NOVARTIS

VIGAMOX

(moxifloxacin)

0.5 % w/v eye drops, solution

Professional Information

Document status: Final

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SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

VIGAMOX 0.5 % w/v eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

VIGAMOX is a clear, greenish-yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VIGAMOX is indicated for

- the topical treatment of bacterial conjunctivitis, blepharitis, dacryocystitis, hordeolum, tarsadenitis, keratitis (including corneal ulcer) caused by susceptible organisms. (See section 5.1)
- preoperative and postoperative sterilization for ophthalmic surgery

Changes in the international and local antimicrobial resistance patterns should also be a consideration.

4.2 Posology and method of administration

Posology

Use in adults including the elderly

For conjunctivitis, blepharitis, dacryocystitis, hordeolum, tarsadenitis, keratitis (including corneal ulcer): instill one drop in the affected eye(s) 3 times a day for 7 days. Increase or decrease of frequency of instillation can be adjusted according to the symptoms.

For preoperative and postoperative sterilization: The recommended dose is one drop of VIGAMOX in the affected eye(s) 5 times per day for 2 days before ophthalmic surgery, and 3 times per day for 14 days after ophthalmic surgery.

Special populations

Paediatric population

VIGAMOX has been shown to be safe and effective for bacterial infection treatment in paediatric patients including neonates and can be used at the same dose as in adults.

Use of VIGAMOX for surgical sterilization in paediatric patients has not been studied.

There is no evidence that the ophthalmic administration of VIGAMOX has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Elderly population

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

Hepatic and renal 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 is needed in patients with hepatic impairment.

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

Method of administration

- For ocular use. Not for injection. VIGAMOX should not be injected sub-conjunctivally or introduced directly into the anterior chamber of the eye.
- To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.
- After cap is removed, if tamper evident snap collar is loose, remove before using product.
- Patients should be instructed to take at least 5 minutes between administrations if using VIGAMOX concurrently with other ophthalmic solutions.

4.3 Contraindications

VIGAMOX is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Principles of antibiotics stewardship should be adhered to.

For ocular use only. Not for injection. VIGAMOX should not be injected sub-conjunctivally or introduced directly into the anterior chamber of the eye (see section 4.2)

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 drug. 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.

Prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.

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

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including moxifloxacin as contained in VIGAMOX, particularly in elderly patients and in those treated

concurrently with corticosteroids. Therefore, treatment with VIGAMOX should be discontinued at the first sign of tendon inflammation (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

While drug-drug interaction studies have not been conducted with VIGAMOX, they have been performed with the oral product at much higher systemic exposures than are achieved by the topical ocular route.

Unlike some other fluoroquinolones, no clinically significant drug-drug interactions between systemically administered moxifloxacin and itraconazole, theophylline, warfarin, digoxin, oral contraceptives, probenicid, ranitidine or glyburide have been observed.

In vitro studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolised by these cytochrome P450 isozymes.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

Since there are no adequate and well-controlled studies in pregnant women, VIGAMOX should be used during pregnancy with caution. However, no effects on pregnancy are anticipated since the systemic exposure to moxifloxacin as contained in VIGAMOX from topical ocular application is negligible.

Breastfeeding

Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when VIGAMOX is administered to a nursing mother. However, at therapeutic doses of VIGAMOX no effects on the suckling child are anticipated.

Fertility

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

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision. If blurred vision occurs at instillation, the patient should wait until their vision clears before driving or using machinery.

4.8 Undesirable effects

a. Summary of the safety profile

In clinical studies involving 1060 subjects, VIGAMOX was administered twice or three times daily. No serious ophthalmic or systemic undesirable effects related to VIGAMOX were reported in clinical studies. The most frequently reported treatment-related undesirable effect was ocular discomfort (4.1 %), which was mild in 95.3 % of those subjects who experienced it. The discontinuation rate due to ocular discomfort was 0.1 %.

