PRODUCT MONOGRAPH

[Pr]TEVA-MOXIFLOXACIN

Moxifloxacin Ophthalmic Solution, USP

0.5% w/v moxifloxacin (as moxifloxacin hydrochloride)

Sterile

Antibacterial (ophthalmic)

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Toronto, Ontario
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Ophthalmic	Solution / 0.5% w/v	Boric acid, sodium chloride and water for injection. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH.

INDICATIONS AND CLINICAL USE

TEVA-MOXIFLOXACIN (moxifloxacin hydrochloride) ophthalmic solution is indicated for the treatment of patients 1 year of age and older with bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic, Gram-Positive:
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae
Streptococcus viridans group

Aerobic, Gram-Negative:
Acinetobacter species
Haemophilus influenzae

CONTRAINDICATIONS

TEVA-MOXIFLOXACIN (moxifloxacin hydrochloride) 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 (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

WARNINGS AND PRECAUTIONS

For ocular use only.

TEVA-MOXIFLOXACIN (moxifloxacin hydrochloride) ophthalmic solution is not for injection into the eye.

TEVA-MOXIFLOXACIN (moxifloxacin hydrochloride) ophthalmic solution should not be injected subconjunctivally, nor should it be 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 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.

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving therapy with all oral antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson Syndrome), vasculitis, arthralgia, myalgia, serum sickness, allergic pneumonitis, interstitial nephritis, acute renal insufficiency or failure, hepatitis, jaundice, acute hepatic necrosis or failure, anemia including hemolytic and aplastic, thrombocytopenia including thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia, and/or other hematologic abnormalities.

General: As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

In general, patients with signs and symptoms of bacterial conjunctivitis should be advised not to wear contact lenses.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. Treatment with TEVA-MOXIFLOXACIN should be discontinued at the first sign of tendon inflammation.

There are no studies on the effect of ocular administration of moxifloxacin hydrochloride ophthalmic solution on fertility.

TEVA-MOXIFLOXACIN may cause temporary blurred vision or other visual disturbances, which 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.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemically administered quinolones have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

The potential of moxifloxacin hydrochloride ophthalmic solution to produce arthropathy in animals has not been studied. Moxifloxacin and other members of the quinolone class have been shown to cause arthropathy in immature Beagle dogs following oral administration (see **TOXICOLOGY**).

Drug Interactions: Drug-drug interaction studies have not been conducted with moxifloxacin hydrochloride ophthalmic solution. Moxifloxacin can be chelated by polyvalent ions such as Mg^{++}, $A1^{+++}$, Fe^{++} and Zn^{++}. There is limited information available on the concurrent use of moxifloxacin hydrochloride ophthalmic solution and other ophthalmic products.

Following oral administration, no clinically significant drug-drug interactions between theophylline, warfarin, digoxin, oral contraceptives or glyburide have been observed with moxifloxacin. Theophylline, digoxin, probenecid, and ranitidine have been shown not to alter the pharmacokinetics of moxifloxacin. *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.

Special Populations

Pregnancy: Since there are no adequate and well-controlled studies in pregnant women moxifloxacin hydrochloride ophthalmic solution should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Moxifloxacin hydrochloride ophthalmic solution has not been studied in pregnant animals. Oral and IV studies in pregnant animals indicated that moxifloxacin is not teratogenic. Decreased fetal birth weights and slightly delayed fetal skeletal development were observed in rats and rabbits following oral and intravenous administration of moxifloxacin, respectively. An increased incidence of smaller fetuses was observed in monkeys following oral dosing (see **TOXICOLOGY**). When ^{14}C-moxifloxacin was administered orally to pregnant rats, radioactivity penetrated the placenta and was absorbed to a moderate extent by the fetus. The ratio for AUC (0-24 h) for fetal plasma to maternal plasma was 0.656.

As with other members of the quinolone class, moxifloxacin has caused arthropathy in immature Beagle dogs following oral administration. The significance of these findings to humans is unknown (see **TOXICOLOGY)**.

Nursing Mothers: Moxifloxacin is excreted in the breast milk of rats following oral and intravenous administration. Because of the potential for unknown effects from moxifloxacin in infants being nursed by mothers taking TEVA-MOXIFLOXACIN ophthalmic solution, a decision should be made to either discontinue nursing or discontinue the administration of TEVA-MOXIFLOXACIN ophthalmic solution, taking into account the importance of TEVA-MOXIFLOXACIN ophthalmic solution therapy to the mother and the possible risk to the infant (see **TOXICOLOGY**).

Pediatric Use: The safety and efficacy of moxifloxacin hydrochloride ophthalmic solution in patients less than one year of age has not been established.

The effect of TEVA-MOXIFLOXACIN ophthalmic solution on weight bearing joints has not been assessed. Oral administration of some quinolones, including moxifloxacin, has been shown to cause arthropathy in immature animals (see **TOXICOLOGY**).

