Alcon GLOBAL GRAPHICS

FILE NAME: 485175-0207 i Vigamox

ARTIST APPROVAL: CONCURRER:

PRINTING COLORS

BLACK

VARNISH

NON-PRINTING COLORS

NOTATIONS-DIE VINYL

PREPRESS USE ONLY

PREPRESS TECH: DATE:

ARTIST	REV	REASON FOR CHANGE	DATE
J. Yonkman		New Using 485175-0404	06/16/04
J. Yonkman	A	Text Revisions	07/07/04
J. Yonkman	B	Text Revisions	07/09/04
J. Yonkman	C	Text Revisions	08/24/05
C.Steen	D	Text Revisions	02/08/07
C.Steen	F	Text Revisions	02/12/07

FW3LBL.04863.R04 REVISED 7/29/02

INSROLL 5" X 12 1/2"

PKG. ENG. USE ONLY

A00939AB

02/25/00 REMOVED EYE SPOT;

MOVED BAR CODE

VLL APPROVAL:

Z00100A-

PKG/DATE: VLL 02/25/00

PKG/DATE: GDH 02/25/00

1. TEXT, COLOR & COATING AREA.
2. DWG. NO. & CONTROL DATE LOCATION.
3. QUIET AREA, NO TEXT, COLOR OR COATING ALLOWED, EXCEPT AS INDICATED.
4. BAR CODE AREA, BAR CODE TO BLEED OFF EDGE.

A00939AB

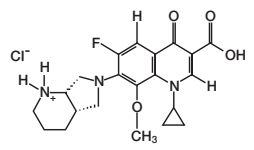
CUT OFF

5027

VIGAMOX®

(moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

DESCRIPTION: VIGAMOX® (moxifloxacin HCl ophthalmic solution) 0.5% 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.



$C_{21}H_{24}FN_3O_4 \bullet HCl$ Mol Wt 437.9

Chemical Name:

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolol[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride. Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8 position, and an S,S- configured diazabicyclononyl ring moiety at the 7-position.

Moxifloxacin hydrochloride is a slightly yellow to yellow crystalline powder.

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

Contains: Active: Moxifloxacin 0.5% (5 mg/mL); **Preservative:** None. Product is self-preserved. **Inactives:** sodium chloride, boric acid and purified water. May also contain hydrochloric acid/sodium hydroxide to adjust pH.

VIGAMOX® Solution is isotonic and formulated at pH 6.8 with an osmolality of approximately 290 mOsm/kg.

CLINICAL PHARMACOLOGY:

Pharmacokinetics/Pharmacodynamics: 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 2.7 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.

Microbiology: 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 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. 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. 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.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

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 microorganisms:
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:
Arthrobacter species
Bacillus cereus
Bacillus thuringensis
Corynebacterium accolens
Corynebacterium amycolatum
Corynebacterium bovis
Corynebacterium macginleyi
Corynebacterium propinquum
Corynebacterium pseudodiptheriticum
Enterococcus faecalis
Exiguobacterium species
Kocuria kristinae
Kocuria "lindaea"
Kocuria rhizophila
Listeria monocytogenes
Microbacterium "harmaniae"
Microbacterium "otitidis"
Rothia mucilaginosus
Staphylococcus arlettae
Staphylococcus capitis
Staphylococcus caprae
Staphylococcus cohnii
Staphylococcus lugdunensis
Staphylococcus pasteuri
Staphylococcus saprophyticus
Staphylococcus sciuri
Streptococcus agalactiae
Streptococcus "conjunctiviae"
Streptococcus cristatus
Streptococcus dysgalactiae
Streptococcus mitis
Streptococcus Groups C, G and F
Streptococcus "ocularis"
Streptococcus oralis
Streptococcus parasanguinis
Streptococcus pyogenes
Streptococcus salivarius
Streptococcus sanguis
Streptococcus "schlechii"

Gram-negative bacteria:
Achromobacter xylosoxidans
Acinetobacter baumannii
Acinetobacter calcoaceticus
Acinetobacter johnsonii
Acinetobacter junii
Acinetobacter lwoffi
Acinetobacter "mumbaiae"
Acinetobacter schindleri
Acinetobacter ursingii
Aeromonas caviae
Chryseobacterium indologenes
Chryseobacterium species
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Enterobacter hormaechei
Escherichia coli
Klebsiella oxytoca
Moraxella osloensis
Morganella morganii
Neisseria gonorrhoeae
Pantoea agglomerans
Proteus mirabilis
Proteus vulgaris
Pseudomonas orzyihabitans
Pseudomonas stutzeri
Serratia liquefaciens
Serratia marcescens
Stenotrophomonas maltophilia

Anaerobic microorganisms:
Clostridium perfringens
Fusobacterium species
Porphyromonas species
Prevotella species
Propionibacterium acnes

Other Organisms:
Atypical *Mycobacterium*
Chlamydia pneumoniae
Legionella pneumophila
Mycobacterium avium
Mycobacterium marinum
Mycoplasma pneumoniae

Clinical Studies: VIGAMOX® Solution has been studied in patients from newborns to adults, including geriatric patients.

In three randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX® Solution 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 85% to 97%.

In one of these trials in pediatric patients from birth to one month of age, VIGAMOX® Solution 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 randomized, double-masked, multicenter, controlled clinical trial in which patients were dosed 2 times a day for 3 days, VIGAMOX® Solution produced clinical cure in 74% of patients treated for bacterial conjunctivitis. Microbiological success rate for the eradication of the baseline pathogens was 81%.

Special Populations: 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.

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.

INDICATIONS AND USAGE: VIGAMOX® Solution is indicated for the treatment of bacterial conjunctivitis caused by 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 microorganisms:
Chlamydia trachomatis

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

CONTRAINDICATIONS: VIGAMOX® Solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication.

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, dyspnea, urticaria, and itching. If an allergic reaction to moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS:

General: 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. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source. Systemically administered quinolones have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Drug Interactions: While drug-drug interaction studies have not been conducted with VIGAMOX® Solution, 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 metabolized by these cytochrome P450 isozymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility: 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.

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.

Pregnancy: Teratogenic Effects.

Pregnancy Category C: 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 fetal body weights and slightly delayed fetal 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 fetuses was observed at 100 mg/kg/day.

Since there are no adequate and well-controlled studies in pregnant women VIGAMOX® Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: 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® Solution is administered to a nursing mother.

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.

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

ADVERSE REACTIONS: No serious ophthalmic or systemic adverse reactions related to VIGAMOX® Solution were reported.

Adverse reactions were generally mild and occurred at an incidence similar to placebo (vehicle). The most frequently reported event was transient ocular discomfort (burning/stinging) reported at an incidence of 2.9%. Other reported events included headache, keratitis, ocular pain, ocular pruritus, ocular hyperemia, pharyngitis and subconjunctival hemorrhage which were reported at an incidence of 0.5% to 1.0%.

DOSAGE AND ADMINISTRATION: Instill one drop in the affected eye 3 times a day for 4 days.

HOW SUPPLIED: VIGAMOX® (moxifloxacin ophthalmic solution) 0.5% is supplied as a sterile ophthalmic solution in Alcon's DROP-TAINER® dispensing system. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

5 mL

Storage: Store at 2°C to 25°C (36°F to 77°F).

Rx Only

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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U.S. PAT. NO. 5,607,942
U.S. PAT. NO. 6,716,830

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Alcon®
Alcon Laboratories, Inc.
Fort Worth, Texas USA