/10), uncommon (/1/1,000, <1/100), rare (≥1/10,000, <1/1,000) very rare (<1/10,000). In each frequency group, adverse reactions were reported in order of decreasing severity.

System organ classification	Frequency	Adverse reaction
Immune system disorders	Unknown	Anaphylactic reactions, hypersensitivity
Endocrine disorders	Unknown	Cushing's syndrome, adrenal suppression (see section 4.4)
Nervous system disorders	Uncommon	Headache
	Unknown	Dizziness
Eye disorders	Uncommon	Eye pain, eye itching, ocular discomfort, ocular hypertension, conjunctival edema, increased intraocular pressure, eye irritation
	Rare	Keratitis, eye allergy, blurred vision (see also section 4.4), dry eye, ocular hyperemia
	Unknown	Eyelid edema, erythema of the eyelids, mydriasis, increased lacrimation
Respiratory, thoracic and mediastinal disorders	Uncommon	Runny nose, laryngospasm
Gastrointestinal disorders	Rare	Dysgeusia
	Unknown	Nausea, abdominal discomfort
Skin and subcutaneous tissue disorders	Unknown	Erythema multiforme, rash, facial swelling, itching

Description of selected adverse reactions
The following adverse reactions have been observed after use with dexamethasone ophthalmic suspension:

System organ classification	Frequency	Adverse reaction
Nervous system disorders	Common	Headache
Eye disorders	Common	Eye irritation*, ocular hyperemia*, eyelid erythema, abnormal sensation in the eye*
Respiratory, thoracic and mediastinal disorders	Common	Postnasal drip

The following adverse reactions have been observed after use with tobramycin ophthalmic solution:

System organ classification	Frequency	Adverse reaction
Eye disorders	Common	Ocular hyperemia*, eye pain*
	Uncommon	Eye itching*, ocular

		discomfort*, eye allergy, eyelid edema*, conjunctivitis*, glare, increased lacrimation*, keratitis*

* These adverse reactions were also observed with post-marketing tobramycin/dexamethasone.

Long-term use of topical corticosteroids may cause optic nerve damage and increased intraocular pressure, decreased visual acuity and visual field defects, subcapsular cataract formation and delayed wound healing.

Due to the presence of corticosteroids, there is a greater risk of perforation in disorders that cause thinning of the cornea or sclera, especially after prolonged treatment (see section 4.4).

The development of secondary infections has occurred following the use of combinations containing corticosteroids and antimicrobials. Long-term corticosteroid administration may facilitate the development of fungal infections of the cornea.

Serious adverse reactions such as neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients treated systemically with tobramycin (see section 4.4).

Some patients may develop sensitivity to topically applied aminoglycoside antibiotics (see section 4.4).

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 effects are to be expected with an overdose (even in the event of accidental ingestion of the contents of the tube). Overdose of OFTAMYCIN-DX applied topically can be washed out of the eyes with warm water.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiinflammatory agents and antiinfectives in combination; Corticosteroids and antiinfectives in combination; Dexamethasone and antiinfectives
ATC code: S01CA01

Mechanism of action
OFTAMYCIN-DX contains tobramycin, an antibiotic, and dexamethasone, a corticosteroid. Topical corticosteroids have anti-inflammatory effects and are widely used. They suppress some aspects of the inflammatory process such as edema, fibrin deposition, capillary dilatation, leukocyte migration, capillary proliferation, collagen deposition, scar formation and fibroblast proliferation. Topical corticosteroids are effective in acute inflammatory conditions in the conjunctiva, sclera, cornea, eyelid, iris and anterior segment of the eyeball and in eye allergy conditions.

Dexamethasone is one of the most powerful corticosteroids. Dexamethasone, which is essential for local treatment, is 2000 times more soluble than hydrocortisone and prednisolone. The exact mechanism of the anti-inflammatory effect of dexamethasone is unknown. It inhibits multiple inflammatory cytokines and induces multiple glucocorticoid and mineralocorticoid effects. Dexamethasone is a potent corticosteroid. Corticosteroids suppress the inflammatory response to many agents and may delay or slow healing. Since corticosteroids can suppress the body's defense mechanism against infections, an antimicrobial medicine may be used concomitantly when this inhibition is considered clinically significant.

