

1. NAME OF THE MEDICINAL PRODUCT

VIGAMOX

(moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of VIGAMOX solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VIGAMOX (moxifloxacin HCl ophthalmic solution) 0.5% is a sterile topical ophthalmic solution.

4. Clinical particulars

4.1 Therapeutic indications

VIGAMOX Solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains or organisms.

For a full list of susceptible strains and organisms, see sections 5.1

4.2 Posology and method of administration

For ocular use only. Not for injection. VIGAMOX 5 mg/ml eye drops, solution should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye.

Dosage and administration: Instill one drop in the affected eye 3 times a day for 4 days.

Pediatric Use: VIGAMOX Solution has been shown to be safe and effective in pediatric patients including neonates. There is no evidence that the ophthalmic administration of VIGAMOX Solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

No dosage adjustment is necessary.

Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Special Populations:

Patients with renal impairment:

The pharmacokinetic parameters of oral moxifloxacin are not significantly altered by mild, moderate or severe renal impairment. No dosage adjustment of VIGAMOX Solution is necessary in patients with renal impairment.

Patients with hepatic impairment:

Pharmacokinetic parameters of oral moxifloxacin were not significantly altered in patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B).

Studies were not performed in patients with severe hepatic impairment (Child Pugh Class C).

Because of the low systemic exposure by the topical route of administration, no dosage adjustment of VIGAMOX Solution is needed in patients with hepatic impairment.

In order to prevent the drops from being absorbed via the nasal mucosa, particularly in newborn infants or children, the nasolacrimal ducts should be held closed for 2 to 3 minutes with the fingers after administering the drops. After cap is removed, if tamper evident snap collar is loose, remove before using the product.

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Warnings:

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, dyspnoea, urticaria and itching (see section 4.8).

If an allergic reaction to VIGAMOX 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 as clinically indicated.

Precautions:

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 oedema), airway obstruction, dyspnoea, urticaria, and itching (see section 4.8).

If an allergic reaction to VIGAMOX 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.

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

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including moxifloxacin, particularly in older patients and those treated concurrently with corticosteroid. Following ophthalmic administration of VIGAMOX plasma concentrations of moxifloxacin are much lower than after therapeutic oral doses of moxifloxacin (see section 4.5 and 5.2), however caution should be exercised and treatment with VIGAMOX should be discontinued at the first sign of tendon inflammation (see section 4.8).

Data are very limited to establish efficacy and safety of VIGAMOX in the treatment of conjunctivitis in neonates. Therefore use of this medicinal product to treat conjunctivitis in neonates is not recommended.

VIGAMOX 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 gonorrhoeae*. Patients with eye infections caused by *Neisseria gonorrhoeae* should receive appropriate systemic treatment.

The medicinal product is not recommended for the treatment of *Chlamydia trachomatis* in patients less than 2 years of age as it has not been 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 treatment for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with VIGAMOX 5 mg/ml Eye Drops, Solution. Given the low systemic concentration of moxifloxacin following topical ocular administration of the medicinal product (see Section 5.2), drug interactions are unlikely to occur.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of VIGAMOX in pregnant women. However, no effects on pregnancy are anticipated since the systemic exposure to moxifloxacin is negligible. The medicinal product can be used during pregnancy.

Breastfeeding

It is unknown whether moxifloxacin/metabolites are excreted in human milk. Animal studies have shown excretion of low levels in breast milk after oral administration of moxifloxacin. However, at therapeutic doses of VIGAMOX no effects on the suckling child are anticipated. The medicinal product can be used during breast-feeding.

Fertility

Studies have not been performed to evaluate the effect of ocular administration of VIGAMOX on fertility.

4.7 Effects on the ability to drive and use machines

VIGAMOX has no or negligible influence on the ability to drive and use machines, however, as with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient should wait until their vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving 2,252 patients, VIGAMOX 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 the medicinal product were reported in any of the clinical studies. The most frequently reported treatment-related undesirable effects with the medicinal product were eye irritation and eye pain, occurring at an overall incidence of 1 to 2%. These reactions were mild in 96% of those patients who experienced them, with only 1 patient discontinuing therapy as a result.

The following adverse reactions are classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness.

System Organ Classification	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare	haemoglobin decreased
Immune system disorders	Not known	hypersensitivity
Nervous system disorders	Uncommon	headache
	Rare	paresthesia
	Not known	dizziness
Eye disorders	Common	eye pain, eye irritation
	Uncommon	punctate keratitis, dry eye, conjunctival haemorrhage, ocular hyperaemia, eye pruritus, eyelid oedema, ocular discomfort,
	Rare	corneal epithelium defect, corneal disorder, conjunctivitis, blepharitis, eye swelling, conjunctival oedema, vision blurred, visual acuity reduced, asthenopia, erythema of eyelid
	Not known	endophthalmitis, ulcerative keratitis, corneal erosion, corneal abrasion, intraocular pressure increased, corneal opacity, corneal infiltrates, corneal deposits, eye allergy, keratitis, corneal oedema, photophobia, eyelid oedema, lacrimation increased, eye discharge, foreign body sensation in eyes
Cardiac disorders	Not known	palpitations
Respiratory, thoracic and mediastinal disorders	Rare	nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat)
	Not known	dyspnoea
Gastrointestinal disorders	Uncommon	dysgeusia, vomiting
	Not known	nausea
Hepatobiliary disorders	Rare	alanine aminotransferase increased, gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Not known	erythema, rash, pruritus, urticaria

Description of selected adverse reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria and itching (see section 4.4).

