PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-MOXIFLOXACIN
Moxifloxacin Ophthalmic Solution
0.5% w/v moxifloxacin (as moxifloxacin hydrochloride)
USP

Sterile

Antibacterial (Ophthalmic)

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montréal, Canada
H4P 2T4

www.pharmascience.com

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[Pr]pms-MOXIFLOXACIN
Moxifloxacin Ophthalmic Solution, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Ophthalmic (topical)	Solution / 0.5 % w/v moxifloxacin (as moxifloxacin hydrochloride)	Boric Acid, Purified Water and Sodium Chloride. May also contain Hydrochloric Acid/Sodium Hydroxide, used to adjust pH.

INDICATIONS AND CLINICAL USE

pms-MOXIFLOXACIN (moxifloxacin 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 influenza

To reduce the development of the drug-resistant bacteria and maintain the effectiveness of pms-MOXIFLOXACIN and other antibacterial drugs, pms-MOXIFLOXACIN should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Geriatrics (> 65 years of age)

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

Pediatrics (< 1 year of age)

The safety and efficacy of moxifloxacin ophthalmic solution in patients less than one year of age have not been established.

CONTRAINDICATIONS

pms-MOXIFLOXACIN is contraindicated in patients with:

- Hypersensitivity to moxifloxacin or to any ingredient in the formulation or component of the container (for a complete listing, see the DOSAGE FORMS, COMPOSITION, AND PACKAGING section of the Product Monograph).
- Hypersensitivity to other quinolones.

WARNINGS AND PRECAUTIONS

General

For ocular use only.

pms-MOXIFLOXACIN is not for injection into the eye.

pms-MOXIFLOXACIN should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

Prescribing pms-MOXIFLOXACIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

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 pms-MOXIFLOXACIN. 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.

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. Treatment with pms-MOXIFLOXACIN should be discontinued at the first sign of tendon inflammation.

pms-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.

Ophthalmologic

Patients with signs and symptoms of bacterial conjunctivitis should be advised not to wear contact lenses.

Sexual Function/Reproduction

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

Special Populations

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. pms-MOXIFLOXACIN should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Moxifloxacin 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 was observed only at doses > 4,000 times the highest recommended total daily human ophthalmic dose (see TOXICOLOGY).

Nursing Women

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 pms-MOXIFLOXACIN, a decision should be made to either discontinue nursing or discontinue the administration of pms-MOXIFLOXACIN, taking into account the importance of pms-MOXIFLOXACIN therapy to the mother and the possible risk to the infant (see TOXICOLOGY).

Geriatrics (> 65 years of age)

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

Pediatrics (< 1 years of age)

The safety and efficacy of moxifloxacin ophthalmic solution in patients less than one year of age have not been established.

Pediatrics (< 18 years of age)

The effect of 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 Beagle dogs (see TOXICOLOGY). The significance of these findings to humans is unknown.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical trials involving 1,068 subjects/patients, moxifloxacin 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 ophthalmic solution, 6.6% (71 out of 1,068) 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 ophthalmic solution were reported.

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

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Eye disorders: abnormal sensation in eye, conjunctival hemorrhage, conjunctivitis, corneal epithelium defect, eyelid edema, eye pain, keratoconjunctivitis sicca, ocular discomfort, ocular hyperemia, visual acuity reduced;
General disorders and administration site conditions: sensation of foreign body;
Investigations: alanine aminotransferase increased, corneal staining;
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, asthenopia, blepharitis, conjunctival edema, corneal deposits, corneal disorder, corneal infiltrates, dry eye, endophthalmitis, erythema of eyelid, eye discharge, eye irritation, eye swelling, keratitis, lacrimation 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

DRUG INTERACTIONS

Overview

Specific drug interaction studies have not been conducted with moxifloxacin ophthalmic solution. There is limited information available on the concurrent use of moxifloxacin ophthalmic solution and other ophthalmic products.

Drug-Drug Interactions

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.

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

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including moxifloxacin, particularly in those treated concurrently with corticosteroids (see WARNINGS AND PRECAUTIONS, General).

Drug-food, drug-herb and drug-laboratory interactions have not been studied.

DOSAGE AND ADMINISTRATION

Recommended Dose

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.

Missed Dose

If a dose is missed, the missed dose should be administered as soon as possible. Treatment should then be continued with the next dose as planned.

Administration

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

OVERDOSAGE

No information is available on overdose of moxifloxacin ophthalmic solution in humans. A topical overdose of pms-MOXIFLOXACIN 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 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 immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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).

Pharmacodynamics/Pharmacokinetics

Following topical ocular administration of moxifloxacin 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 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 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 mcg/mL, respectively. Thereafter, they decline rapidly in a biphasic manner with the means ranging approximately 1 to 4 mcg/mL over the 1 to 8-hour sampling period. Pre-dose morning tear concentrations on Days 2 to 4 averaged over 4 mcg/mL. Studies conducted in animals indicate penetration into the conjunctiva and ocular tissues with prolonged binding to melanin.

Special Populations and Conditions

Geriatrics

The effects of age on the pharmacokinetic parameters of oral moxifloxacin have been studied. Plasma levels were 24 to 29% higher in the elderly than in young subjects. But, when normalized for body weight, the differences were minimized.