Tobramycin is an antibacterial medicine that prevents bacterial growth by inhibiting protein synthesis.

Mechanism of resistance
Resistance to tobramycin occurs by different mechanisms. These included the following: 1) Changes of the ribosomal subunit in the bacterial cell; 2) Interference with intracellular transport of tobramycin; 3) Inactivation of tobramycin through a series of adenylation, phosphorylation and acetylating enzymes. The genetic information for the production of inactivating enzymes can be carried on bacterial or plasmid chromosomes. Cross-resistance with other aminoglycosides may occur.

Limit values
The limit values and *in vitro* spectrum listed below are based on systemic use. These limit values may not apply to topical ocular use of the medicinal product, as higher concentrations are achieved locally and local physical/chemical conditions may affect the activity of the product at the site of application. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the following limit values are set 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
- Non-species-associated S ≤ 2 mg/l, R > 4 mg/l

Clinical efficacy against specific pathogens
The information listed below provides only an estimate of the likelihood that microorganisms may be susceptible to tobramycin in this medicine. Bacterial species isolated from external infections of the eye that cannot be observed in conjunctivitis are presented here.

The prevalence of acquired resistance may vary geographically and over time for selected species; local knowledge of resistance is desirable, especially when treating serious infections. Specialist advice should be sought as necessary at a level where the local prevalence of resistance is such that the usefulness of tobramycin is questionable, at least in some types of infection.

GENERAL SENSITIVE SPECIES
Gram-positive microorganisms
Bacillus cereus
Bacillus megaterium

Bacillus pumilus
Bacillus thuringiensis

Corynebacterium macginleyi
Corynebacterium pseudodiphtheriticum
Kocuria kristinae
Staphylococcus aureus (sensitive to methicillin - MSSA)
Staphylococcus epidermidis
Staphylococcus haemolyticus (sensitive to methicillin - MSSH)
Stepptococci, other coagulative-negative species

Gram-negative microorganisms
Acinetobacter baumanii
Acinetobacter calcoaceticus
Acinetobacter junii
Acinetobacter ursingii
Citrobacter koseri
Enterobacter aerogenes
Escherichia coli
Haemophilus aegyptius
Klebsiella oxytoca
Klebsiella pneumoniae
Kocuria rhizophila
Morganella morganii
Moraxella catarrhalis
Moraxella lacunata
Moraxella oslonensis

Neisseria perflava
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia liquifaciens
Serratia marcescens

RESISTANT ORGANISMS
Gram-positive microorganisms
Enterococcus faecalis
Propionibacterium acnes
Staphylococcus aureus (sensitive to methicillin - MRSA)
Staphylococcus haemolyticus (sensitive to methicillin - MRSH)
Streptococcus mitis
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus sanguis

Gram-negative microorganisms
Chryseobacterium indologenes
Haemophilus influenzae
Stenotrophomonas maltophilia

Pediatric population:
The safety and efficacy of the tobramycin/dexamethasone combination in children has been established based on extensive clinical experience, but only limited data are available. In a clinical study with tobramycin/dexamethasone combination, 29 pediatric patients aged 1 to 17 years were treated with tobramycin/dexamethasone combination 1 or 2 drops every 4 or 6 hours for 5 or 7 days for the treatment of bacterial conjunctivitis. In this study, no difference in safety profile was observed between adults and pediatric patients.

Pharmacokinetic/pharmacodynamic relationship:
No specific pharmacokinetic/pharmacodynamic relationship has been established for the tobramycin/dexamethasone combination. Published *in vivo* and *in vitro* studies have shown that tobramycin has a long-lasting post-antibiotic effect, with effective suppression of bacterial growth even in the presence of low serum medicine concentrations.

In studies of systemic administration of tobramycin, higher maximum concentrations were reported with once-daily administration compared with a daily repeated administration regimen. However, the available evidence suggests that once-daily practice is as effective as multiple daily practices. Tobramycin has concentration-dependent bactericidal activity and greater efficacy with increasing levels of antibiotic above the MIC (Minimum Inhibitory Concentration) or MBC (Minimum Bactericidal Concentration).

