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Regulatory Affairs

# **VIGAMOX®** (moxifloxacin)
# 5 mg/mL Eye drops, solution

## International Package Leaflet

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# VIGAMOX®

Ophthalmologicals; anti-infectives, other anti-infectives

## DESCRIPTION AND COMPOSITION

### Pharmaceutical form

Eye drops, solution.

### Active substance

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

### Excipients

Sodium chloride, boric acid, sodium hydroxide and/or hydrochloric acid (for pH adjustment) and purified water.

## INDICATIONS

Vigamox solution is indicated for the treatment of bacterial conjunctivitis caused by bacteria susceptible to moxifloxacin. Vigamox is indicated in adults and pediatric patients including neonates, infants, children and adolescents aged 0 to 18 years.

## DOSAGE REGIMEN AND ADMINISTRATION

### Dosage regimen

The recommended dose is 1 drop of Vigamox in the affected eye(s) 3 times a day for 7 days.

### Special populations

#### Renal impairment

Dose adjustment of moxifloxacin does not appear to be necessary in patients with renal dysfunction.

### Hepatic impairment

Dose adjustment of moxifloxacin does not appear to be necessary in patients with mild to moderate hepatic impairment. The pharmacokinetics of moxifloxacin has not been studied in patients with severe hepatic insufficiency.

### Pediatric patients (below 18 years)

Vigamox may be used in pediatric patients at the same dose as in adults.

### Geriatric patients (65 years or above)

No overall difference in effectiveness has been observed between elderly and younger patients.

### Method of administration

- Vigamox is for topical ophthalmic use only.
- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.
- After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product.
- If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointment should be administered last.
- Either nasolacrimal occlusion or gently closing the eyelid(s) after administration is recommended. This may reduce the systemic absorption of medicinal products administered via ocular route and result in a decrease in systemic adverse reactions.

## CONTRAINDICATIONS

Hypersensitivity to the active substance, to other quinolones or to any of the excipients.

## WARNINGS AND PRECAUTIONS

- For ocular use only. Not for injection. Vigamox 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 Vigamox occurs, discontinue use of the product. Serious acute hypersensitivity reactions to moxifloxacin 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 elderly patients and in those treated concurrently with corticosteroids. Therefore, treatment with Vigamox should be discontinued at the first sign of tendon inflammation.
- Contact lens wear is not recommended if patients have signs and symptoms of bacterial conjunctivitis.

## ADVERSE DRUG REACTIONS

### Tabulated summary of adverse drug reactions from clinical trials

The following adverse reactions have been reported during clinical trials. Based on data from clinical trials involving pediatric patients, including neonates, the type and severity of adverse reactions in the pediatric population are similar to those in adults. Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ

class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

**Table 1 Frequency of adverse drug reactions in clinical trials**

| System organ class | Adverse reactions | Frequency category |
|---|---|---|
| **Blood and lymphatic system disorders** | Haemoglobin decreased | Rare |
| **Nervous system disorders** | Headache | Uncommon |
| | Paresthesia | Rare |
| **Eye disorders** | Eye pain, eye irritation | Common |
| | Punctate keratitis, dry eye, conjunctival haemorrhage, ocular hyperaemia, eye pruritus, eyelid edema, ocular discomfort | Uncommon |
| | Corneal epithelium defect, corneal disorder, conjunctivitis, blepharitis, eye swelling, conjunctival edema, vision blurred, visual acuity reduced, asthenopia, erythema of eyelid | Rare |
| **Respiratory, thoracic and mediastinal disorders** | Nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat) | Rare |
| **Gastrointestional disorders** | Dysgeusia | Uncommon |
| | Vomiting | Rare |
| **Hepatobiliary disorders** | Alanine aminotransferase increased, gammaglutamyltransferase increased | Rare |

## Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Vigamox Eye drops, solution via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

**Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)**

| System organ class | Adverse reactions |
|---|---|
| Immune system disorders | Hypersensitivity |
| Nervous system disorders | Dizziness |
| Eye disorders | Ulcerative keratitis, keratitis, lacrimation increased, photophobia, eye discharge |
| Cardiac disorders | Palpitations |
| Respiratory, thoracic and mediastinal disorders | Dyspnea |
| Gastrointestinal disorders | Nausea |
| Skin and subcutaneous tissue disorders | Erythema, pruritus, rash, urticaria |

## INTERACTIONS

Drug-drug interaction studies have not been conducted with Vigamox. *In vitro* studies indicate that moxifloxacin or the N-sulfonate of moxifloxacin do not inhibit P-450 isoforms; CYP3A, CYP2D6, CYP2C9, CYP2C19 or CYP1A2. Given the low systemic concentration of moxifloxacin following topical ocular administration of the medicinal product, drug interactions are unlikely to occur.

## PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

### Pregnancy

### Risk summary

There are no adequate and well-controlled studies with Vigamox in pregnant women to inform a product-associated risk. However, no effects on pregnancy are anticipated since the systemic exposure to moxifloxacin from topical ocular application is negligible.

Oral administration of moxifloxacin to rats and monkeys and intravenously to rabbits during the period of organogenesis did not produce adverse maternal or fetal effects at 30 times higher than the maximum recommended ophthalmic human dose (MROHD) based on area under the curve (AUC) (see Animal data).

### Animal data

Embryofetal studies were conducted in pregnant rats administered with 20, 100 or 500 mg/kg/day moxifloxacin by oral gavage on gestation days 6 to 17, to target the period of organogenesis. Decreased fetal body weight and delayed skeletal development were observed at 500 mg/kg/day (277 times higher than MROHD based on AUC). No-observed-adverse-effect-level (NOAEL) for developmental toxicity was 100 mg/kg/day (30 times higher than MROHD based on AUC).

Embryofetal studies were conducted in pregnant rabbits administered with 2, 6.5 or 20 mg/kg/day moxifloxacin by intravenous route on gestation days 6 to 20, to target the period of organogenesis. Abortions, increased fetal malformations, delayed fetal skeletal ossification, and reduced placental and fetal body weights were observed at 20 mg/kg/day (1086 times higher than MROHD based on AUC), a dose that produced maternal body weight loss and death. The NOAEL for developmental toxicity was 6.5 mg/kg/day (246 times higher than MROHD based on AUC).

Pregnant cynomolgus monkeys were administered moxifloxacin at doses of 10, 30 or 100 mg/kg/day by intragastric intubation between gestation days 20 to 50, targeting the period of organogenesis. At the maternal toxic doses of ≥ 30 mg/kg/day, increased abortions, vomiting and diarrhea were observed. Smaller fetuses reduced fetal body weights were observed at 100 mg/kg/day (2864 times higher than MROHD based on AUC). The NOAEL for fetal toxicity was 10 mg/kg/day (174 times higher than MROHD based on AUC).

In a pre and postnatal study, rats were administered moxifloxacin by oral gavage at doses of 20, 100 and 500 mg/kg/day from gestation day 6 until the end of lactation. Maternal death occurred

during gestation at 500 mg/kg/day. Slight increase in the duration of pregnancy, reduced pup birth weight, and decreased prenatal and neonatal survival were observed at 500 mg/kg/day (277 times higher than MROHD based on AUC). The NOAEL for pre- and postnatal development was 100 mg/kg/day (30 times higher than MROHD based on AUC).

### Lactation

### Risk summary

It is not known if moxifloxacin is transferred into human milk following topical ocular administration. A study in lactating rats has shown transfer of moxifloxacin into milk following oral administration (see Animal data).

Systemic levels of moxifloxacin following topical ocular administration are low (see section CLINICAL PHARMACOLOGY), and it is not known whether measurable levels of moxifloxacin would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Vigamox and any potential adverse effects on the breast-fed child from Vigamox.