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

ADVERSE REACTIONS

In clinical trials involving 1068 subjects/patients, moxifloxacin hydrochloride ophthalmic solution was administered twice-daily for three days, three-times-daily for four to fourteen days and eight-times-daily for fourteen days. During treatment with moxifloxacin hydrochloride ophthalmic solution, 6.6% (71 out of 1068) subjects/patients experienced treatment-related adverse drug reactions and of these only two (0.2%) discontinued study participation. No serious ophthalmic or systemic adverse reactions related to moxifloxacin hydrochloride ophthalmic solution were reported.

Clinical Trial Adverse Drug Reactions

The most frequently reported treatment-related adverse drug reactions were transient eye irritation (3.9%) (burning and/or stinging) and eye pruritus (1.1%).

Treatment-related adverse drug reactions that occurred at an incidence of 0.1% to less than 1.0% included the following:

Eye disorders: ocular hyperaemia, keratoconjunctivitis sicca, abnormal sensation in eye, ocular discomfort, corneal epithelium defect, conjunctivitis, conjunctival haemorrhage, visual acuity reduced, eyelid oedema, eye pain.

General disorders and administration site conditions: sensation of foreign body.

Investigations: corneal staining, alanine aminotransferase increased.

Nervous system disorders: dysgeusia, headache.

Respiratory, thoracic, and mediastinal disorders: pharyngolaryngeal pain.

Post-Market Adverse Drug Reactions
Adverse reactions identified from spontaneous reporting and subsequent clinical trials are listed below.

Blood and lymphatic system disorders: hemoglobin decreased

Cardiac disorders: palpitations

Eye disorders: anterior chamber cells, asthenopenia, blepharitis, conjunctival edema, corneal deposits, corneal disorders, corneal infiltrates, dry eye, endophthalmitis, erythema of eyelid, eye discharge, eye irritation, eye swelling, keratitis, lacrimination increased, photophobia, punctate keratitis, ulcerative keratitis, vision blurred, visual acuity reduced

Gastrointestinal disorders: nausea, vomiting

Hepatobiliary disorders: gamma-glutamyltransferase increased

Immune system disorders: hypersensitivity NOS

Nervous system disorders: dizziness, paresthesia

Respiratory, thoracic and mediastinal disorders: dyspnea, nasal discomfort

Skin and subcutaneous tissue disorders: erythema, pruritis, rash, urticaria

DOSAGE AND ADMINISTRATION

The recommended dosage regimen for patients one year of age and older is one drop in the affected eye(s) 3 times a day for 7 days.

OVERDOSE

No information is available on overdose of moxifloxacin hydrochloride ophthalmic solution in humans. A topical overdose of TEVA-MOXIFLOXACIN ophthalmic solution may be flushed from the eye(s) with warm tap water.

In an oral (gavage) monkey study, doses of moxifloxacin hydrochloride up to 15 mg/kg/day did not produce any toxicity. This dose is at least 10 times higher than the accidental ingestion of the contents of a 3 mL bottle of moxifloxacin hydrochloride ophthalmic solution by a 10 kg child.

No toxic effects are expected with an ocular overdose of the product, or in the event of accidental ingestion of the contents of one bottle.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Moxifloxacin is a synthetic fluoroquinolone antibacterial agent active *in vitro* against a broad spectrum of Gram-positive and Gram-negative ocular pathogens, atypical microorganisms and anaerobes.

The antibacterial action of moxifloxacin results from inhibition of 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 (see **MICROBIOLOGY**).

Pharmacokinetics/Pharmacodynamics:
Following topical ocular administration of moxifloxacin hydrochloride ophthalmic solution, moxifloxacin was absorbed into the systemic circulation. Plasma concentrations of moxifloxacin were measured in 21 male and female adult subjects who received bilateral topical ocular doses of moxifloxacin hydrochloride ophthalmic solution every 8 hours for a total of 13 doses. The mean steady-state C_{max} and AUC were 2.7 ng/mL and 41.9 ng·hr/mL, respectively. These systemic exposure values were at least 1,600 and 1,000 times lower than the mean C_{max} and AUC reported after therapeutic 400 mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours. Moxifloxacin is widely distributed in the body and is excreted in feces or urine either unchanged or as glucuronide or sulfate conjugates.
Tear film concentrations were studied in 31 healthy male and female adult volunteers who were administered 1 drop of moxifloxacin hydrochloride ophthalmic solution to both eyes every 8 hours for a total of 10 doses. Mean tear concentrations at 5 minutes following the first and last topical dose were 46.0 and 55.2 µg/mL, respectively. Thereafter, they decline rapidly in a biphasic manner with the means ranging approximately 1 to 4 µg/mL over the 1 to 8 hour sampling period. Pre-dose morning tear concentrations on Days 2 to 4 averaged over 4 µg/mL. Studies conducted in animals indicate penetration into the conjunctiva and ocular tissues with prolonged binding to melanin.

STORAGE AND STABILITY

Store at 2°C - 25°C. Protect from light. Discard 28 days after opening.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition: Each mL of TEVA-MOXIFLOXACIN (moxifloxacin hydrochloride) ophthalmic solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base. TEVA-MOXIFLOXACIN ophthalmic solution contains the following inactive ingredients; sodium chloride, boric acid and water for injection. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH.

