SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEMOXIDEX 0.5% + 0.1% Eye Drops, Solution
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution contains:
Active substances:
Moxifloxacin hydrochloride 5.45 mg (equivalent to 5 mg moxifloxacin)
Dexamethasone sodium phosphate 1.1 mg (equivalent to 1 mg dexamethasone phosphate)
Excipients with known effect:
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
A clear, greenish-yellow solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DEMOXIDEX is indicated:

- For the topical treatment of bacterial infections caused by moxifloxacin-sensitive strains in the anterior segment of the eye requiring a combination of corticosteroids and antibiotics.
- For steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.
- For the treatment of inflammation and prophylaxis of infection following cataract surgery.

4.2. Posology and method of administration

Posology / Frequency of administration and duration
For adults and elderly:
It is administered as 1 drop three times a day. Treatment duration should be decided by the physician. If clinical improvement is not observed within 5 days, the accuracy of the diagnosis and/or treatment should be reconsidered. The duration of treatment may vary depending on the severity of the disease and the clinical and bacteriological course of the infection.

Method of administration
To avoid contamination of the dropper tip and the solution, the dropper tip should not be exposed to the eyelids, surrounding skin, or other surfaces. When not in use, the bottle should be tightly closed.

To prevent absorption of drops through the nasal mucosa, especially in newborns or young children, tear ducts should be closed for 2-3 minutes after application by a gentle pressure with fingers.

In case of treatment with other topical ocular products, an interval of 5-10 minutes should be allowed between successive administrations.

Additional information on special populations
Renal/Hepatic impairment
The eye drop form of the moxifloxacin and dexamethasone combination (DEMOXIDEX) has not been studied in patients with renal and hepatic impairment. Oral moxifloxacin pharmacokinetic parameters have not shown significant differences in patients with mild to moderate hepatic and renal impairment. No studies have been conducted in patients with severe hepatic impairment. Due to the low systemic exposure from topical administration, no dose adjustment is necessary for

DEMOXIDEX in patients with hepatic impairment. Oral moxifloxacin pharmacokinetic parameters do not show significant differences in patients with mild, moderate, or severe renal impairment. No dose adjustment is required for DEMOXIDEX in patients with renal impairment.

Pediatric population
No dose adjustment is necessary (for detailed information, see section 4.4 Special warnings and precautions for use).

Due to the presence of dexamethasone, treatment in children should be limited to the shortest possible duration (preferably less than 5 days) due to the risk of adrenal suppression.

Geriatric population
No dose adjustment is necessary in elderly patients.

4.3. Contraindications
DEMOXIDEX is contraindicated in individuals with hypersensitivity to dexamethasone, moxifloxacin, other quinolones, or any of the components of this product.

Due to its dexamethasone content, it should not be used in corneal injuries and ulcers, superficial *Herpes simplex* keratitis (dendritic keratitis) and acute infection periods of viral diseases of the cornea and conjunctiva *(*such as *Herpes simplex, Herpes zoster, Varicella* and *Vaccinia*), mycobacterial and fungal infections of the eye and vaccination with live vaccines.

4.4. Special warnings and precautions for use
For ocular use only, not for injection. DEMOXIDEX cannot be injected subconjunctivally or directly into the anterior chamber of the eye.

Moxifloxacin
Serious and sometimes fatal hypersensitivity (anaphylactic) reactions have been reported in some patients receiving systemic quinolone treatment, occurring after the first dose. Some reactions included cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal, and facial edema), airway obstruction, shortness of breath, urticaria, and pruritus.

If an allergic reaction occurs to DEMOXIDEX, the medication should be discontinued immediately. Severe acute hypersensitivity reactions to moxifloxacin or any other component of the product may require urgent medical intervention.

Oxygen administration and airway management should be applied as clinically indicated.

Tendon inflammation and rupture may occur with systemic fluoroquinolone treatment, including moxifloxacin, especially in patients receiving corticosteroids concurrently or in elderly patients. Therefore, DEMOXIDEX treatment should be discontinued at the first sign of tendon inflammation.

As with other antibacterial preparations, prolonged use of moxifloxacin may result in the overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the treatment should be discontinued, and alternative therapy should be initiated.

