

Contents

MOXIFLOXACIN Ophthalmic Solution USP, 0.5%	1
INDICATIONS AND USAGE	2
DOSAGE AND ADMINISTRATION	2
DOSAGE FORMS AND STRENGTHS	2
CONTRAINDICATIONS	2
WARNINGS AND PRECAUTIONS	2
ADVERSE REACTIONS	3
USE IN SPECIFIC POPULATIONS	3
DESCRIPTION	5
CLINICAL PHARMACOLOGY	5
NONCLINICAL TOXICOLOGY	8
CLINICAL STUDIES	8
HOW SUPPLIED/STORAGE AND HANDLING	8
PATIENT COUNSELING INFORMATION	9

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Moxifloxacin Ophthalmic Solution USP, 0.5% safely and effectively. See full prescribing information for Moxifloxacin Ophthalmic Solution USP, 0.5%.

MOXIFLOXACIN Ophthalmic Solution USP, 0.5%
for topical ophthalmic use
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions (5.1) 8/2021

INDICATIONS AND USAGE

Moxifloxacin Ophthalmic Solution USP is a topical fluoroquinolone anti-infective indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

*Aerococcus viridans**, *Corynebacterium macginleyi**, *Enterococcus faecalis**, *Micrococcus luteus**, *Staphylococcus arlettae**, *Staphylococcus aureus*, *Staphylococcus capitis*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus saprophyticus**, *Staphylococcus warneri**, *Streptococcus mitis**, *Streptococcus pneumoniae*, *Streptococcus parasanguinis**, *Escherichia coli**, *Haemophilus influenzae*, *Klebsiella pneumoniae**, *Propionibacterium acnes*, *Chlamydia trachomatis**

*Efficacy for this organism was studied in fewer than 10 infections. (1)

DOSAGE AND ADMINISTRATION

Instill 1 drop in the affected eye(s) 2 times daily for 7 days. (2)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing moxifloxacin 0.5%. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Corneal Endothelial Damage and Toxic Anterior Segment Syndrome:** Intracameral injections will cause harm to endothelium. (5.1)
- Hypersensitivity Reactions:** Hypersensitivity and anaphylaxis have been reported with systemic use of moxifloxacin. (5.2)
- Prolonged Use:** May result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. (5.3)
- Avoid Contact Lens Wear:** Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis. (5.4)

ADVERSE REACTIONS

The most common adverse reactions reported in 1% to 2% of patients were eye irritation, pyrexia, and conjunctivitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Corneal Endothelial Damage and Toxic Anterior Segment Syndrome
 - Hypersensitivity Reactions
 - Growth of Resistant Organisms With Prolonged Use
 - Avoidance of Contact Lens Wear
- ADVERSE REACTIONS
- USE IN SPECIFIC POPULATIONS
 - Pregnancy
 - Lactation
 - Pediatric Use
 - Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacokinetics
- Microbiology

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Moxifloxacin ophthalmic solution USP is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

*Aerococcus viridans**
*Corynebacterium macginleyi**
*Enterococcus faecalis**
*Micrococcus luteus**
*Staphylococcus arlettae**
Staphylococcus aureus
Staphylococcus capitis
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
*Staphylococcus saprophyticus**
*Staphylococcus warneri**
*Streptococcus mitis**
Streptococcus pneumoniae
*Streptococcus parasanguinis**
*Escherichia coli**
Haemophilus influenza
*Klebsiella pneumoniae**
Propionibacterium acnes
*Chlamydia trachomatis**

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

2 DOSAGE AND ADMINISTRATION

Instill 1 drop in the affected eye(s) 2 times daily for 7 days.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing moxifloxacin 0.5%.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Corneal Endothelial Damage and Toxic Anterior Segment Syndrome

NOT FOR INTRACAMERAL USE OR INJECTION. Moxifloxacin ophthalmic solution will cause damage to the corneal endothelium if introduced directly into the anterior chamber of the eye.

Toxic Anterior Segment Syndrome (TASS) has been reported following intraocular administration of moxifloxacin. TASS is typically characterized by anterior chamber inflammatory reactions, such as fibrin, cell or flare and corneal edema, but other events, such as hypopyon, keratic precipitates or vitreous opacities may also occur.

5.2 Hypersensitivity Reactions

In patients receiving systemically administered quinolones, including moxifloxacin, 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.

5.3 Growth of Resistant Organisms With Prolonged Use

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.

5.4 Avoidance of Contact Lens Wear

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to moxifloxacin ophthalmic solution in 1263 patients, between 4 months and 92 years of age, with signs and symptoms of bacterial conjunctivitis. The most frequently reported adverse reactions were eye irritation, pyrexia and conjunctivitis, reported in 1% to 2% of patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with moxifloxacin ophthalmic solution in pregnant women to inform any drug-associated risks.