TEVA-MOXIFLOXACIN ophthalmic solution is preservative-free, the product is self-preserved.

TEVA-MOXIFLOXACIN ophthalmic solution is isotonic and formulated at pH 6.4-7.2 with an osmolality of approximately 260-320 mOsm/kg.

TEVA-MOXIFLOXACIN ophthalmic solution, 0.5% is supplied as a 3 mL sterile ophthalmic solution in a white plastic bottle with dropper and a tan tamper evident closure cap.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

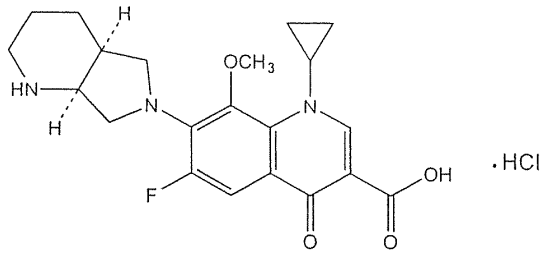
Drug Substance: Moxifloxacin hydrochloride

Proper Name: Moxifloxacin Hydrochloride

Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridine-6-yl]-4-oxo-3-quinolone carboxylic acid, monohydrochloride

1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride

Structural Formula:



Molecular Formula: $C_{21}H_{24}FN_3O_4$•HCl

Molecular Weight: 437.93

Description: Moxifloxacin hydrochloride is light yellow to yellow crystalline powder. Moxifloxacin hydrochloride has a specific optical rotation of -125° to -138°. The pH of moxifloxacin hydrochloride is 3.65 and the pKa is 6.19 and 9.28.

CLINICAL STUDIES

In two, randomized, double-masked, multicenter, controlled trials in which 547 patients dosed with moxifloxacin hydrochloride ophthalmic solution 3 times a day for 4 days, moxifloxacin hydrochloride ophthalmic solution produced clinical cures on day 5 to 6 in 66% to 69% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 84% to 94% at the test-of-cure visit (day 9). Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

DETAILED PHARMACOLOGY

Animal Pharmacokinetics:
Ocular tissue concentrations of moxifloxacin were determined in pigmented rabbits following a single bilateral 30 µL topical administration of 0.3% ophthalmic solution of moxifloxacin (n=3 rabbits sampled at each time point). Mean maximum concentrations (C_{max}) in cornea and aqueous humor were 12.5 ± 3.8 µg/g and 1.78 ± 0.39 µg/mL, respectively, and were achieved within 30 minutes after dosing. In iris-ciliary body, a moxifloxacin C_{max} of 10.4 ± 5.6 µg/g was observed at 1 hour and declined slowly relative to other tissues, presumably due to binding to melanin pigment, which is characteristic of fluoroquinolones. The accumulation in ocular tissues of moxifloxacin after multiple dosing has not been studied. Maximum plasma concentrations were low (approximately 0.01 µg/mL) and declined rapidly.

The distribution of radiolabeled moxifloxacin was also studied in pigmented rabbits after a single unilateral 30 µL dose of a 0.3% ^{14}C-moxifloxacin solution (n=4 rabbits sampled at each time point). Mean C_{max} values in cornea, conjunctiva, aqueous humor and iris-ciliary body were 10.6 ± 2.8 µg/g, 2.54 + 0.40 µg/g, 1.36 ± 0.33 µg/mL and 7.54 ± 3.34 µg/g, respectively. Maximum concentrations and half-lives in ocular tissues are summarized in Table 1.

Table 1: Maximum Concentrations and Half-Lives of Radiolabeled Moxifloxacin in Ocular Tissues from Pigmented Rabbits

Tissue	C_{max} (µg equivalents/g) ± SD	$t_{½}$ (hours)
Cornea	10.6 ± 2.8	92
Conjunctiva	2.54 ± 0.40	43
Aqueous Humor	1.36 ± 0.33	5.6
Iris-Ciliary Body	7.54 ± 3.34	649
Lens	0.08 ± 0.06	37
Anterior Sclera	2.86 ± 1.01	1080
Posterior Sclera	0.09 ± 0.03	92
Choroid	0.441 ±0.178	872
Retina	0.066 ± 0.016	48

Tear film concentrations of moxifloxacin were measured in pigmented rabbits (n=3) after single unilateral administration of 30 µL of a 0.3% moxifloxacin ophthalmic solution. The mean concentration of moxifloxacin was 366 ± 214 µg/mL at the first sampling point of 1 minute after dosing. The levels then declined rapidly such that by 5 minutes after dosing the concentrations were approximately 20 µg/mL. The concentrations in the tear film were 1.73 ± 1.50 µg/mL at 6 hours post-dosing. Tear concentration data are summarized in Table 2.

