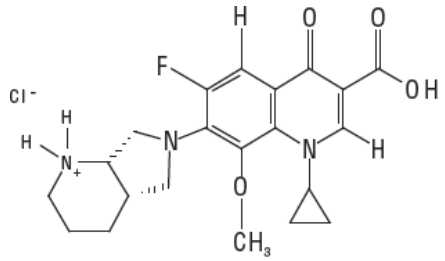
1. NAME OF THE MEDICINAL PRODUCT

VIGAMOX®

5 mg/ml eye drops, solution
(moxifloxacin hydrochloride ophthalmic solution)

VIGAMOX® (moxifloxacin HCl ophthalmic solution) 0.5% is a sterile ophthalmic solution. It is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.



$C_{21}H_{24}FN_3O_4 \bullet HCl$ 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 hydrochloride is a slightly yellow to yellow crystalline powder.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

VIGAMOX solution is an isotonic solution with an osmolality of approximately 290 mOsm/kg.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Eye drops (solution)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIGAMOX solution is indicated for the treatment of bacterial conjunctivitis, blepharitis, dacryocystitis, hordeolum, tarsadenitis, keratitis (including corneal ulcer) caused by susceptible strains, as well as preoperative and postoperative prophylaxis.

Susceptible strains include:

Aerobic Gram-positive microorganisms:

Corynebacterium species
*Enterococcus faecalis**
*Micrococcus luteus**
Staphylococcus aureus
*Staphylococcus capitis**
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
*Staphylococcus lugdunensis**
*Staphylococcus warneri**
Streptococcus pneumoniae
Streptococcus viridans group

Aerobic Gram-negative microorganisms:

*Acinetobacter lwoffii**
*Burkholderia cepacia**
Haemophilus influenzae
*Haemophilus parainfluenzae**
*Klebsiella planticola**
*Klebsiella pneumoniae**
*Moraxella catarrhalis**
*Proteus mirabilis**
*Proteus vulgaris**
*Pseudomonas aeruginosa**
*Serratia liquefaciens**
*Serratia marcescens**
*Stenotrophomonas (Xanthomonas) maltophilia**

Other microorganisms:

Chlamydia trachomatis
Propionibacterium acnes

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

Pediatric Use: The safety and effectiveness of VIGAMOX solution in bacterial conjunctivitis have

been established in all ages including children and 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 younger patients.

4.2 Posology and method of administration

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

For preoperative and postoperative prophylaxis: Usually, instill one drop in the affected eye 5 times per day for 2 days before operation, and 3 times a day up to 14 days after operation.

Patients should be instructed to leave at least 5 minutes between administrations if using VIGAMOX solution concurrently with other ophthalmic solutions.

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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

• For ocular use only. Not for injection.

• 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 solution 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.

• Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

• 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 solution 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.

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.

4.5. Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Fertility

Studies have not been performed to evaluate the effect of ocular administration of VIGAMOX solution 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 Non-clinical safety data).

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).

Breast-feeding

Risk summary

It is not known if moxifloxacin is transferred into human milk following topical ocular administration. However, at therapeutic doses of VIGAMOX solution no effects on the suckling child are anticipated. 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 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.

4.7 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.

4.8 Undesirable effects

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 trial

System Organ Class	**Adverse reactions**
Blood and lymphatic system disorders	*Rare:* haemoglobin decreased
Nervous system disorders	*Uncommon:* headache *Rare:* paresthesia
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
Respiratory, thoracic and mediastinal disorders	*Rare*: nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat)
Gastrointestinal disorders	*Uncommon*: dysgeusia *Rare*: vomiting
Hepatobiliary disorders	*Rare:* alanine aminotransferase increased, gammaglutamyltransferase increased

Non ocular adverse events reported at a rate of 1-4% were fever, increased cough, infection, otitis media, pharyngitis, and rhinitis.

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 adverse drug reactions (ADRs) are presented in order of decreasing seriousness.