The efficacy and safety of DEMOXIDEX in treating conjunctivitis in neonates are limited; therefore, its use is not recommended for neonates with conjunctivitis.

Due to the prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae*, DEMOXIDEX should not be used for the prophylaxis or empirical treatment of gonococcal conjunctivitis, including gonococcal ophthalmia neonatorum.

DEMOXIDEX is not recommended for the treatment of *Chlamydia trachomatis* in patients under 2 years of age, as it has not been evaluated in this age group. For patients older than 2 years with ocular infections caused by *Chlamydia trachomatis*, appropriate systemic therapy should be provided.

Neonates with ophthalmia neonatorum should receive proper treatment, including systemic therapy for cases caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae.*

Patients presenting with symptoms of bacterial ocular conjunctivitis should be advised not to use contact lenses.

Dexamethasone
Prolonged treatment with corticosteroids should be avoided. Long-term use may result in optic nerve damage, reduced visual acuity or visual field defects, posterior subcapsular cataracts, ocular hypertension, and/or glaucoma. Corticosteroids may also suppress the host defense mechanisms, leading to secondary ocular infections or persistent fungal infections. In cases of acute purulent eye diseases, corticosteroids may mask infection symptoms or worsen the condition.

DEMOXIDEX should be used cautiously in patients with primary open-angle glaucoma or a family history of glaucoma, diabetes mellitus, or myopia greater than 5 diopters. Regular monitoring of intraocular pressure and lens condition is particularly essential for glaucoma patients or those requiring long-term treatment.

Topikal corticosteroids may cause perforation in the cornea or sclera when used in diseases that lead to thinning of these tissues.

Bacterial keratitis can develop after using topical ophthalmic medications containing multiple doses, particularly in patients with pre-existing corneal disease or compromised ocular epithelial integrity.

Sudden discontinuation of high-dose corticosteroid therapy may result in withdrawal effects or exacerbation of the existing condition.

If a new event (such as trauma, eye surgery or infection) develops in the eyes of patients during treatment, they should be advised to consult their physician about whether to continue using the medication they are currently using.

4.5. Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted with DEMOXIDEX. However, systemic studies involving oral moxifloxacin at doses significantly higher than the topical ophthalmic dose have been performed. Unlike some other fluoroquinolones, systemic moxifloxacin has not shown clinically significant interactions with itraconazole, theophylline, warfarin, digoxin, oral contraceptives, probenecid, ranitidine, or glyburide. Dexamethasone is not associated with any known drug interactions. When administering multiple ophthalmic medicinal products, there should be an interval of at least 5 minutes between applications.

Contact with soft contact lenses should be avoided. Contact lenses should be removed before application and should not be reinserted for at least 15 minutes. It is known to cause discoloration of soft contact lenses.

Additional information on special populations
No interaction studies have been identified for special populations.

Pediatric population
No interaction studies specific to pediatric populations have been identified.

4.6. Fertility, pregnancy and lactation
General principles
Pregnancy category "C".

Women of childbearing potential / Contraception in males and females
Women of childbearing potential must use effective contraception during treatment.

Pregnancy
There are inadequate data regarding the use of moxifloxacin in pregnant women. Experimental animal studies have shown reproductive toxicity following systemic administration (refer to section 5.3).

In experimental animal studies, dexamethasone applied topically to the eyes of mice and rabbits at doses multiple times higher than those used in humans has been shown to be teratogenic. In mice, corticosteroids cause fetal resorption and a specific malformation known as cleft palate. In rabbits, corticosteroids lead to fetal resorption and multiple malformations in tissues such as the head, ears, limbs, and palate. No adequate or controlled study has been conducted to demonstrate that dexamethasone is harmless during pregnancy in humans.

Additionally, infants of mothers who used high doses of corticosteroids during pregnancy should be carefully monitored for hypoadrenalism. No adequate or controlled study has been conducted to demonstrate that dexamethasone is harmless during pregnancy in humans.

DEMOXIDEX should only be used in pregnant women if absolutely necessary, and in such cases, the risk/benefit ratio should be carefully considered.