Table 2: Tear Concentrations of Moxifloxacin Following Administration of a 0.3% Moxifloxacin Solution to Pigmented Rabbits

Time After Dose (minutes)	Mean Concentration ± SD (µg/mL)	Sample Size
1	366 ± 214	3
2	74.2 ± 70.6	3

Time After Dose (minutes)	Mean Concentration ± SD (µg/mL)	Sample Size
3	60.9 ± 11.9	3
5	23.7 ± 17.2	3
10	19.4 ± 4.03	3
20	23.4 ± 11.6	3
30	10.3 ± 3.6	3
45	1.21 ± 0.65	3
60	7.14 ± 6.12	3
90	2.69 ± 1.32	3
120	7.27 ± 9.96	2*
180	1.67 ± 1.06	2*
360	1.73 ± 1.50	2*

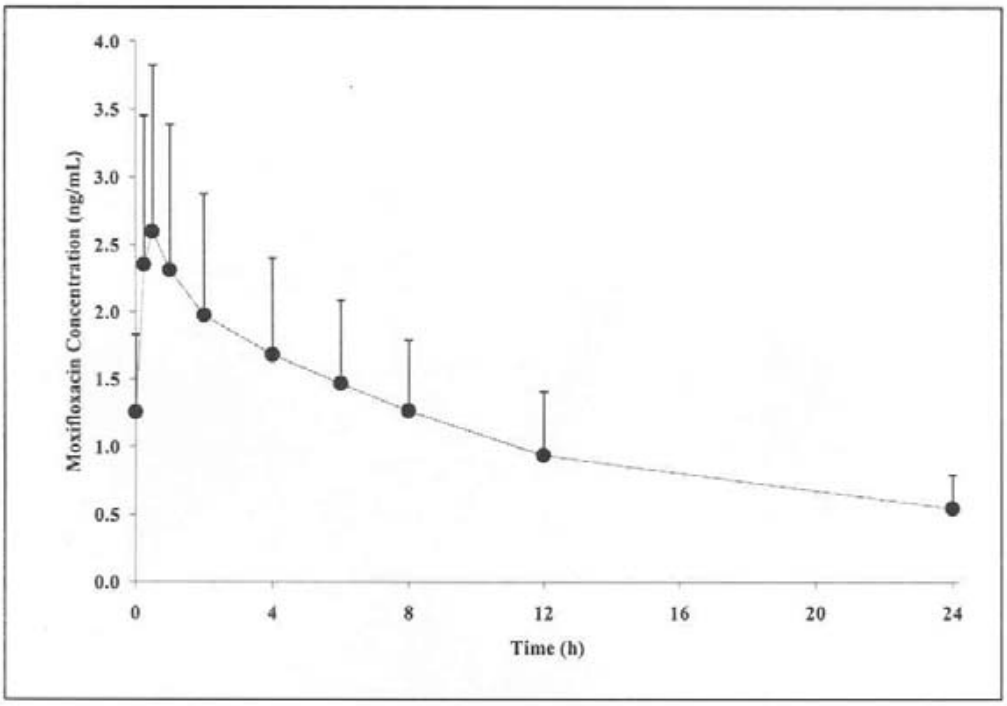
* 1 of 3 samples below quantitation limit of the assay. These samples were assigned a value of one half the limit of quantitation for calculation of the mean (1 µg/mL/2 = 0.5 µg/mL)

Human Pharmacokinetics:
Plasma concentrations were studied in 21 healthy male and female subjects who were administered moxifloxacin hydrochloride ophthalmic solution to both eyes every 8 hours for a total of 13 doses. The results showed measurable plasma concentrations of moxifloxacin (≥ 0.75 ng/mL) in 16 of 21 subjects at 4-hours following the first dose, and in all subjects following the last dose. Figure 1 shows the mean moxifloxacin plasma concentrations following the last dose.

The mean steady-state estimates for C_{max} and AUC were 2.7 ng/mL and 41.9 ng·hr/mL, respectively. The steady-state parameter estimates for C_{max} and AUC were at least 1,600 and 1,000 fold lower than mean C_{max} and AUC values reported after therapeutic 400 mg oral doses of moxifloxacin. The steady-state plasma half-life of moxifloxacin was estimated to be 13 hours.

Subgroup analysis by race (Caucasian, Asian) showed no meaningful differences in the mean steady-state pharmacokinetic parameters of moxifloxacin. Gender differences in the steady-state C_{max} and AUC were seen; however, when adjusted for body weight, the differences were minimized and not clinically relevant.

Figure 1: Mean (+ SD) Moxifloxacin Plasma Profile Following the Last Topical Ocular Dose of Moxifloxacin Hydrochloride Ophthalmic Solution in Healthy Subjects



Tear film concentrations of moxifloxacin were studied in 31 healthy male and female adult volunteers who were administered 1 drop of moxifloxacin hydrochloride ophthalmic solution to both eyes every 8 hours for a total of 10 doses.

Mean tear concentrations at 5 minutes following the first and last topical dose were 46.0 and 55.2 µg/mL, respectively. Thereafter, mean tear concentrations rapidly declined in a biphasic manner with means ranging from approximately 1 to 4 µg/mL over the 1 to 8 hour sampling period. Pre-dose morning tear concentrations on Days 2 to 4 averaged over 4 µg/mL, demonstrating that concentrations are above the MICs for most of the common organisms in conjunctivitis over the 24-hour period.