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

System Organ Classification	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	Dyspnoea
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Erythema, pruritus, rash, urticaria

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Ophthalmologicals; anti-infectives, other anti-infectives.

ATC code: S01AE07

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 v2.0) are as follows:

- Staphylococcus species S ≤ 0.5, R > 1
- Streptococcus A,B,C,G S ≤ 0.5, R > 1
- Streptococcus pneumoniae S ≤ 0.5, R > 0.5

• Haemophilus influenzae S ≤ 0.5, R > 0.5
• Moraxella catarrhalis S ≤ 0.5, R > 0.5
• Enterobacteriaceae S ≤ 0.5, R > 1
• Not species-related S ≤ 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.

Microbiology

Moxifloxacin is an 8-methoxy fluoroquinolone with a diazabicyclononyl ring at the C7 position. The antibacterial action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, aminoglycosides, or tetracyclines. Therefore, moxifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to moxifloxacin. There is no cross-resistance between moxifloxacin and the aforementioned classes of antibiotics. Cross resistance has been observed between systemic moxifloxacin and some other quinolones.

In vitro resistance to moxifloxacin develops via multiple-step mutations. Resistance to moxifloxacin occurs in vitro at a general frequency of between 1.8×10^{-9} to $< 1 \times 10^{-11}$ 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 section 4.1:

Aerobic Gram-positive microorganisms:

Corynebacterium species
*Enterococcus faecalis**
Micrococcus luteus
Staphylococcus aureus
Staphylococcus capitis
Staphylococcus epidermidis

Staphylococcus haemolyticus
Staphylococcus hominis
*Staphylococcus lugdenesis**
Staphylococcus warneri
Streptococcus pneumoniae
Streptococcus viridans group

Aerobic Gram-negative microorganisms:
Acinetobacter lwoffii
Burkholderia cepacia
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella planticola
Klebsiella pneumoniae
*Moraxella catarrhalis**
*Proteus mirabilis**
*Proteus vulgaris**
Pseudomonas aeruginosa
Serratia liquefaciens
*Serratia marcescens**
Stenotrophomonas (Xanthomonas) maltophilia

Other microorganisms:
Chlamydia trachomatis
Propionibacterium acnes

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

The following *in vitro* data are also available, **but their clinical significance in ophthalmic infections is unknown.** The safety and effectiveness of VIGAMOX solution in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Moxifloxacin exhibits in vitro minimal inhibitory concentrations (MICs) of 2µg/mL or less (systemic susceptible breakpoint) against most (≥90%) of strains of the following ocular pathogens.

Aerobic Gram-positive microorganisms:
Listeria monocytogenes
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus mitis
Streptococcus pyogenes
Streptococcus Group C, G and F

Aerobic Gram-negative microorganisms:
Acinetobacter baumannii
Acinetobacter calcoaceticus
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Morganella morganii
Neisseria gonorrhoeae
Pseudomonas stutzeri

Anaerobic microorganisms:
Clostridium perfringens
Fusobacterium species
Prevotella species

Other microorganisms:
Chlamydia pneumoniae
Legionella pneumophila
Mycobacterium avium
Mycobacterium marinum
Mycoplasma pneumoniae

Pharmacokinetics (PK)
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).

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

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

Effects on preoperative and postoperative prophylaxis

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, Serratia, Proteus, Pseudomonas, Acinetobacter, 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 9 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 30 °C.

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

6.4 Nature and content of container

VIGAMOX (moxifloxacin hydrochloride ophthalmic solution) 0.5% is supplied as a sterile ophthalmic solution in a natural low density polyethylene bottle and dispensing plug and white polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

1.5 ml, 3ml, 5ml

Not all presentations are available locally.

6.5 Special precautions for disposal

No special requirement.

6.6 Manufacturer

Refer to folding box.

Rx Only

(Information Issued: Jul 2021.SIN)

Novartis Pharma AG, Basel, Switzerland