

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEMOXIF 0.5% Eye Drops, Solution
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution contains:

Active substance(s):

Moxifloxacin 5 mg (as 5.45 mg moxifloxacin hydrochloride)

Excipient(s) with known effect:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, greenish-yellow solution, free of preservatives and particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEMOXIF is indicated for the topical treatment of bacterial infections in the anterior segment of the eye caused by moxifloxacin susceptible strains (see section 5.1).

Official guidelines for the appropriate use of antibacterial agents should be taken into account.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

Use in adults and the elderly:

Instill 1 drop into the infected eye(s) 3 times a day.

The infection normally improves after 5 days. However, the treatment should be continued for a further 2 or 3 days.

Method of administration:

For ocular use.

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.

In order to prevent the drops from being absorbed via the nasal mucosa, particularly in newborn infants or young children, the nasolacrimal ducts should be held closed with the fingers for 2 to 3 minutes after administering the drops.

Additional information on special populations:

Renal/Hepatic failure:

Pharmacokinetic parameters of oral moxifloxacin were not significantly altered in patients with mild to moderate hepatic and renal failure. Studies were not performed in patients with severe hepatic failure. Due to the low systemic exposure by the topical route of application, no dose adjustment of DEMOXIF is needed for patients with hepatic failure.

The pharmacokinetic parameters of oral moxifloxacin are not significantly altered in those with mild, moderate or severe renal failure. No dosage adjustment for DEMOXIF is required in patients with renal failure.

Pediatric population:

No dosage adjustment is necessary (for detailed information, see section 4.4 ‘Special warnings and precautions for use’).

Geriatric population:

No differences in efficacy and safety have been observed between elderly and other adults.

4.3 Contraindications

DEMOMUX is contraindicated in people with hypersensitivity to moxifloxacin, to other quinolones, or to any of the excipients of this product.

4.4 Special warnings and precautions for use

For ocular use only. Not for injection. DEMOMUX should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye.

In patients receiving systemically administered quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching.

If an allergic reaction to DEMOMUX occurs, discontinue use of the medicinal product. Serious acute hypersensitivity reactions to moxifloxacin or any other product ingredient may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including moxifloxacin, particularly in older patients and those treated concurrently with corticosteroids. So, treatment with DEMOMUX should be discontinued at the first sign of tendon inflammation.

As with other antibacterial preparations, prolonged use of moxifloxacin may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.

Data are very limited to establish efficacy and safety of moxifloxacin in the treatment of conjunctivitis in neonates. Therefore, use of DEMOMUX to treat conjunctivitis in neonates is not recommended.

DEMOMUX should not be used for the prophylaxis or empiric treatment of gonococcal conjunctivitis, including gonococcal ophthalmia neonatorum, because of the prevalence of fluoroquinolone-resistant *Neisseria gonorrhoea*.

DEMOMUX is not recommended to treat *Chlamydia trachomatis* in patients less than 2 years of age, as it was not evaluated in such patients. Patients older than 2 years of age with eye infections caused by *Chlamydia trachomatis* should receive appropriate systemic treatment.

Neonates with ophthalmia neonatorum should receive appropriate therapy for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomatis* or *Neisseria gonorrhoea*.

Patients should be advised not to wear contact lenses if they have signs and symptoms of a bacterial ocular conjunctivitis.

4.5 Interaction with other medicinal products and other forms of interaction

While drug-drug interaction studies have not been conducted with DEMOMUX, systemic studies have been conducted with oral moxifloxacin at doses far greater than the topical ocular dose. Unlike some other fluoroquinolones, no clinically significant drug-drug interactions have been observed between systemic moxifloxacin and itraconazole, theophylline, warfarin, digoxin, oral contraceptives, probenecid, ranitidine, or glyburide. If more than one topical ophthalmic medicinal product is being used, these medicines should be administered to the eye at least 5 minutes apart.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category is C.

Women of childbearing potential / Birth control (Contraception)

No sufficient information present.

Pregnancy

No sufficient data is available regarding the use of DEMOMUX in pregnant women. Experimental studies on animals showed reproductive toxicity after systemic administration (see section 5.3). DEMOMUX can be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.

Lactation

After oral administration in animals, moxifloxacin is excreted into breast milk. It is unknown whether moxifloxacin is excreted via human breast-milk. As with other quinolones, moxifloxacin may cause lesions in the cartilage of the weight-bearing joints of immature animals (see section 5.3). Even though the systemic exposure to moxifloxacin after ocular administration to nursing mother is very low, DEMOMUX may be used during breast-feeding if the potential benefit justifies the potential risk to the fetus.

Reproduction ability/Fertility

No sufficient information present.

4.7 Effects on ability to drive and use machines

As with all other eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient should wait to drive or use machines until clear vision is regained.

4.8 Undesirable effects

In clinical studies involving 2,252 patients, moxifloxacin was administered up to 8 times a day, with over 1,900 of these patients receiving treatment 3 times daily. The overall safety population that received the medicinal product consisted of 1,389 patients from the United States and Canada, 586 patients from Japan and 277 patients from India. No serious ophthalmic or systemic undesirable effects related to moxifloxacin were reported in clinical studies. The most frequently undesirable effects reported for this medicinal product were eye irritation and eye pain, occurring at an incidence of 2 to 1%. These undesirable effects were mild in 96% of those patients who experienced them, with only 1 patient discontinuing therapy as a result.