Lactation Period
The moxifloxacin contained in the formulation passes into the breast milk of animals after oral administration. It is unknown whether moxifloxacin and dexamethasone are excreted in human milk. Similar to other quinolones, moxifloxacin can cause damage to the weight-bearing joint cartilage in developing animals (see section 5.3). Although systemic exposure is expected to be minimal following ocular application in breastfeeding mothers, DEMOXIDEX may be used during lactation only if the potential benefit outweighs the potential risk. Additionally, topically applied steroids undergo systemic absorption. Before prescribing DEMOXIDEX to breastfeeding mothers, a decision must be made to either discontinue breastfeeding or discontinue the medication, considering the benefit to the mother.

Fertility
Moxifloxacin and dexamethasone contained in this product have no known effect on fertility.

4.7 Effects on ability to drive and use machines
As with other eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after application, wait until the blurriness subsides before driving or using machinery.

4.8 Undesirable effects
There are no sufficient studies demonstrating the adverse effects of DEMOXIDEX. However, the adverse effects for each active ingredient can be summarized as follows:

In clinical studies with 1,060 patients, ophthalmic moxifloxacin was applied two or three times a day. No serious ophthalmic or systemic adverse effects related to ophthalmic moxifloxacin were reported in these clinical studies.

Adverse effects have been evaluated in relation to its administration and classified according to the following criteria: 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), not known (cannot be estimated from the available data). In each frequency group, adverse effects are listed in descending order of severity.

Moxifloxacin

Blood and Lymphatic System Disorders
Uncommon: Decreased hemoglobin

Immune System Disorders
Not known: Hypersensitivity

Nervous System Disorders
Common: Dysgeusia

Uncommon: Headache, paresthesia

Not known: Dizziness

Eye Disorders
Common: Eye pain, eye irritation, dry eyes, eye itching, conjunctival hyperemia, ocular hyperemia

Uncommon: Corneal epithelial defect, punctate keratitis, corneal staining, conjunctival hemorrhage, conjunctivitis, eye swelling, ocular discomfort, blurred vision, decreased visual acuity, eyelid disorders, eyelid edema, eyelid erythema, abnormal eye sensitivity

Not known: Endophthalmitis, ulcerative keratitis, corneal erosion, corneal abrasion, increased intraocular pressure, corneal opacity, corneal infiltrates, corneal deposits, eye allergy, keratitis, corneal edema, photophobia, corneal disorder, blepharitis, eyelid swelling, increased lacrimation, eye discharge, foreign body sensation in the eye

Cardiac Disorders
Not known: Palpitations

Respiratory, Thoracic, and Mediastinal Disorders
Uncommon: Nasal discomfort, pharyngolaryngeal pain, foreign body sensation in the throat

Not known: Dyspnea

Gastrointestinal Disorders
Uncommon: Vomiting

Not known: Nausea

Hepatobiliary Disorders
Uncommon: Increased alanine aminotransferase, increased gamma-glutamyltransferase

Skin and Subcutaneous Tissue Disorders
Not known: Erythema, pruritus, rash, urticaria

Dexamethasone

Infections and Infestations

Not known: Secondary infections caused by pathogens, including Herpes simplex

Eye Disorders
Not known: Topically applied corticosteroids to the eye can cause an increase in intraocular pressure in some susceptible cases. This pressure increase is directly related to the corticosteroid used, frequency of use, and duration of treatment. The elevation in intraocular pressure due to long-term use usually returns to normal values within a few weeks after discontinuation of the drug.

Prolonged use of topical ophthalmic corticosteroids (over 1 year) may result in glaucoma with damage to the optic nerve, decreased visual acuity, visual field defects, posterior subcapsular cataracts, and perforation of the globe.

General Disorders and Administration Site Conditions
Rare: Irritation-related or allergic reactions, such as stinging and burning, may occur.

Additional Information on Special Populations
Pediatric Population
Based on the data of clinical studies involving pediatric patients, including neonates (see section 5.1), the type and severity of adverse effects in pediatric population are similar to those observed in adults.

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
The limited capacity of the conjunctival sac to retain ophthalmic products essentially prevents overdose situations with DEMOXIDEX.

Treatment
In the event of an overdose, appropriate monitoring and follow-up of the patient are required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group **:** Dexamethasone and antiinfectives
ATC code **:** S01CA01

Moxifloxacin is a fourth-generation fluoroquinolone antibacterial agent effective against Gram-positive and Gram-negative ocular pathogens, atypical microorganisms, and anaerobes within its broad spectrum.

