

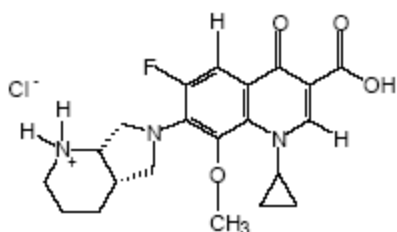
VIGAMOX[®] Eye Drops 0.5%

Moxifloxacin hydrochloride

Name of the Medicine

VIGAMOX[®] Eye Drops is a sterile topical ophthalmic solution. 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.

Moxifloxacin hydrochloride



Empirical formula: C₂₁H₂₃FN₃O₄.HCl

Molecular weight: 437.9

CAS Registry No: 186826-86-8

Chemical name: 1-Cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride

Description

VIGAMOX[®] Eye Drops is a clear, greenish-yellow solution formulated as a sterile, multiple-dose product, for topical ophthalmic use.

Each 1 mL of VIGAMOX[®] Eye Drops solution contains 5.45 mg/mL moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base. It also contains sodium chloride, boric acid, hydrochloric acid / sodium hydroxide (to adjust pH) and purified water. Product is self-preserved.

Pharmacology

Mechanism of Action

VIGAMOX[®] Eye Drops contains the fourth-generation fluoroquinolone, moxifloxacin. Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative micro-organisms. 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 compared to the C8-H moiety found in older fluoroquinolones. Moxifloxacin's bulky C-7 substituent group interferes with the quinolone efflux pump mechanism of bacteria. Moxifloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Mechanism(s) of Resistance

Fluoroquinolones, including moxifloxacin, differ in chemical structure and mode of action from β -lactam antibiotics, macrolides and aminoglycosides, and therefore may be active against bacteria resistant to β -lactam antibiotics, macrolides and aminoglycosides. Therefore, organisms resistant to these drugs may be susceptible to moxifloxacin.

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.

Breakpoints

There are no official topical ophthalmic breakpoints for moxifloxacin and although systemic breakpoints have been used, their relevance to topical ophthalmic therapy is doubtful. The systemic breakpoint used for this antibiotic is $S \leq 2\text{mg/l}$, $R \geq 4\text{mg/l}$.

Susceptibility to Moxifloxacin

Moxifloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections:

Aerobic Gram-positive micro-organisms:

Corynebacterium species

Microbacterium species

Micrococcus luteus: including erythromycin, gentamicin, tetracycline, and/or trimethoprim resistant strains

Staphylococcus aureus: including methicillin, erythromycin, gentamicin, ofloxacin, tetracycline and/or trimethoprim resistant strains

Staphylococcus epidermidis: including methicillin, erythromycin, gentamicin, ofloxacin, tetracycline and/or trimethoprim resistant strains

Staphylococcus haemolyticus: including methicillin, erythromycin, gentamicin, ofloxacin, tetracycline and/or trimethoprim resistant strains

Staphylococcus hominis: including methicillin, erythromycin, gentamicin, ofloxacin, tetracycline and/or trimethoprim resistant strains

Staphylococcus warneri: including erythromycin resistant strains

Streptococcus mitis: including penicillin, erythromycin, tetracycline and/or trimethoprim resistant strains

Streptococcus pneumoniae: including penicillin, erythromycin, gentamicin, tetracycline and/or trimethoprim resistant strains

Streptococcus viridans: including penicillin, erythromycin, tetracycline and/or trimethoprim resistant strains

Aerobic Gram-negative micro-organisms:

- *Acinetobacter* species
- *Haemophilus "alconae"*: including ampicillin resistant strains
- *Haemophilus influenzae*: including ampicillin resistant strains
- *Klebsiella pneumoniae*
- *Moraxella catarrhalis*
- *Pseudomonas aeruginosa*

Other micro-organisms:

- *Chlamydia trachomatis*

Moxifloxacin has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown.