Oral administration of moxifloxacin to pregnant rats and monkeys and intravenously to pregnant rabbits during the period of organogenesis did not produce adverse maternal or fetal effects at clinically relevant doses. Oral administration of moxifloxacin to pregnant rats during late gestation through lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant doses (*see Data*).

Data

Animal Data

Embryo-fetal 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 (1420 times the human area under the curve (AUC) at the recommended human ophthalmic dose). The No-Observed-Adverse-Effect-Level (NOAEL) for developmental toxicity was 100 mg/kg/day (152 times the human AUC at the recommended human ophthalmic dose).

Embryo-fetal studies were conducted in pregnant rabbits administered with 2, 6.5, or 20 mg/kg/day moxifloxacin by intravenous administration on Gestation Days 6 to 20, to target the period of organogenesis. Abortions, increased incidence of fetal malformations, delayed fetal skeletal ossification, and reduced placental and fetal body weights were observed at 20 mg/kg/day (5569 times the human AUC at the recommended human ophthalmic dose), a dose that produced maternal body weight loss and death. The NOAEL for developmental toxicity was 6.5 mg/kg/day (1261 times the human AUC at the recommended human ophthalmic dose).

Pregnant cynomolgus monkeys were administered moxifloxacin at doses of 10, 30, or 100 mg/kg/day by intragastric intubation between Gestation Days 20 and 50, targeting the period of organogenesis. At the maternal toxic doses of ≥ 30 mg/kg/day, increased abortion, vomiting and diarrhea were observed. Smaller fetuses/reduced fetal body weights were observed at 100 mg/kg/day (14688 times the human AUC at the recommended human ophthalmic dose). The NOAEL for fetal toxicity was 10 mg/kg/day (894 times the human AUC at the recommended human ophthalmic dose).

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 increases in the duration of pregnancy, reduced pup birth weight, and decreased prenatal and neonatal survival were observed at 500 mg/kg/day (estimated 1420 times the human AUC at the recommended human ophthalmic dose). The NOAEL for pre- and postnatal development was 100 mg/kg/day (estimated 152 times the human AUC at the recommended human ophthalmic dose).

8.2 Lactation

Risk Summary

There are no data regarding the presence of moxifloxacin ophthalmic solution in human milk, the effects on the breastfed infants, or the effects on milk production/excretion to inform risk of moxifloxacin ophthalmic solution to an infant during lactation. A study in lactating rats has shown transfer of moxifloxacin into milk following oral administration. Systemic levels of moxifloxacin following topical ocular administration are low [*see Clinical Pharmacology (12.3)*], 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 breastfeeding should be considered along with the mother's clinical need for moxifloxacin ophthalmic solution and any potential adverse effects on the breastfed child from moxifloxacin ophthalmic solution.

8.4 Pediatric Use

The safety and effectiveness of moxifloxacin ophthalmic solution in infants below 4 months of age have not been established.

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

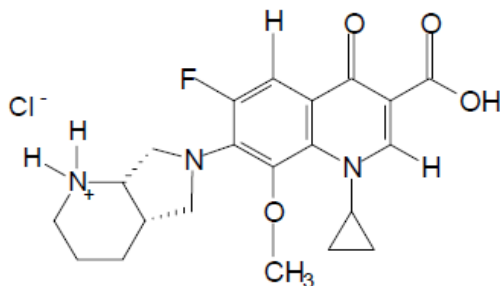
8.5 Geriatric Use

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

11 DESCRIPTION

Moxifloxacin ophthalmic solution USP is a sterile solution for topical ophthalmic use.

Moxifloxacin hydrochloride is an 8-methoxy fluoroquinolone anti-infective, with a diazabicyclononyl ring at the C7 position.



$C_{21}H_{24}FN_3O_4 \cdot HCl$

Molecular Weight: 437.9 g/mol

Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolol[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride.

Each mL of moxifloxacin ophthalmic solution USP, 0.5 % contains 5.45 mg moxifloxacin hydrochloride USP, equivalent to 5 mg moxifloxacin base.

Inactives: boric acid, sodium chloride, sorbitol, tyloxapol, xanthan gum, hydrochloric acid and/or sodium hydroxide to adjust pH, and water for injection.

Moxifloxacin ophthalmic solution USP, 0.5% is a greenish-yellow, isotonic solution with an osmolality of 300 to 370 mOsm/kg and a pH of approximately 7.4. Moxifloxacin hydrochloride is a slightly yellow to yellow crystalline powder.