Glucocorticoids are adrenocortical steroids that can be naturally occurring or synthetically produced. Dexamethasone is a synthetic analogue of the natural glucocorticoids hydrocortisone and cortisone. Dexamethasone sodium phosphate is a water-soluble inorganic ester of dexamethasone with a molecular weight of 516.41.

Mechanism of Action of Moxifloxacin
Moxifloxacin is effective *in vitro* against a wide range of Gram-positive and Gram-negative microorganisms. It exerts its effect by inhibiting topoisomerase II (DNA gyrase) and topoisomerase

IV, enzymes required for bacterial DNA replication, transcription, repair, and recombination.

Resistance Mechanism

Resistance to fluoroquinolones, including moxifloxacin, typically arises due to chromosomal mutations in genes encoding DNA gyrase and topoisomerase IV. In Gram-negative bacteria, resistance to moxifloxacin may result from mutations in the *mar* (multiple antibiotic resistance) and *qnr* (quinolone resistance) gene systems. Due to differences in mechanisms of action, cross-resistance with beta-lactams, macrolides, and aminoglycosides is not expected.

Breakpoints

For the topical ophthalmic use of moxifloxacin, there are no established official susceptibility breakpoints for microorganisms. Although systemic breakpoints are utilized, their applicability to topical ophthalmic treatment is uncertain. The systemic breakpoint for moxifloxacin is ≤2 mg/l for susceptibility and >4 mg/l for resistance.

Sensitivity to Moxifloxacin

The prevalence of acquired resistance may vary geographically and over time for selected strains. Local data are especially important for the treatment of serious infections. When necessary, if local resistance is widespread or some infection types are suspected, expert advice regarding the utility of the active substance should be sought.

Commonly Susceptible Species
Aerobic Gram-positive Microorganisms: *Corynebacterium* species, including *Corynebacterium diphtheriae* *Staphylococcus aureus* (methicillin-resistant) *Streptococcus pneumoniae* *Streptococcus pyogenes* *Streptococcus viridans* group
Aerobic Gram-negative Microorganisms: *Enterobacter cloacae* *Haemophilus influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Serratia marcescens* **Anaerobic Microorganisms:** *Proprionibacterium acnes* **Other Microorganisms:** *Chlamydia trachomatis*
Species with Acquired Resistance That Could Pose Problems
Aerobic Gram-positive Microorganisms: *Staphylococcus aureus* (methicillin-resistant) Coagulase-negative *Staphylococcus* species (methicillin-resistant) **Aerobic Gram-negative Microorganisms:** *Neisseria gonorrhoeae* **Other Microorganisms:** None identified.
Organisms Naturally Resistant to Moxifloxacin
Aerobic Gram-negative Microorganisms: *Pseudomonas aeruginosa*

Other Microorganisms: None identified.

The above information is based on microbiological surveillance studies conducted in various parts of Europe. The ocular infection bacterial isolates were collected from Belgium, the Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, Switzerland, and the United Kingdom.

Moxifloxacin was studied in a wide patient group ranging from neonates to adults, including elderly.

Mechanism of Action of Dexamethasone

While corticosteroids have numerous effects, their anti-inflammatory effects are the most relevant in ophthalmology. They prevent or suppress the symptoms observed in inflammatory reactions. Corticosteroids inhibit signs of inflammation, such as edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, collagen accumulation, and scar tissue formation.

Although the exact mechanisms of corticosteroids applied to the eye are not fully understood, it is generally accepted that their effects are mediated through the induction of a group of proteins called lipocortins, which are phospholipase A2 proteins. These proteins are believed to control the biosynthesis of mediators, such as prostaglandins and leukotrienes, which play significant roles in inflammation. They do so by inhibiting the release of arachidonic acid, the precursor of these mediators. Arachidonic acid is a substance released from membrane phospholipids with the help of phospholipase A2.

In addition to these effects, corticosteroids' cellular effects are also explained by several other mechanisms, some of which are as follows:

- Inhibition of prostaglandin synthesis
- Inhibition of platelet-activating factor
- Inhibition of tumor necrosis factor
- Inhibition of interleukin-1
- Inhibition of leukocyte and monocyte migration
- Stabilization of lysosomal membranes
- Prevention of kinin release

Dexamethasone Sodium Phosphate has strong anti-inflammatory and anti-allergic effects. It effectively suppresses inflammation in many diseases involving the anterior segment of the eye.