### Animal data

Following oral administration of 5 mg/kg $^{14}$C-moxifloxacin to lactating rats, the amount of radioactivity or unchanged moxifloxacin was lower in milk than plasma. No radioactivity was detected in milk after 24 hours.

### Females and males of reproductive potential

Studies have not been performed to evaluate the effect of ocular administration of Vigamox on fertility. There is limited clinical data to evaluate the effect of moxifloxacin on male or female fertility. Moxifloxacin did not impair fertility in rats (see section NON-CLINICAL SAFETY DATA).

## OVERDOSAGE

Due to the characteristics of this preparation, no toxic effects are expected with an ocular overdose of this product, or in the event of accidental ingestion of the contents of one bottle.

## CLINICAL PHARMACOLOGY

### Mechanism of action (MOA)

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

**Mechanisms of Resistance**

Resistance to fluoroquinolones, including moxifloxacin, occurs generally by chromosomal mutations in genes encoding DNA gyrase and topoisomerase IV. In Gram-negative bacteria, moxifloxacin resistance can be due to mutations in *mar* (the 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**

The minimal inhibitory concentration (MIC) breakpoints (mg/L) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

- Staphylococcus species $S \leq 0.5, R > 1$
- Streptococcus A,B,C,G $S \leq 0.5, R > 1$
- Streptococcus pneumoniae $S \leq 0.5, R > 0.5$
- Haemophilus influenzae $S \leq 0.5, R > 0.5$
- Moraxella catarrhalis $S \leq 0.5, R > 0.5$
- Enterobacteriaceae $S \leq 0.5, R > 1$
- Not species-related $S \leq 0.5, R > 1$

The *in vitro* breakpoints have been useful in predicting clinical efficacy of moxifloxacin when administered systemically. These breakpoints might not be applicable on topical ocular use of the medicinal product as higher concentrations are obtained in the eye and the local physical/chemical circumstances can influence the activity of the product on the site of administration.

**Clinical efficacy against specific pathogens**

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 microorganisms:**

*Corynebacterium* species including

*Corynebacterium diphtheriae*

*Staphylococcus aureus* (methicillin susceptible)

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

*Streptococcus viridans* Group

**Aerobic Gram-negative microorganisms:**

*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 microorganisms:**

*Staphylococcus aureus* (methicillin resistant)

*Staphylococcus* coagulase-negative species (methicillin resistant)

**Aerobic Gram-negative microorganisms:**

*Neisseria gonorrhoeae*

**Inherently resistant organisms**

**Aerobic Gram-negative microorganisms:**

*Pseudomonas aeruginosa*

## Pharmacokinetics (PK)

The systemic pharmacokinetics of moxifloxacin has not been studied in humans following topical ocular dosing of moxifloxacin ophthalmic solution, 0.5% or gel. However, the pharmacokinetics of moxifloxacin in humans has been well characterized following oral, intravenous and topical ocular administration.

## Absorption

Following 3 times daily dosing of moxifloxacin eye drops 0.5% solution to both eyes for five days (one dose on the 5th day); mean maximal steady-state plasma concentration (Cmax) and area under the plasma concentration time curve (AUC0-∞) of moxifloxacin was 2.7 ± 1.29 ng/mL ng/mL and 41.9 ± 15.6 ng*hr/mL, respectively. This Cmax value is 1667-fold lower and the AUC0-∞ value is 917-fold lower than the reported steady-state concentration and AUC0-∞ value after 400 mg oral doses of moxifloxacin. In a clinical pharmacokinetics study reported in the literature, oral absorption of moxifloxacin of healthy volunteers is rapid and the bioavailability is almost complete at 86%.

## Distribution

Moxifloxacin distributes into human tear film after topical ocular administration of 0.5% moxifloxacin. After 3 days of bilateral TID dosing, a peak tear concentration of moxifloxacin was 55.2 µg/mL and trough concentration after 1 day of bilateral TID dosing was 4.2 µg/mL. These values are above the minimum inhibitory concentrations for many of the common pathogens associated with bacterial conjunctivitis.