USP pH and Osmolality tests are pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Moxifloxacin is a member of the fluoroquinolone class of anti-infective drugs [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

Moxifloxacin steady-state plasma pharmacokinetics were evaluated in healthy adult male and female subjects who were administered multiple, bilateral, topical ocular doses of moxifloxacin ophthalmic solution two times daily for four days with a final dose on Day 5. The average steady-state AUC_{0-12} was 8.17 ± 5.31 ng*h/mL. Moxifloxacin C_{max} following twice-daily bilateral ophthalmic administration of moxifloxacin 0.5% for 5 days is approximately 0.02% of that achieved with the oral formulation of moxifloxacin hydrochloride (C_{max} following oral dosing of 400 mg AVELOX[®], 4.5 ± 0.5 mcg/mL).

12.4 Microbiology

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 Indications and Usage section:

*Aerococcus viridans**
*Corynebacterium macginleyi**
*Enterococcus faecalis**
*Micrococcus luteus**
*Staphylococcus arlettae**
Staphylococcus aureus
Staphylococcus capitis
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
*Staphylococcus saprophyticus**
*Staphylococcus warneri**
*Streptococcus mitis**
Streptococcus pneumoniae
*Streptococcus parasanguinis**
*Escherichia coli**
Haemophilus influenza
*Klebsiella pneumoniae**
Propionibacterium acnes
*Chlamydia trachomatis**

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

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

Moxifloxacin has been shown to be active *in vitro* against most strains of the microorganisms listed below. These organisms are considered susceptible when evaluated using systemic breakpoints; however, a correlation between the *in vitro* systemic breakpoint and ophthalmologic 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 2 mcg/mL or less (systemic susceptible breakpoint) against most ($\geq 90\%$) strains of the following ocular pathogens.

Aerobic Gram-Positive Microorganisms

Staphylococcus caprae
Staphylococcus cohnii
Staphylococcus lugdunensis
Staphylococcus pasteurii
Streptococcus agalactiae
Streptococcus milleri group
Streptococcus oralis
Streptococcus pyogenes
Streptococcus salivarius
Streptococcus sanguis

Aerobic Gram-Negative Microorganisms

Acinetobacter baumannii
Acinetobacter calcoaceticus
Acinetobacter junii
Enterobacter aerogenes
Enterobacter cloacae
Haemophilus parainfluenzae
Klebsiella oxytoca
Moraxella catarrhalis
Moraxella osloensis
Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
Pantoea agglomerans
Proteus vulgaris
Pseudomonas stutzeri
Serratia liquefaciens
Serratia marcescens
Stenotrophomonas maltophilia

Anaerobic Microorganisms

Clostridium perfringens
Peptostreptococcus anaerobius
Peptostreptococcus magnus
Peptostreptococcus micros
Peptostreptococcus prevotii

Other Microorganisms

Mycobacterium tuberculosis
Mycobacterium avium
Mycobacterium kansasii
Mycobacterium marinum

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 in rats following up to 38 weeks of oral dosing at 500 mg/kg/day (4741 times the recommended daily human ophthalmic dose for a 60 kg person, based on body surface area).

Mutagenesis

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.

Impairment of Fertility

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 4741 times the highest recommended daily human ophthalmic dose. 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.

14 CLINICAL STUDIES

In one randomized, double-masked, multicenter, vehicle-controlled clinical trial in which patients with bacterial conjunctivitis were dosed with moxifloxacin ophthalmic solution 2 times a day, moxifloxacin ophthalmic solution was superior to its vehicle for both clinical and microbiological outcomes. Clinical cure achieved on Day 4 was 63% (265/424) in moxifloxacin ophthalmic solution treated patients, versus 51% (214/423) in vehicle-treated patients. Microbiologic success (eradication of baseline pathogens) was achieved on Day 4 in 75% (316/424) of moxifloxacin ophthalmic solution-treated patients versus 56% (237/423) of vehicle treated patients. Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

Moxifloxacin ophthalmic solution USP, 0.5% is supplied as a sterile ophthalmic solution in a sterile 5 mL natural low density polyethylene bottle fitted with a natural low density polyethylene nozzle and sealed with a tan coloured high density polyethylene cap as follows:

3 mL in a 5 mL bottle (NDC 68180-421-01)

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

17 PATIENT COUNSELING INFORMATION

Avoid Contamination of the Product

Advise patients not to touch the dropper tip to any surface to avoid contaminating the contents.

Avoid Contact Lens Wear

Advise patients not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Hypersensitivity Reactions

Systemically administered quinolones, including moxifloxacin, have been associated with hypersensitivity reactions, even following a single dose. Advise patients to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction [*see Warnings and Precautions (5.2)*].

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