Elimination and Metabolism: Moxifloxacin is widely distributed in the body tissues and approximately 50% is bound to serum proteins. Animal studies indicate some penetration into conjunctiva and ocular tissues with prolonged binding to melanin. Approximately 45% of an oral dose is excreted as unchanged drug, and most of the rest as glucuronide and sulfate conjugates in feces and urine. The cytochrome P450 enzyme system is not involved in metabolizing the drug.

Drug-Drug Interactions: Specific drug-drug pharmacokinetic interaction studies were not conducted with moxifloxacin hydrochloride ophthalmic solution. Given the low systemic exposure observed for moxifloxacin after topical ocular administration of moxifloxacin hydrochloride ophthalmic solution, clinically relevant drug-drug interactions through protein binding, renal elimination or hepatic metabolism are unlikely following topical ocular

administration. Moxifloxacin can be chelated by polyvalent ions such as Mg^{++}, $A1^{+++}$, Fe^{++} and Zn^{++}.

In vitro studies with cytochrome P450 isozymes have shown 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 enzymes.

Special Populations:
The pharmacokinetics of moxifloxacin hydrochloride ophthalmic solution has not been studied in patients with hepatic or renal impairment. However, the pharmacokinetics of orally administered moxifloxacin has been studied in these special populations.

The pharmacokinetic parameters of oral moxifloxacin are not significantly altered by mild, moderate or severe renal impairment. No dosage adjustment of moxifloxacin hydrochloride ophthalmic solution is necessary in patients with renal impairment.

Pharmacokinetic parameters of oral moxifloxacin were not significantly altered in patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). Studies were not performed in patients with severe hepatic impairment (Child Pugh Class C). Because of the low systemic exposure by the topical route of administration, no dosage adjustment of moxifloxacin hydrochloride ophthalmic solution is needed in patients with hepatic impairment.

MICROBIOLOGY

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative microorganisms.

The antibacterial action of moxifloxacin results from inhibition of 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 presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, a proposed mechanism of fluoroquinolone resistance.

Moxifloxacin concentrations at twice the MIC are sufficient to be bactericidal for most strains of *Staphylococcus aureus. Streptococcus pneumoniae*, and *Haemophilus influenzae*. Concentrations of moxifloxacin somewhat greater than twice the MIC were bactericidal for strains of *Escherichia coli* while those greater than ten times the MIC were bactericidal for *Streptococcus pyogenes*.

Resistance: The mechanism of resistance of quinolones, including moxifloxacin, is different from that of macrolides, aminoglycosides, tetracyclines or ß-lactams. 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 slowly via multiple-step mutations and occurs *in vitro* at a general frequency of between 1.8×10^{-9} to less than 1×10^{-11} in one strain of *Staphylococcus aureus* and one strain of *Streptococcus pneumoniae*.

Moxifloxacin has been shown to be active against most strains of the following microorganisms (see Table 3), both *in vitro* and in clinical infections from the US and India (see **INDICATIONS**).

Table 3: Moxifloxacin *In Vitro* Activity Against Clinical Isolates

Pathogen	N	MIC Range µg/mL	MIC_{50} µg/mL	MIC_{90} µg/mL
Aerobic, Gram-Positive				
Staphylococcus aureus	49	≤ 0.016 – 2.0	0.06	1.0
Staphylococcus epidermidis	119	≤ 0.016 – 2.0	0.06	0.25
Staphylococcus haemolyticus	22	0.03 – 2.0	0.13	1.0
Staphylococcus hominis	11	0.06 – 1.0	0.06	0.13
Streptococcus pneumoniae	42	0.03 – 0.25	0.13	0.25
Streptococcus viridans group	22	0.06 – 2.0	0.25	0.25
Aerobic, Gram-Negative				
Acinetobacter species	15	≤ 0.016 – 0.25	0.03	0.06
Haemophilus influenzae	68	≤ 0.016 – 0.25	0.06	0.13

The following *in vitro* data (Table 4) are also available, but their clinical significance in ophthalmic infections is unknown. The safety and effectiveness of moxifloxacin hydrochloride ophthalmic solution in treating ophthalmic infections due to these organisms 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 ophthalmic efficacy has not been established. This list of organisms (Table 4) 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 breakpoint susceptibility) against most (greater than or equal to 90%) strains of the following ocular isolates:

Table 4: Susceptibility of Bacterial Conjunctivitis Isolates to Moxifloxacin

Bacterial Species	N	MIC Range µg/mL	MIC_{50} µg/mL	MIC_{90} µg/mL
Aerobic Gram-positive Microogranisms				
Bacillus cereus	15	0.032-0.25	0.13	0.13
Corynebacterium species	35	0.016-16	0.25	2.0
Kocuria species	11	0.25-0.50	0.25	0.50
Micrococcus luteus	35	0.03-1.0	0.5	1.0
Staphylococcus capitis	68	0.03-1.0	0.13	0.25