Gram-positive bacteria

- *Aerococcus viridans*
- *Arthrobacter species*
- *Arthrobacter ureafaciens*
- *Bacillus cereus*
- *Bacillus simplex*
- *Bacillus thuringensis*
- *Brevibacillus agri*
- *Brevibacterium species*
- *Corynebacterium accolens*
- *Corynebacterium amycolatum*
- *Corynebacterium argentoratense*
- *Corynebacterium bovis*
- *Corynebacterium macginleyi*
- *Corynebacterium propinquum*
- *Corynebacterium pseudodiphtheriticum*
- *Corynebacterium simulans*
- *Corynebacterium striatum*
- *Corynebacterium tuberculostearicum*
- *Enterococcus faecalis*
- *Enterococcus faecium*
- *Enterococcus gallinarum*
- *Exiguobacterium acetylicum*
- *Gamella haemolysans*
- *Kocuria kristinae*
- *Kocuria "lindaea"*
- *Kocuria rhizophila*
- *Microbacterium arborescens*
- *Microbacterium "harmaniae"*
- *Microbacterium "otitidis"*
- *Micrococcus species*
- *Paenibacillus species*
- *Planococcus species*
- *Rothia mucilaginosus*
- *Staphylococcus arlettae*
- *Staphylococcus capitis*
- *Staphylococcus caprae*
- *Staphylococcus cohnii*
- *Staphylococcus intermedius*
- *Staphylococcus lugdunensis*
- *Staphylococcus pasteurii*
- *Staphylococcus saprophyticus*
- *Staphylococcus sciuri*
- *Staphylococcus xylosus*
- *Streptococcus "conjunctivae"*
- *Streptococcus constellatus*
- *Streptococcus cristatus*
- *Streptococcus dysgalactiae*
- *Streptococcus "ocularis"*
- *Streptococcus oralis*
- *Streptococcus parasanguinis*
- *Streptococcus pyogenes*
- *Streptococcus salivarius*
- *Streptococcus sanguis*
- *Streptococcus "schlechii"*
- *Streptococcus vestibularis*

Gram-negative bacteria:

- *Achromobacter xylosoxidans*
- *Acinetobacter baumani*
- *Acinetobacter calcoaceticus*
- *Acinetobacter johnsonii*
- *Acinetobacter junii*
- *Acinetobacter lwoffii*
- *Acinetobacter "mumbaiiae"*
- *Acinetobacter schindleri*
- *Acinetobacter ursingii*
- *Aeromonas caviae*
- *Chryseobacterium indologenes*
- *Chryseobacterium species*
- *Chryseomonas luteola*
- *Chryseomonas meningosepticum*
- *Citrobacter koseri*
- *Empedobacter species*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Enterobacter hormaechei*
- *Escherichia coli*
- *Haemophilus hemolyticus*
- *Janthinobacterium species*
- *Klebsiella oxytoca*
- *Leclercia adecarboxylata*
- *Moraxella osloensis*
- *Morganella morganii*
- *Neisseria species*
- *Ochrobactrum anthropi*
- *Pantoea agglomerans*
- *Pantoea dispersa*
- *Proteus mirabilis*
- *Providencia stuartii*
- *Pseudomonas oryzihabitans*
- *Pseudomonas stutzeri*
- *Ralstonia species*
- *Rhizobium radiobacter*
- *Roseateles species*
- *Serratia liquefaciens*
- *Serratia marcescens*
- *Shewanella species*
- *Stenotrophomonas maltophilia*

Anaerobic microorganisms

- *Fusobacterium* species
- *Granulicatella* species
- *Lactobacillus gasseri*
- *Porphyromonas* species
- *Prevotella* species
- *Propionibacterium acnes*
- *Veillonella* species

Other Organisms

- *Atypical Mycobacterium*
- *Chlamydia pneumoniae*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*

Pharmacokinetics

Following topical ocular administration of VIGAMOX[®] Eye Drops, 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[®] Eye Drops 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 400mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours.