Ruptures of the shoulder, hand, Achilles, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic quinolones indicate that a risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including Achilles tendon (see section 4.4).

Paediatric population

In clinical trials, VIGAMOX has shown to be safe in paediatric patients, including neonates. In patients under 18 years old, the two most frequent adverse reactions were eye irritation and eye pain, both occurring at an incidence rate of 0.9%.

Based on data from clinical trials involving paediatric patients, including neonates (see section 5.1), the type and severity of adverse reactions in the paediatric population are similar to those in adults.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>).

4.9 Overdose

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

The total amount of moxifloxacin in a single container is too small to induce adverse effects after accidental ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; anti-infectives, other anti-infectives, ATC code: S01AE07

Mode of Action:

Moxifloxacin, a fourth-generation fluoroquinolone, inhibits the DNA gyrase and topoisomerase IV required for bacterial DNA replication, repair, and recombination.

Resistance to fluoroquinolones, including moxifloxacin generally occurs by chromosomal mutations in genes 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. Resistance is also associated with expression of

bacteria efflux proteins and inactivating enzymes. Cross-resistance with beta-lactams, macrolides and aminoglycosides is not expected due to differences in mode of action.

Susceptibility Testing Breakpoints: There are no pharmacological data correlated with clinical outcome for moxifloxacin administered as a topical agent. As a result, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) suggests the following epidemiological cut-off values (ECOFF mg/l) derived from MIC distribution curves to indicate susceptibility to topical moxifloxacin:

<i>Corynebacterium</i>	ND
<i>Staphylococcus aureus</i>	0.25 mg/l
<i>Staphylococcus</i> , coag-neg.	0.25 mg/l
<i>Streptococcus pneumoniae</i>	0.5 mg/l
<i>Streptococcus pyogenes</i>	0.5 mg/l
<i>Streptococcus</i> , viridans group	0.5 mg/l
<i>Enterobacter</i> spp.	0.25 mg/l
<i>Haemophilus influenzae</i>	0.125 mg/l
<i>Klebsiella</i> spp.	0.25 mg/l
<i>Moraxella catarrhalis</i>	0.25 mg/l
<i>Morganella morganii</i>	0.25 mg/l
<i>Neisseria gonorrhoeae</i>	0.032 mg/l
<i>Pseudomonas aeruginosa</i>	4 mg/l
<i>Serratia marcescens</i>	1 mg/l

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 moxifloxacin in at least some types of infections is questionable.

COMMONLY SUSCEPTIBLE SPECIES

Aerobic Gram positive micro organisms:

Corynebacterium species including

Corynebacterium diphtheriae

Staphylococcus aureus (methicillin susceptible)

Streptococcus pneumoniae

Streptococcus pyogenes

Streptococcus viridans Group

Aerobic Gram negative micro organisms:

Enterobacter cloacae

Haemophilus influenzae

Klebsiella oxytoca

Moraxella catarrhalis

Serratia marcescens

Anaerobic micro-organisms:

Propionibacterium acnes

Other micro organisms:

Chlamydia trachomatis

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

Aerobic Gram positive micro organisms:

Staphylococcus aureus (methicillin resistant)

Staphylococcus, coagulase-negative species (methicillin resistant)

Aerobic Gram negative micro organisms:

Neisseria gonorrhoeae

Other micro organisms:

None

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram negative micro organisms:

Pseudomonas aeruginosa

Other micro organisms:

None

5.2 Pharmacokinetic properties

Following topical ocular administration of VIGAMOX, Moxifloxacin was absorbed into the systemic circulation. Plasma concentrations of moxifloxacin were measured in 21 male and female subjects who received bilateral topical ocular doses of VIGAMOX solution 3 times a day for 4 days. The mean steady-state C_{max} and AUC were 2.7ng/mL and 41.9ng-hr/mL, respectively. These exposure values are approximately 1,600 and 1,200 times lower than the mean C_{max} and AUC reported after therapeutic 400 mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure following administration to the eye indicating little relevance to clinical use.

As with other quinolones, moxifloxacin was also genotoxic in vitro in bacteria and mammalian cells. As these effects can be traced to the interaction with bacterial gyrase and in considerably higher concentrations to the interaction with topoisomerase II in mammalian cells, a threshold level for genotoxicity can be assumed. In in vivo tests, no evidence of genotoxicity was found, despite high doses of moxifloxacin. The therapeutic doses for human use therefore provide adequate safety margin. No indication of a carcinogenic effect was observed in an initiation promotion model in rats.

Unlike other quinolones, moxifloxacin showed no phototoxic or photogenotoxic properties in extensive in vitro and in vivo studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Boric Acid

Hydrochloric Acid OR Sodium Hydroxide

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life after opening: 28 days

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and content of container

How supplied: VIGAMOX (moxifloxacin ophthalmic solution) 0.5% is supplied as a sterile ophthalmic solution in Alcon's DROP-TAINER® dispensing system consisting of a natural low density polyethylene bottle and dispensing plug and tan polypropylene closure. Tamper evidence is provided with 3 shrink band around the closure and neck area of the package.
5mL

6.6 Special precautions for disposal and other handling

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

7. MANUFACTURER

Manufacturer:

Alcon Laboratories, Fort Worth, USA for Alcon Pharmaceuticals Ltd., Fribourg, Switzerland.

8. MARKETING AUTHORISATION HOLDER

License Holder: Novartis Israel Ltd., 36 Shacham St., Petach-Tikva.

9. MARKETING AUTHORISATION NUMBER

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