Geriatric population:
No differences in efficacy and safety were observed in elderly patients compared to the adult population.

5.2 Pharmacokinetic properties

General properties

Absorption:
Following topical ocular application of tobramycin, it is poorly absorbed through the cornea and conjunctiva in humans. A peak concentration of 3 mcg/ml in aqueous humor is reached 2 hours after topical application of 0.3% tobramycin, followed by a rapid decline. However, the tobramycin/dexamethasone combination reaches 542 ± 425 mcg/ml tobramycin in human tears 2 minutes after ocular administration, a concentration that often exceeds the MIK of many resistant organisms (MIK > 64 mcg/ml).

In humans, peak dexamethasone concentration in the aqueous humor is usually reached 2 hours after administration of the tobramycin/dexamethasone combination at an average of 32 ng/ml.

Systemic tobramycin absorption following administration of the tobramycin/dexamethasone combination is low, with plasma concentrations generally below the quantification threshold.

After administration of the tobramycin/dexamethasone combination, very low dexamethasone plasma concentrations were detected at values below 1 ng/ml.

The bioavailability of oral dexamethasone is in the range of 70-80% in normal subjects and patients.

Distribution:
For tobramycin, the systemic volume of distribution is 0.26 l/kg in humans. Also in humans, tobramycin binding to plasma proteins is less than 10%.

The sustained volume of distribution for dexamethasone is 0.58 l/kg after intravenous administration. Dexamethasone binding to plasma proteins is 77%.

Biotransformation:
Tobramycin is not metabolized, whereas dexamethasone is metabolized mainly to 6β-hydroxymethasone and to a lesser extent to 6β-hydroxy-20-dihydrodexamethasone.

Elimination:
Tobramycin is rapidly and extensively excreted in the urine via glomerular filtration, primarily as unchanged medicine. Systemic clearance in normal weight patients after intravenous administration is 1.43 ± 0.34 mL/min/kg and decreases in proportion to renal function. The plasma half-life is approximately 2 hours.

After systemic administration of dexamethasone, clearance is 0.125 l/h/kg, with 70% of the dose converted to metabolites, while 2.6% is recovered as an unchanged medicine dose. The half-life was assessed at around 3-4 hours and was slightly longer in males. This observed difference was attributed to differences in volume of distribution and body weight and not to changes in systemic clearance of dexamethasone.

Linearity / Non-linearity of pharmacokinetics:
Ocular or systemic exposure has not been evaluated with increasing tobramycin dose concentrations following topical ocular application of tobramycin. Therefore, the linearity of exposure with topical ocular dose could not be determined. The mean C_{max} for Dexamethasone at a topical ocular dose concentration of 0.033% with 0.3% tobramycin appeared to be lower than the tobramycin/dexamethasone combination at approximately 25 ng/ml; however, this decrease was not proportional to dose.

Characteristics in patients
Renal / Hepatic impairment:
The pharmacokinetics of tobramycin or dexamethasone after administration of the tobramycin/dexamethasone combination has not been studied in these patient populations.

Effect of age on pharmacokinetics
There is no change in tobramycin pharmacokinetics in older patients when compared to younger adults. No correlation between age and plasma concentrations of dexamethasone was observed after oral administration of dexamethasone as well.

5.3 Preclinical safety data
Preclinical data from conventional ocular toxicity studies, repeated dosing, genotoxicity studies or carcinogenic studies have not revealed any special risk to humans from topical ocular exposure to tobramycin or dexamethasone. Effects in non-clinical reproductive and developmental studies with tobramycin and dexamethasone 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

Chlorobutanol anhydrous
Liquid paraffin
White paraffin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C. Do not freeze.
Once opened, the tube should be used within 28 days provided that it is stored at room temperature below 25°C. Close the cap of the tube tightly when not in use.

6.5 Nature and contents of container

Collapsible aluminum tube with epoxy phenolic coating inside, white plastic application tip and white plastic cap. Available in a tube of 3.5 g.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

DEVA HOLDİNG A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER(S)

2020/182

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization : 21.08.2020
Renewal of the authorization :

10. DATE OF REVISION OF THE TEXT