Observed undesirable effects are classified as follows: very common ($\geq 1/10$); common ($> 1/100$ to $< 1/10$); uncommon ($> 1/1,000$ to $\leq 1/100$); rare ($> 1/10,000$ to $\leq 1/1,000$), very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Uncommon: Hemoglobin decreased

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 eye, eye pruritus, conjunctival hyperemia, ocular hyperemia

Uncommon: Corneal epithelium defect, punctate keratitis, corneal spots, conjunctival hemorrhage, conjunctivitis, eye edema, ocular discomfort, vision blurred, visual acuity reduced, eyelid disorder, eyelid edema, erythema of eyelid, increased sensitivity in the eye

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

Cardiac disorders

Not known: Palpitations

Respiratory, thoracic and mediastinal disorders

Uncommon: Nasal discomfort, pharyngolaryngeal pain, foreign body sensation in throat

Not known: Dyspnea

Gastrointestinal disorders

Uncommon: Vomiting

Not known: Nausea

Hepato-biliary disorders

Uncommon: Alanine aminotransferase increased, gamma-glutamyltransferase increased

Skin and subcutaneous tissue disorders

Not known: Erythema, pruritus, rash, urticarial

Additional information on special populations

Pediatric population

Based on data from the clinical trials involving pediatric patients, including neonates (see section 5.1), the type and severity of undesirable effects in the pediatric population are the same as those seen 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 and treatment

The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of DEMOMUX.

Moxifloxacin dose in the product is too small to induce side effects after accidental ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiinfectives

ATC code: S01AE07

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

Mode of Action

Moxifloxacin is effective *in vitro* against a wide range of Gram-positive and Gram-negative micro-organisms. It shows its effect by inhibiting the topoisomerase II (DNA gyrase enzyme) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination.

Resistance Mechanism

Resistance to fluoroquinolones, including moxifloxacin generally occurs by chromosomal mutations encoding DNA gyrase and topoisomerase IV. In Gram-negative bacteria, moxifloxacin resistance can be due to mutations in *mar* (multiple antibiotic resistance) and the *qnr* (quinolone resistance) gene systems. Cross-resistance with beta-lactams, macrolides and aminoglycosides is not expected due to differences in mode of action.

Breakpoints

There are no official micro-organisms susceptibility breakpoints for topical ophthalmic use for moxifloxacin. Although systemic breakpoints have been used, their relevance to topical ophthalmic therapy is doubtful. The systemic breakpoint used for moxifloxacin is ≤ 2 mg/l for susceptibility, >4 mg/l for resistance.

Susceptibility to Moxifloxacin

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is important, 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 active substance in at least some types of infections is questionable.

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

Propionibacterium acnes

Other microorganisms

Chlamydia trachomatis

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

Aerobic Gram-positive microorganisms

Staphylococcus aureus (methicillin resistant)
Staphylococcus, coagulase-negative species (methicillin resistant)

Aerobic Gram-negative microorganisms

Neisseria gonorrhoeae

Other microorganisms

None.

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-negative microorganisms

Pseudomonas aeruginosa

Other microorganisms

None.

The above data is based on microbiological screening surveys conducted in various parts of Europe. The bacterial isolates from ocular infections were acquired from are Belgium, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Portugal, Spain, Switzerland and England.

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

5.2 Pharmacokinetic properties

General properties

Absorption and Distribution:

Moxifloxacin is absorbed into the systemic circulation following topical ocular administration. Plasma concentrations of moxifloxacin were measured in 21 male and female subjects who instilled bilateral topical ocular drops of moxifloxacin 3 times a day for 4 days.

The mean steady state C_{max} and AUC were 2.7 ng/ml and 41.9 ng•hr/ml, respectively. These values are approximately 1,600 and 1,200 times lower than the well-tolerated 400 mg oral therapeutic doses of moxifloxacin.

Elimination

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

5.3 Preclinical safety data

Effects on the hematopoietic system (slight decreases in the number of erythrocytes and platelets) were seen in rats and monkeys. As with other quinolones, hepatotoxicity (elevated liver enzymes and vacuolar degeneration) was seen in rats, monkeys and dogs. In monkeys CNS (central nervous system) toxicity (convulsions) occurred. These effects were seen only after treatment with high doses of moxifloxacin or after prolonged treatment.

Moxifloxacin, like other quinolones, was genotoxic in *in vitro* tests using bacteria or mammalian cells. Since these effects can be explained by an interaction with the gyrase in bacteria and - at higher concentrations - by an interaction with the topoisomerase II in mammalian cells, a threshold concentration for genotoxicity can be assumed. In *in vivo* tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Thus, a sufficient margin of safety to the therapeutic dose in man can be provided. No evidence of carcinogenic effects was observed in rats.

Many quinolones are photoreactive and can induce phototoxic, photomutagenic and photocarcinogenic effects. In contrast, moxifloxacin was proven to be devoid of phototoxic and photogenotoxic properties in *in vitro* and *in vivo* studies. Similar effects were observed with other quinolones under the same conditions.

Reproductive Toxicity:

Quinolones are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals. In juvenile dogs, moxifloxacin produced joint toxicity at oral doses of 30 mg/kg/day or more.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid (pH adjustment)

Sodium chloride

Sodium hydroxide and/or hydrochloric acid (pH adjustment)

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Once the bottle has been opened, the medicine should be used within 28 days provided it is kept at room temperature below 25°C and then the unused portion should be discarded after.

6.4 Special precautions for storage

Store at room temperature below 25°C.



6.5 Nature and contents of container

The product is available in packages of an opaque, white, low-density polyethylene (LDPE) bottle containing 5 ml eye drops, with LDPE dropper tip and HDPE orange screw cap.

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 AUTHORIZATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER(S)

2016/747

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 19.10.2016

Date of renewal :

10. DATE OF REVISION OF THE TEXT

19.02.2024