5.2. Pharmacokinetic properties

General Properties

Moxifloxacin

Absorption and Distribution

Following the topical ocular application of DEMOXIDEX, moxifloxacin was found to enter systemic circulation. Plasma concentrations of moxifloxacin were measured in 21 male and female subjects who received bilateral topical ocular moxifloxacin three times a day for 4 days. The average steady-state C_{max} and area under the curve (AUC) were 2.7 ng/ml and 41.9 ng·s/ml, respectively. These values were approximately 1600 and 1200 times lower than those observed with the well-tolerated 400 mg oral therapeutic doses of moxifloxacin.

Biotransformation

Data unavailable.

Elimination
The plasma half-life of moxifloxacin is estimated to be 13 hours.

Dexamethasone
Dexamethasone is practically insoluble in water, partially soluble in anhydrous ethyl alcohol, and slightly soluble in methylene chloride. Its pH range is 7.0–7.7. Dexamethasone sodium phosphate, an inorganic ester of dexamethasone that is water-soluble, is approximately three thousand times more soluble in water than hydrocortisone at 25°C.

Absorption
Corticosteroids are absorbed into the aqueous humor, cornea, iris, ciliary body, and retina of the eye. Although a certain amount is absorbed systemically, the amounts that enter systemic circulation are not significant unless used in high doses or for prolonged periods in children.

Distribution
The amounts that enter systemic circulation are not significant unless used in high doses or for prolonged periods in children.

Biotransformation
When corticosteroids are absorbed systemically, they are primarily metabolized in the liver. However, metabolism also occurs in the kidneys. Additionally, studies conducted on experimental animals have shown that local degradation occurs in the eye.

Elimination
It is excreted in the urine.

5.3. Preclinical safety data
Moxifloxacin
In rats and monkeys, hematopoietic effects (a slight decrease in red blood cells and platelet count) have been observed. Like other quinolones, hepatotoxicity (increased liver enzymes and vacuolar degeneration) has been noted in rats, monkeys, and dogs. Central nervous system (CNS) toxicity (seizures) occurred in monkeys. These effects were only observed following high doses of moxifloxacin or prolonged treatment.

As with other quinolones, moxifloxacin is genotoxic in vitro in bacteria and mammalian cells. If these effects can be linked to bacterial gyrase and, at higher concentrations, mammalian cell interactions with topoisomerase II, a threshold for genotoxicity could be assumed. However, no evidence of genotoxicity was found in in vivo tests, even with very high doses of moxifloxacin. Therefore, therapeutic doses for human use provide a sufficient safety margin. No carcinogenic effects were found in rats.

Most quinolones are photoreactive and may trigger phototoxic, photomutagenic, and photocarcinogenic effects. In contrast, in vitro and in vivo studies have shown that moxifloxacin does not have phototoxic and photogenotoxic properties. Similar effects have been observed in other quinolones under the same conditions.

Reproductive Toxicity
It is known that quinolones cause damage to the cartilage in the large joints of developing animals. In puppies, moxifloxacin caused joint toxicity at oral doses of 30 mg/kg/day or higher.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Sodium chloride
Sorbitol 70% (non-crystalline)
Tiloxapol
Boric acid
Disodium EDTA
Hydrochloric acid or sodium hydroxide (for pH adjustment)
Water for injection

6.2. Incompatibilities
No known incompatibilities.

6.3. Shelf life
24 months.
Once the bottle is opened, use within 30 days if stored at room temperature below 25°C.

6.4. Special precautions for storage
Store below 25°C at room temperature.

6.5. Nature and contents of container
The primary packaging material for the product is an opaque, white, low-density polyethylene (LDPE) bottle, containing 5 ml of eye drops solution, with a LDPE dropper tip and white HDPE screw cap. It is presented in a cardboard box with a package leaflet.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

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

8. MARKETING AUTHORISATION NUMBER(S)
2023/441

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
Date of first authorization : 08.11.2023
Date of latest renewal :

10. DATE OF REVISION OF THE SPC