

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MOXIFLOXACIN OPHTHALMIC SOLUTION, USP safely and effectively. See full prescribing information for MOXIFLOXACIN OPHTHALMIC SOLUTION, USP.

MOXIFLOXACIN ophthalmic solution, USP 0.5%

Sterile topical ophthalmic solution
Initial U.S. Approval: 1999

-----INDICATIONS AND USAGE-----

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

Corynebacterium species*, *Micrococcus luteus**,
Staphylococcus aureus, *Staphylococcus epidermidis*,
Staphylococcus haemolyticus,
Staphylococcus hominis, *Staphylococcus warneri**,
Streptococcus pneumoniae,
Streptococcus viridans group, *Acinetobacter lwoffii**,
Haemophilus influenzae, *Haemophilus parainfluenzae**,
Chlamydia trachomatis

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

-----DOSAGE AND ADMINISTRATION-----

Instill one drop in the affected eye(s) 3 times a day for 7 days. (2)

-----DOSAGE FORMS AND STRENGTHS-----

5 mL bottle filled with 3 mL sterile ophthalmic solution of moxifloxacin 0.5%. (3)

-----CONTRAINDICATIONS-----

Moxifloxacin ophthalmic solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication. (4)

-----WARNINGS AND PRECAUTIONS-----

- Topical ophthalmic use only. (5.1)
- 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. (5.3)
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis. (5.4)

-----ADVERSE REACTIONS-----

The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of patients. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-667-4708 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Corynebacterium species*
*Micrococcus luteus**
Staphylococcus aureus
Staphylococcus epidermidis
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*Acinetobacter lwoffii**
Haemophilus influenza
*Haemophilus parainfluenzae**
Chlamydia trachomatis

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

2 DOSAGE AND ADMINISTRATION

Instill one drop in the affected eye(s) 3 times a day for 7 days.

3 DOSAGE FORMS AND STRENGTHS

5 mL bottle filled with 3 mL sterile ophthalmic solution of moxifloxacin 0.5%.

4 CONTRAINDICATIONS

Moxifloxacin ophthalmic solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication.

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

NOT FOR INJECTION. Moxifloxacin ophthalmic solution is for topical ophthalmic use only and should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye.

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 most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of patients.

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

7 DRUG INTERACTIONS

Drug-drug interaction studies have not been conducted with moxifloxacin ophthalmic solution. *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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Teratogenic Effects: Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased 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, moxifloxacin ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 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 moxifloxacin ophthalmic solution is administered to a nursing mother.

8.4 Pediatric Use

The safety and effectiveness of moxifloxacin ophthalmic solution 0.5% have been established in all ages. Use of moxifloxacin ophthalmic solution is supported by evidence from adequate and well controlled studies of moxifloxacin ophthalmic solution in adults, children, and neonates [see *Clinical Studies (14)*].

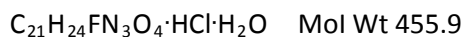
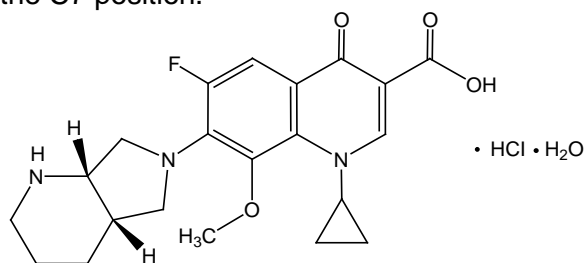
There is no evidence that the ophthalmic administration of moxifloxacin ophthalmic solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

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 0.5% 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.



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-quinoline carboxylic acid, monohydrochloride monohydrate.

Moxifloxacin hydrochloride monohydrate is a light yellow or yellow powder or crystals. Each mL of moxifloxacin ophthalmic solution, USP contains 5.45 mg moxifloxacin hydrochloride, equivalent to 5 mg moxifloxacin base.

Contains: Active: Moxifloxacin 0.5% (5 mg/mL); **Inactives:** Boric acid, sodium chloride, sodium hydroxide and water for injection. May also contain hydrochloric acid and/or additional sodium hydroxide to adjust pH to approximately 6.8.

Moxifloxacin ophthalmic solution, USP is an isotonic solution with an osmolality of approximately 290 mOsm/kg.

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

Plasma concentrations of moxifloxacin were measured in healthy adult male and female subjects who received bilateral topical ocular doses of moxifloxacin ophthalmic solution 3 times a day. The mean steady-state C_{max} (2.7 ng/mL) and estimated daily exposure AUC (45 ng•hr/mL) values were 1,600 and 1,000 times lower than the mean C_{max} and AUC reported after therapeutic 400 mg doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours.

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:

Aerobic Gram-positive microorganisms:

Corynebacterium species*
*Micrococcus luteus**
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
*Staphylococcus warneri**
Streptococcus pneumoniae
Streptococcus viridans group

Aerobic Gram-negative microorganisms:

*Acinetobacter lwoffii**
Haemophilus influenza
*Haemophilus parainfluenzae**

Other microorganisms:

Chlamydia trachomatis

*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 moxifloxacin ophthalmic 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 2 µg/ml or less (systemic susceptible

breakpoint) against most ($\geq 90\%$) 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
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Pseudomonas stutzeri

Anaerobic microorganisms:

Clostridium perfringens
Fusobacterium species
Prevotella species
Propionibacterium acnes

Other microorganisms:

Chlamydia pneumoniae
Legionella pneumophila
Mycobacterium avium
Mycobacterium marinum
Mycoplasma pneumoniae

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 (approximately 21,700 times the highest recommended total daily human ophthalmic dose for a 50 kg person, on a mg/kg basis).

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. At 500 mg/kg 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 two randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, moxifloxacin ophthalmic solution produced clinical cures on day 5-6 in 66% to 69% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of baseline pathogens ranged from 84% to 94%.

In a randomized, double-masked, multicenter, parallel-group clinical trial of pediatric patients with bacterial conjunctivitis between birth and 31 days of age, patients were dosed with moxifloxacin ophthalmic solution or another anti-infective agent. Clinical outcomes for the trial demonstrated a clinical cure rate of 80% at Day 9 and a microbiological eradication success rate of 92% at Day 9.

Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

Moxifloxacin ophthalmic solution, USP is supplied as a sterile ophthalmic solution in a white translucent 5 mL LDPE bottle with an LDPE dropper tip, and a tan HDPE cap.

3 mL in a 5 mL bottle - NDC 60505-0582-4

Storage:

Store at 2°- 25°C (36°- 77°F).

17 PATIENT COUNSELING INFORMATION

Risk of Contamination: Advise patients not to touch the dropper tip to any surface to avoid contaminating the contents.

Concomitant Use of Contact Lenses: Advise patients not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Potential for Hypersensitivity Reactions: Systemically administered quinolones including moxifloxacin have been associated with hypersensitivity reactions, even following a single dose. Instruct 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)].

Rx Only

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