Toxicological properties

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

Clinical Studies

VIGAMOX[®] Eye Drops 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[®] Eye Drops 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[®] Eye Drops produced clinical cure in 80% of patients with bacterial conjunctivitis. The microbiological success rates 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[®] Eye Drops produced clinical cure in 74% of patients treated for bacterial conjunctivitis. The microbiological success rates for the eradication of the baseline pathogens was 81%.

Indications

VIGAMOX[®] Eye Drops are indicated for the topical treatment of bacterial infections of the anterior segment of the eye caused by moxifloxacin susceptible strains of the following organisms:

Gram-positive bacteria:

Corynebacterium species*

Microbacterium species

*Micrococcus luteus**: including erythromycin, gentamicin, tetracycline, and/or trimethoprim resistant strains

Staphylococcus aureus: including methicillin, erythromycin, gentamicin, ofloxacin, tetracycline and/or trimethoprim resistant strains

Staphylococcus epidermidis: including methicillin, erythromycin, gentamicin, ofloxacin, tetracycline and/or trimethoprim resistant strains

Staphylococcus haemolyticus: including methicillin, erythromycin, gentamicin, ofloxacin, tetracycline and/or trimethoprim resistant strains

*Staphylococcus hominis**: including methicillin, erythromycin, gentamicin, ofloxacin, tetracycline and/or trimethoprim resistant strains

*Staphylococcus warneri**: including erythromycin resistant strains

*Streptococcus mitis**: including penicillin, erythromycin, tetracycline and/or trimethoprim resistant strains

Streptococcus pneumoniae: including penicillin, erythromycin, gentamicin, tetracycline and/or trimethoprim resistant strains

Streptococcus viridans: including penicillin, erythromycin, tetracycline and/or trimethoprim resistant strains

Gram-negative bacteria:

- *Acinetobacter* species
- *Haemophilus "alconae"*: including ampicillin resistant strains
- *Haemophilus influenzae*: including ampicillin resistant strains
- *Klebsiella pneumoniae**
- *Moraxella catarrhalis**
- *Pseudomonas aeruginosa**

Other micro-organisms:

- *Chlamydia trachomatis*

*Efficacy for this organism was studied in fewer than 10 infections

Consideration should be given to official guidance on the appropriate use of antibiotic agents.

Contraindications

VIGAMOX[®] Eye Drops are contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, to any of the excipients in this medication.

Precautions

OPHTHALMIC USE ONLY

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.

If an allergic reaction to VIGAMOX[®] Eye Drops 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.

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

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy. Therefore, treatment with VIGAMOX[®] Eye Drops should be discontinued at the first sign of tendon inflammation.

Effects on Fertility

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.

Use in Pregnancy- Category B3

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 was 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.

Since no adequate or well controlled studies in pregnant women have been conducted, VIGAMOX[®] Eye Drops should not be used during pregnancy unless clearly necessary and only if the potential benefit justifies the potential risk to the foetus.

Women of child-bearing potential

There are no special recommendations for women of childbearing potential.

Use in Lactation

Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Animal studies have shown excretion of low levels in breast milk

after oral administration of moxifloxacin. Caution should be exercised if VIGAMOX[®] Eye Drops are administered during lactation. There are no special recommendations.

Use in Children and Elderly

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

VIGAMOX[®] Eye Drops have been shown to be safe and effective in paediatric patients including neonates and can be used at the same dose as in adults.

Renal & 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[®] Eye Drops 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[®] Eye Drops is needed in patients with renal impairment.

Carcinogenicity and Mutagenicity

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* revision 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.

Genotoxicity

Moxifloxacin has shown no evidence of genotoxicity in vivo in a micronucleus test or a dominant lethal test in mice.