The following adverse reactions have been reported during clinical trials with VIGAMOX and are classified according to the following convention:

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). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Body System			
	Common	**Uncommon**	**Rare**
Blood and the lymphatic system disorders:			decreased haemoglobin
Nervous system disorders:		headache	paraesthesia
Eye disorders:	ocular pain, eye irritation	punctate keratitis, dry eye, conjunctival haemorrhage, ocular hyperaemia, ocular pruritus and ocular discomfort (burning or stinging upon instillation)	corneal epithelium defect, corneal disorder, conjunctivitis, blepharitis, eye swelling, eyelid oedema, conjunctival oedema, vision blurred, visual acuity reduced, asthenopia, erythema of eyelid
Respiratory, thoracic and mediastinal disorders:			nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat)

Gastrointestinal disorders:		taste perversion (altered, bitter or bad taste following instillation)	vomiting
Hepato-biliary disorders:			increased alanine aminotransferase, increased gamma-glutamyl transferase

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

System organ classification	**Adverse reactions**
Immune system disorders	Hypersensitivity
Nervous system disorders	Dizziness
Eye disorders	ulcerative keratitis, keratitis, increased lacrimation, photophobia, eye discharge
Cardiac disorders	Palpitations
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	erythema, pruritus, rash, 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, the type and severity of adverse reactions in the paediatric population are similar to those in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “Report Drug Reaction Process”, found online under SAHPRA’s safety publications: https://www.sahpra.org.za/

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

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

Intoxication after inadvertent oral ingestion can also be ruled out.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.15.1 Ophthalmic preparations with antibiotics and/or sulphonamides.

Pharmacotherapeutic group: Ophthalmologicals; anti-infectives, ATC code: S01A E07.

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.

Mechanisms of Action

Moxifloxacin has in vitro activity against a wide range of Gram-positive and Gram-negative microorganisms. Moxifloxacin inhibits the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. The C8-methoxy moiety of moxifloxacin also lessens the selection of resistant mutants of Gram-positive bacteria.

Mechanism(s) of Resistance

In vitro resistance to moxifloxacin develops slowly via multiple-step mutations and occurs at a general frequency between 10^{-9} to 10^{-11} for Gram-positive bacteria. Fluoroquinolones, including moxifloxacin,

differ in chemical structure and mode of action from ß-lactam antibiotics, macrolides and aminoglycosides, and therefore may be active against bacteria resistant to ß-lactam antibiotics, macrolides and aminoglycosides.

Breakpoints

There are no pharmacological data correlated with clinical outcome for moxifloxacin administered as a topical agent.

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.

Susceptibility to Moxifloxacin

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:

Proprionibacterium 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-positive micro-organisms

Pseudomonas aeruginosa

Gram-negative micro-organisms

None

Other micro-organisms

None

VIGAMOX has been studied in patients from newborns to adults, including geriatric patients.

In four randomised, double-masked, multicentre, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX produced clinical cures in 80 % to 94 % of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 78 % to 97 %.

In paediatric patients from birth to one month of age, VIGAMOX produced clinical cure in 80 % of patients with bacterial conjunctivitis. The microbiological success rate for the eradication of the baseline pathogens was 92 %.

In a randomised, double-masked, multicentre, controlled clinical trial in which patients were dosed twice a day for 3 days, VIGAMOX produced clinical cure in 74 % of patients treated for bacterial conjunctivitis. Microbiological success rate for the eradication of the baseline pathogens was 81 %.

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 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 exposure values are approximately 1,600 and 1,200 times lower than the mean C_{max} and AUC reported after well-tolerated therapeutic 400 mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic following up to 38 weeks of oral dosing at 500 mg/kg/day. Moxifloxacin was not mutagenic in four bacterial strains used in the Ames Salmonella reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity in vivo in a micronucleus test or a dominant lethal test in mice. Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose.

Teratogenic Effects:

Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased foetal body weights and slightly delayed foetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller foetuses was observed at 100 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Boric acid

Hydrochloric acid (E507) and/or sodium hydroxide (E524) (to adjust pH)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

Discard four weeks after first opening.

6.4 Special precautions for storage

Store at or below 25 °C.

Discard four weeks after first opening.

Store in the original package/container.

6.5 Nature and contents of container

Bottle with 5 ml fill and dispensing plug, both natural low-density polyethylene, with a white polypropylene closure.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

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Manufacturer

Siegfried El Masnou, S.A., Camil Fabra 58, El Masnou, Barcelona