Moxifloxacin does bind to melanin, resulting in a long half-life in the iris-ciliary body (pigmented rabbit) after ocular administration.

Plasma protein binding of moxifloxacin is low with a reported unbound fraction of 55% in human males, which is independent of concentration over a wide concentration range (0.1 to 10 μg/mL).

## Metabolism

Moxifloxacin undergoes both sulfation of the secondary amine (M1), major pathway and glucuronidation of the carboxyl group (M2), secondary pathway in man. Sulfation occurs on the secondary amine of moxifloxacin while glucuronidation occurs on the carboxylic acid to form an acyl glucuronide. N-sulfonate and the acyl glucuronide are approximately one-third and one-tenth of parent drug maximal concentration after oral administration. Substantial percentage of the acyl glucuronide exposure after oral administration is the result of first-pass phase II metabolism. Neither the N-sulfonate metabolite nor the acyl glucuronide appeared to be pharmacologically active.

## Elimination

The reported systemic half-life of moxifloxacin after topical ocular administration is approximately 13 hours. After systemic administration of moxifloxacin, >95% of the dose was recovered in urine and feces. Fecal excretion was found to be the major route of elimination. Both parent drug (25% of the dose) and the N-sulfonate metabolite (35% of the dose) accounted for 60% of the total dose in feces. The acyl glucuronide was not detected in feces after systemic administration. Urinary excretion accounted for another 35% of the total dose with 20% as parent drug, 15% as the N-sulfonate metabolite and 5% as the acyl-glucuronide metabolite and the renal clearance was 43 mL/min. Renal excretion is the result of glomerular filtration, active secretion (the acyl glucuronide metabolite) and tubular reabsorption.

## Linearity/non-linearity

The pharmacokinetics of moxifloxacin was linear in the range of 50 to 800 mg following the administration of a single oral dose. The plasma concentration time curves followed very similar patterns for all doses, and no significant dose dependency was detectable.

### Pharmacokinetic/pharmacodynamic relationship(s)

A pharmacodynamic/pharmacokinetic relationship after topical ocular administration has not been established.

## Special populations

Moxifloxacin does not exhibit age or gender-dependent pharmacokinetics comparing young and elderly healthy volunteers.

## Pediatric patients (below 18 years)

No pediatric pharmacokinetic results have been published.

## Renal impairment

No studies have been performed in patients with renal impairment.

### Hepatic impairment

No studies have been performed in patients with hepatic impairment.

## CLINICAL STUDIES

### Bacterial conjunctivitis (Global studies)

In three randomized, double-blind, multicenter, controlled clinical trials, 812 patients (greater than 1 month of age) with bacterial conjunctivitis were dosed 3 times a day for 4 days with moxifloxacin. At Day 9, clinical cure rates ranged from 82% to 94% and microbiological success rates for the eradication of baseline pathogens ranged from 78% to 97%.

In a randomized, double-blind, multicenter, parallel-group clinical trial of pediatric patients with bacterial conjunctivitis between birth and 31 days of age, 107 patients were dosed with moxifloxacin and 102 patients were dosed with ciprofloxacin. At Day 9, clinical cure rate in patients receiving moxifloxacin was 80% and the microbiological eradication success rate was 92%.

In these studies, strains of the following organisms were susceptible to moxifloxacin: *Corynebacterium species*, Micrococcus luteus*, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus warneri*, Streptococcus pneumoniae, Streptococcus viridans group, Acinetobacter lwoffii*, Haemophilus* species including *H. influenza,* and *H. parainfluenzae** and *Chlamydia trachomatis*.

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

### Bacterial conjunctivitis and other ocular conditions (Japan studies)

Clinical effects of moxifloxacin in extraocular infections in 389 cases (Japanese patients) from one double-blind and two open label trials are shown below according to relevant disorders.