Drug Interactions

While drug-drug interaction studies have not been conducted with VIGAMOX[®] Eye Drops, 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 systematically administered moxifloxacin and itraconazole, theophylline, warfarin, digoxin, oral contraceptives, probenecid, 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.

Use of Contact Lenses

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

Effects on Ability to Drive and Use Machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at application, the patient must wait until the vision clears before driving or using machinery.

Adverse Effects

In clinical studies involving 1060 subjects, VIGAMOX[®] Eye Drops was administered twice or three times daily. No serious ophthalmic or systemic undesirable effects related to VIGAMOX[®] Eye Drops 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 undesirable effects assessed as definitely, probably or possibly related to treatment were reported during clinical trial of VIGAMOX[®] Eye Drops. Their incidence was either common (1.0% to 10.0%; maximum observed actual incidence of 4.1%), or uncommon (0.1% to less than 1.0%). All other effects were single reports, of which none were serious and related.

Ocular effects

Common: ocular discomfort (burning or stinging upon instillation) and ocular pruritus.

Uncommon: ocular hyperaemia, dry eye and ocular pain.

Systemic effects

Uncommon: headache

Special Senses

Uncommon: taste perversion (altered, bitter or bad taste following instillation)

Post Marketing Experience

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, adverse reactions are presented in order of decreasing seriousness.

Eye Disorders

Common ($\geq 1\%$ to $< 10\%$): eye pain, eye irritation

Uncommon ($\geq 0.1\%$ to $< 1\%$): punctate keratitis, dry eye, conjunctival haemorrhage, conjunctival hyperaemia, ocular hyperaemia, eye pruritus, abnormal sensation in eye, eyelid oedema

Rare ($\geq 0.01\%$ to $< 0.1\%$): corneal epithelium defect, corneal disorder, corneal staining, conjunctivitis, blepharitis, eye swelling, eyelid pain, conjunctival oedema, ocular discomfort, vision blurred, visual acuity reduced, asthenopia, eyelid disorder, erythema of eyelid

Not Known: ulcerative keratitis, keratitis, lacrimation increased, photophobia, eye discharge

Cardiac Disorders

Not Known: palpitations

Blood and Lymphatic system Disorders

Rare ($\geq 0.01\%$ to $< 0.1\%$): haemoglobin decreased

Immune system Disorders

Not Known: hypersensitivity

Nervous system Disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): headache, dysgeusia

Rare ($\geq 0.01\%$ to $< 0.1\%$): paresthesia

Not Known: dizziness

Respiratory, thoracic and mediastinal Disorders

Rare ($\geq 0.01\%$ to $< 0.1\%$): nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat)

Not Known: dyspnoea

Gastrointestinal Disorders

Rare ($\geq 0.01\%$ to $< 0.1\%$): vomiting

Not Known: nausea

Hepatobiliary Disorders

Rare ($\geq 0.01\%$ to $< 0.1\%$): alanine aminotransferase increased, gammaglutamyltransferase increased

Skin and subcutaneous tissue Disorders

Not Known: erythema, pruritus, rash, urticaria

Dosage and Administration

Instil one drop in the affected eye(s) 3 times a day for 4 days.

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.

Overdosage

The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of VIGAMOX[®] Eye Drops. No cases of overdose have been reported.

In New Zealand call 0800 POISON or 0800 764 766 for advice on management.

Poison Schedule of the Drug

Prescription Only Medicine.

Presentation

VIGAMOX[®] Eye Drops [1 mL (Physician sample) and 3 mL] is packaged in a 4 mL natural low density polyethylene (LDPE) DROP-TAINER[®] dispenser bottle fitted with natural LDPE dispensing plug and tan polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

Storage

Store below 25°C. Do not freeze. Discard four weeks after first opening.

Name and Address of Sponsor

Distributed in New Zealand by:

Alcon New Zealand Limited

c/o Pharmaco NZ Limited

4 Fisher Crescent

Mt wellington, Auckland

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