Bacterial Species	N	MIC Range µg/mL	MIC_{50} µg/mL	MIC_{90} µg/mL
Staphylococcus caprae	13	0.06-0.13	0.06	0.13
Staphylococcus lugdunensis	36	0.06-1.0	0.13	0.25
Staphylococcus pasteuri	15	0.06-1.0	0.13	0.25
Staphylococcus saprophyticus	18	0.13-0.25	0.13	0.25
Staphylococcus warneri	10	0.06-0.13	0.13	0.13
Streptococcus mitis	76	0.06-0.25	0.13	0.25
Streptococcus oralis	10	0.13-0.25	0.13	0.25
Streptococcus parasanguinis	18	0.06-1.0	0.13	0.25
Aerobic, Gram-negative Microorganisms				
Acinetobacter baumannii	23	0.03-0.50	0.13	0.25
Acinetobacter junii	27	0.03-8.0	0.06	0.13
Acinetobacter schindleri	10	0.03-0.06	0.03	0.06
Acinetobacter ursingii	10	0.06-1.0	0.25	0.50
Citrobacter koseri	12	0.016-0.25	0.03	0.13
Enterobacter hormaechei	13	0.06-8.0	0.13	0.5
Escherichia coli	21	0.03-32	0.06	1.0
Klebsiella pneumoniae	17	0.06-2.0	0.13	0.5
Moraxella osloensis	13	0.03-0.25	0.06	0.25
Moraxella catarrhalis	25	0.06-0.13	0.06	0.13
Pseudomonas stutzeri	67	0.03-2.0	0.25	0.50
Serratia marcescens	20	0.25-2.0	0.5	1.0
Stenotrophomonas maltophilia	18	0.25-2.0	0.5	2.0

Susceptibility Tests: There are currently no NCCLS approved standards for assessing *in vitro* susceptibility of conjunctival isolates to topical antibiotics, including moxifloxacin. Standardized systemic susceptibility tests may not be appropriate to predict clinical effectiveness in treating conjunctivitis.

TOXICOLOGY

Topical Ocular Studies: Ophthalmic solutions of moxifloxacin were evaluated in repeat-dose topical ocular studies in rabbits (pigmented) and Cynomolgus monkeys (see Table 5).

Table 5: Results of Topical Ocular Studies

Species/No. per Group	Dose/Route	Duration of Treatment	Findings
Rabbits (pigmented)/ 4 male, 4 female	0.5%, 1%, 3% (80 µL, unilateral, 4 times daily) / topical ocular	1 month	Low ocular irritation potential; no significant ocular or systemic effects
Cynomolgus monkeys/ 4 male, 4 female	0.5%, 1%, 3% (80 µL unilateral, 6 times daily Days 1-16, 3 times daily thereafter) / topical ocular	3 months	Low ocular irritation potential; no significant ocular or systemic effects

Ocular Toxicity Study: A special ocular toxicity study was conducted in dogs following systemic (oral) administration of moxifloxacin (see Table 6). The daily dosages of moxifloxacin evaluated in this study are significantly higher than the recommended daily dose of TEVA-MOXIFLOXACIN ophthalmic solution.

Table 6: Results of Ocular Toxicity Study

Species/No. per Group	Dose/Route	Duration of Treatment	Findings
Dog (Beagle)/ 4 males	30, 60, 90 mg/kg moxifloxacin/orally 100 mg/kg nalidixic acid (positive control)/orally	2 weeks (with 8 week recovery period)	↓ in group mean amplitude of a- and b-waves at 60 and 90 mg/kg moxifloxacin and with nalidixic acid; Histopath: slight to marked atrophy in outer nuclear and plexiform layers and rod and cone layers of two high dose animal; NOEL = 30 mg/kg orally (over 1300 times > the human dose of moxifloxacin ophthalmic solution).

Single and Repeat-Dose Oral and IV Studies: Oral and intravenous single-dose studies conducted with moxifloxacin are summarized in Table 7, and repeat-dose systemic studies that included ocular evaluations are summarized in Table 8. The daily dose levels of moxifloxacin evaluated in these studies are significantly higher than the recommended daily dose of moxifloxacin hydrochloride ophthalmic solution.

Table 7: Single-Dose Systemic Studies

Species	Strain/Sex	No./Group	Route of Administration	LD_{50} mg/kg B.W. (Conf. Int. for 95%)
Mouse	NMRI/male	5	p.o.	Approx. 435
	NMRI/female		p.o.	Approx. 758 (440-1305)
	NMRI/male		i.v.	Approx. 105 (84-132)
	NMRI/female		i.v.	Approx. 130 (116-145)
	WU/male		p.o.	Approx. 1320
	WU/female		p.o.	Approx. 1320
	WU/male		i.v.	Approx. 112
	WU/female		i.v	Approx. 146
Monkey	Cynomolgus/Male	2	p.o.	Approx. 1500

Table 8: Repeat-Dose Systemic Studies

Species/ No. Per Group	Dose/Route	Duration of Treatment	Findings
Wistar rats/ 15 male, 15 female	0, 20, 100, 500, 750 mg/kg/ orally by gavage	13 weeks for all groups; 1 group examined after a 4 week recovery period	↓ body wt gain at 100, 500, 750 mg/kg males; ocular evaluations (indirect ophthalmoscope and slit-lamp) unremarkable; ↑ ASAT, ALAT, LDH at 500, 750 mg/kg males and females at 750 mg/kg,