The dosage and administration was one drop, 3 times per day, except for keratitis（including corneal ulcer), where administration ranged from 3 to 8 times per day. The rate of effectiveness was determined based on disappearance of the etiologic agent identified in the initial examination, resolution of predominant symptoms and the total score of clinical symptoms (combination therapies with other ophthalmic agents were accepted). In the clinical studies of moxifloxacin in Japan, 38/389 cases were infants or children (41 day-old to under 12 year-old), and its rate of effectiveness in this subset was 97.4% (37/38).

**Table 3 Clinical efficacy of moxifloxacin in extraocular infections (Japan studies)**

| Ocular disorders | Rate of effectiveness [more than effective] (number of cases) | Predominant symptoms |
|---|---|---|
| Conjunctivitis | 96.7% (261/270) | Eye discharge, conjunctival hyperemia |
| Blepharitis | 96.2% (25/26) | Secretions at eyelash roots, reddening of eyelids, conjunctival hyperemia |
| Dacryocystitis | 87.5% (14/16) | Watering eye, eye discharge, pus reflux, reddening and/or swelling of the lacrimal sac |
| Hordeolum | 89.6% (43/48) | Reddening and/or swelling of eyelids, eye pain |

| Ocular disorders | Rate of effectiveness [more than effective] (number of cases) | Predominant symptoms |
|---|---|---|
| Tarsadenitis | 89.5% (17/19) | Reddening and/or swelling of tarsal glands, punctate pus |
| Keratitis (including corneal ulcer) | 90.0% (9/10) | Corneal opacity |

In addition, in a preoperative and postoperative sterilization study on Japanese patients, the dosage and administration was one drop 5 times per day before the operation, and one drop 3 times per day after the operation. The bacterial eradication rate before the operation was 85.0% (68/80). The non-bacterial rate on the 15th day after the operation was 98.9% (92/93), with no cases of postoperative infection (endophthalmitis) being reported.

In these studies, strains sensitive to moxifloxacin included *Staphylococcus, Streptococcus (including Streptococcus pneumoniae), Enterococcus, Moraxella, Corynebacterium, Klebsiella, Enterobacter, Serratia, Proteus, Pseudomonas, Acinetobacter, Morganella morganii, Haemophilus influenzae, Burkholderia cepacia, Stenotrophomonas (Xanthomonas) maltophilia* and *Propionibacterium acnes.*

## NON-CLINICAL SAFETY DATA

Non-clinical data revealed no special hazard for humans from topical ocular exposure to moxifloxacin, based on repeated-dose toxicity studies.

Moxifloxacin was not mutagenic in four bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in the Ames *Salmonella* reversion assay. As with other fluoroquinolones, 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.

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 for 38 weeks, moxifloxacin hydrochloride was not carcinogenic in rats when administered orally at a dose of 500 mg/kg/day (277 times higher than MROHD based on AUC).

For information on developmental toxicity studies, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day (277 times higher than MROHD based on AUC). At 500 mg/kg/day orally, there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats. NOAEL for fertility and early embryonic development was considered to be 100 mg/kg/day (30 times higher than MROHD based on AUC).

### Juvenile animal studies

In an oral juvenile toxicity study in dogs with moxifloxacin, chondropathy was noted at doses of 30 mg/kg/day and above. The NOAEL was determined to be 10 mg/kg/day (711 times higher than MROHD based on AUC).

## INCOMPATIBILITIES

Not applicable.

## STORAGE

See folding box.

Vigamox Eye drops, solution should not be used after the date marked “EXP” on the pack.

Vigamox Eye drops, solution must be kept out of the reach and sight of children.

## INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

### Special precautions for disposal

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

### Manufacturer:

See folding box.

### International Package Leaflet

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## Novartis Pharma AG, Basel, Switzerland