Species/ No. Per Group	Dose/Route	Duration of Treatment	Findings
			histopath unremarkable; NOAEL for females 100 mg/kg, 20 mg/kg for males
Wistar rats/ 20 male, 20 female	0, 20, 100, 500 mg/kg / orally by gavage	28 weeks	↓ body wt. gain at 500 mg/kg both sexes; ↑ ASAT, ALAT, LDH, bilirubin 500 mg/kg males; ocular evaluations (indirect ophthalmoscope and slit-lamp) unremarkable, histopath 500 mg/kg both sexes, thyroid 500 mg/kg males NOAEL females 100 mg/kg, males 20 mg/kg
Young Beagle pups/4 male, 4 female	0, 10, 30, 90 mg/kg/p.o.	4 weeks	Vacuolization of subcapsular lens cortex (indirect ophthalmoscope and slit-lamp) at 90 mg/kg; no evidence of co-cataractogenesis; prolongation of QT interval at 90 mg/kg; histopath chondropathy at 30 and 90 mg/kg.
Young Beagle pups/ 2 male, 2 female	0, 10, 30, 90 mg/kg/p.o.	4 weeks	Vomiting, salivation, ↓ body wt. gain at 90 mg/kg; ocular evaluations (indirect ophthalmoscope) unremarkable; histopath blistering of articular cartilage at 30 and 90 mg/kg
Rhesus monkeys/ 3 male, 3 female	0, 100, 150 mg/kg / orally by gavage	4 weeks	↓ body wt. gain at 150 mg/kg; ocular evaluations (indirect ophthalmoscope) unremarkable; histopath liver and bone marrow at 100 and 150 mg/kg
Rhesus monkeys/ 4 male, 4 female	0, 15, 45, 135 mg/kg/orally by gavage	13 weeks	Salivation at 15 mg/kg; salivation, vomiting, ↓ body wt. gain at 135 mg/kg; ocular evaluations (indirect ophthalmoscope) unremarkable; NOAEL 15 mg/kg
Rhesus monkeys, 4 male, 4 female	0, 15, 45, 135 mg/kg/orally by gavage	26 weeks	1 mortality at 135 mg/kg; ocular evaluations (indirect ophthalmoscope) unremarkable; ↑ ALAT and GLDH at 45 mg/kg; histopath liver and bone marrow at 135 mg/kg; NOAEL 15 mg/kg

Mutagenicity: 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 dominant lethal test in mice.

Carcinogenicity: Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic following up to 38 weeks of oral dosing at 500 mg/kg/day.

Reproduction and Teratology: 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.

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 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. In an oral peri/postnatal development study conducted in rats, marginal effects observed at 500 mg/kg/day included extended duration of pregnancy, increased prenatal loss, reduced birth weight and decreased survival index. Maternal mortality occurred at 500 mg/kg/day.

In an intravenous rabbit study, moxifloxacin at 20 mg/kg (approximately 860 times the highest recommended total daily human ophthalmic dose) was found to decrease the gestation rate, decrease fetal weights and delay ossification.

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17. Product Monograph for VIGAMOX™ (Moxifloxacin Hydrochloride Ophthalmic Solution), Alcon Canada Inc. Date of Revision: July 20, 2015, Control No. 183976

PART III: CONSUMER INFORMATION

TEVA-MOXIFLOXACIN
Moxifloxacin Ophthalmic Solution, USP
0.5% w/v moxifloxacin (as moxifloxacin hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when TEVA-MOXIFLOXACIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-MOXIFLOXACIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-MOXIFLOXACIN contains the fluoroquinolone antibiotic, moxifloxacin.
TEVA-MOXIFLOXACIN is an eye drop solution that treats bacterial conjunctivitis (sometimes referred to as "pink eye"), an infection of the white of the eye and works by killing the bacteria causing the infection.

When it should not be used:
Do not use TEVA-MOXIFLOXACIN if you have ever had any unusual or allergic reaction to moxifloxacin or other quinolones or any of the ingredients detailed in the section entitled "**What the non-medicinal ingredients are**".

Do not use TEVA-MOXIFLOXACIN longer than directed by your doctor. If you get a worsening of your infection, contact your doctor as soon as possible.

What the medicinal ingredient is:
Moxifloxacin Hydrochloride

What the non-medicinal ingredients are:
TEVA-MOXIFLOXACIN also contains boric acid, sodium chloride and water for injection. Very small amounts of hydrochloric acid or sodium hydroxide are sometimes added to keep acidity levels (pH levels) normal.

What dosage forms it comes in:
TEVA-MOXIFLOXACIN is a liquid (a solution) supplied in a white plastic bottle which contains 3 mL TEVA-MOXIFLOXACIN.TEVA-MOXIFLOXACIN is a clear greenish-yellow solution.

WARNINGS AND PRECAUTIONS

BEFORE you use TEVA-MOXIFLOXACIN talk to your doctor or pharmacist if:

- If you are pregnant, suspect you may be pregnant or are breast feeding consult your doctor or pharmacist before using TEVA-MOXIFLOXACIN.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking (or recently took) any other medicines. Remember to mention medicines that you bought without prescription, over-the-counter. Do not use other eye products with TEVA-MOXIFLOXACIN unless advised by your doctor.

Taking TEVA-MOXIFLOXACIN and non-steroidal anti-inflammatory drugs (NSAIDs) at the same time may increase the chance of developing tendon pain and/or inflammation.

PROPER USE OF THIS MEDICATION

Usual dose:
The normal dosage is one drop in the affected eye(s) three times a day (in the morning, in the afternoon, and at night). Use this much unless your doctor told you to do something different. Only use TEVA-MOXIFLOXACIN eye drops in both eyes if your doctor told you to. Use TEVA-MOXIFLOXACIN for seven days or for as long as your doctor told you to.

Children
TEVA-MOXIFLOXACIN can be used in children as young as one year of age. The dosage instructions for children are the same as for adults as described above.

TEVA-MOXIFLOXACIN can be used safely in patients over 65 years of age. However, elderly patients may have a higher chance of developing pain or swelling in the tendons.

TEVA-MOXIFLOXACIN can be used safely in patients with kidney or liver problems.

Overdose:
If you put too much of this medicine in your eye(s), rinse it all out with warm tap water. Don't put in any more drops until it's time for your next regular dose.

If TEVA-MOXIFLOXACIN Ophthalmic Solution is accidentally taken by mouth or injected, contact your doctor or pharmacist for advice.

In case of drug overdose, contact a health care practitioner, hospital emergency department of regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of this medicine, use the missed dose as soon as possible and then go back to your regular dosing schedule. If the drop misses your eye, try again.

How do I use TEVA-MOXIFLOXACIN?
- To keep the dropper tip and solution clean, be careful not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.
- Get the bottle of TEVA-MOXIFLOXACIN eye drops and a mirror.
- Wash your hands.
- Open the bottle being careful not to touch the dropper tip. Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in there.
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- Don't touch your eye or eyelid, surrounding areas or other surfaces with the bottle tip. It could contaminate the drops.
- Gently squeeze the bottle to release one drop of TEVA-MOXIFLOXACIN.
- If you take drops in both eyes, repeat the steps for your other eye.

TEVA-MOXIFLOXACIN Ophthalmic Solution is for use as an eye drop only.

Can I drive with using TEVA-MOXIFLOXACIN?
If you experience temporary blurred vision or discomfort after using TEVA-MOXIFLOXACIN you should wait until these symptoms go away before driving or using machinery.

Can I wear contact lenses while using TEVA-MOXIFLOXACIN?
You should not wear contact lenses if you have any signs or symptoms of an eye infection.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some people who use **TEVA-MOXIFLOXACIN** may get side effects. They can be unpleasant, but most of them soon pass. You can usually keep using the drops, unless the effects are serious. If you're worried, talk to your doctor or pharmacist.

While using **TEVA-MOXIFLOXACIN** you may experience some or all of the following reactions in your eye: mild temporary burning or stinging, itching, redness, dryness, sensation of pressure, discomfort, corneal ulcer, irritations or changes, broken blood vessels in the white part of the eye, swelling of the eye or eyelid, blurry vision, temporary reduction of vision, pain, inflammation of the eye surface of eyelid, tired eyes, redness of the eyelid, tearing, sensitivity to light, eye discharge or other ocular irritations.

You may also experience reactions in other areas of your body, including: altered, bitter or bad taste, headache, throat irritation and inflammation, a change in liver enzymes, allergic reaction, skin redness or itching, rash of hives following administration of the drops, abnormal skin sensation, vomiting, nose discomfort, dizziness, irregular heart rhythm, shortness of breath, or nausea.

Other side effects not listed above may also occur in some patients.

If you notice any undesirable effects not mentioned in this information, you should stop using **TEVA-MOXIFLOXACIN** and call your doctor or pharmacist immediately and follow his/her advice.

*This is not a complete list of side effects. For any unexpected effects while taking **TEVA-MOXIFLOXACIN**, contact your doctor or pharmacist.*

REPORTING SIDE EFFECTS
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:
- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting

Form and sending it by:
- Fax to 1-866-678-6789 (toll-free), or
- Mail to: Canada Vigilance Program
  Health Canada, Postal Locator 0701E
  Ottawa, ON
  K1A 0K9
  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Keep **TEVA-MOXIFLOXACIN** in a safe place out of the reach and sight of children.

Store between 2°C and 25°C. Protect from light.

Do not use this medicine after the expiry date (shown on the bottle and on the carton). This medicine should be thrown away 28 days after opening.

This medication has been prescribed for you. Never give it to someone else. It may harm them, even if their symptoms are the same as yours.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:
1-800-268-4127 ext. 1255005 (**English**)
or 1-877-777-9117 (**French**)
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