Gender
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 (see DETAILED PHARMACOLOGY, Human Pharmacokinetics).

Race
Subgroup analysis by race (Caucasian, Asian) showed no meaningful differences in the mean steady-state pharmacokinetic parameters of moxifloxacin (see DETAILED PHARMACOLOGY, Human Pharmacokinetics).

Hepatic Insufficiency
The pharmacokinetic parameters of oral moxifloxacin were not significantly altered in patients with mild to moderate hepatic insufficiency (see DETAILED PHARMACOLOGY, Special Populations).

Renal Insufficiency
The pharmacokinetic parameters of oral moxifloxacin were not significantly altered by mild, moderate or severe renal impairment (see DETAILED PHARMACOLOGY, Special Populations).

STORAGE AND STABILITY

Store between 2°C and 25°C. Preserve in tight containers. Protect from light. Store in cardboard outer box when not in use. Discard 28 days after opening. Keep out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of pms-MOXIFLOXACIN contains:

Medical Ingredient

Moxifloxacin 0.5% (5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base).

Preservative

None. Product is self-preserved.

Non-medicinal ingredients

Sodium Chloride, Boric Acid and Purified Water. May also contain Hydrochloric Acid/Sodium Hydroxide, used to adjust pH.

pms-MOXIFLOXACIN solution is isotonic and formulated at pH 6.8 with an osmolality of approximately 290 mOsm/kg.

pms-MOXIFLOXACIN (moxifloxacin ophthalmic solution) is a sterile, self-preserved, aqueous solution supplied in the plastic dispenser bottle, containing 3 mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

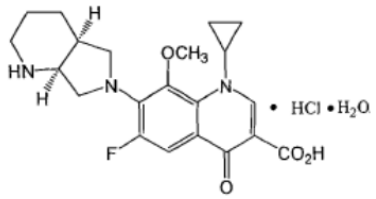
Proper name: Moxifloxacin hydrochloride

Chemical name: 1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4a*S*, 7aS)-octahydro-*6H*-pyrrolol [3, 4-*b*] pyridin-6-yl]-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid, monohydrochloride. Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8 position, and an *S,S*-configured diazabicyclononyl ring moiety at the 7-position.

Molecular formula $C_{21}H_{24}FN_3O_4 \cdot HCl \cdot H_2O$

Molecular mass: 455.9 g/mol

Structural formula:



Physicochemical Properties:

Light yellow or yellow powder or crystals. Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8-position, and an *S, S* configurated diazabicyclononyl ring moiety at the 7-position.

CLINICAL TRIALS

Study demographics and trial design

A summary of the patient demographics for the two studies relevant to the evaluation of the efficacy of moxifloxacin ophthalmic solution is provided in Table 1. Overall, these demographics are representative of the population that would be expected to receive this medicinal product.

Table 1: Summary of Patient Demographics for Clinical Trials

Study #	Trial design	Dosage and route of administration and duration	Treatment duration	No. Patients (Intent to Treat)
C-00-55	Double-masked, randomized, vehicle controlled	0.5% moxifloxacin ophthalmic solution: 1 drop, TID Vehicle: 1 drop, TID	4 days	ITT = 544 270 moxifloxacin ophthalmic solution TID 274 Vehicle TID
C-00-46	Double-masked, randomized, active-controlled	0.5% moxifloxacin ophthalmic solution: 1 drop, TID Ocuflox: 1 drop, QID	4 days	ITT = 554 277 moxifloxacin ophthalmic solution TID 277 Ocuflow QID

Study Results

In two, randomized, double-masked, multicenter, controlled trials in which 547 patients dosed with moxifloxacin ophthalmic solution 3 times a day for 4 days, moxifloxacin 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 mcL 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 mcg/g and 1.78 ± 0.39 mcg/mL, respectively, and were achieved within 30 minutes after dosing. In iris-ciliary body, a moxifloxacin C_{max} of 10.4 ± 5.6 mcg/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 mcg/mL) and declined rapidly.

The distribution of radiolabeled moxifloxacin was also studied in pigmented rabbits after a single unilateral 30 mcL dose of a 0.3% 14C-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 mcg/g, 2.54 ± 0.40 mcg/g, 1.36 ± 0.33 mcg/mL and 7.54 ± 3.34 mcg/g, respectively. Maximum concentrations and half-lives in ocular tissues are summarized in Table 2.

Table 2: Maximum Concentrations and Half-Lives of Radiolabeled Moxifloxacin in Ocular Tissues from Pigmented Rabbits

Tissue	C_{max} (mcg 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	1,080
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 mcL of a 0.3% moxifloxacin ophthalmic solution. The mean concentration of moxifloxacin was 366 ± 214 mcg/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 mcg/mL. The concentrations in the tear film were 1.73 ± 1.50 mcg/mL at 6 hours post-dosing. Tear concentration data are summarized in Table 3.

Table 3: Tear Concentrations of Moxifloxacin Following Administration of a 0.3% Moxifloxacin Solution to Pigmented Rabbits

Time After Dose (minutes)	Mean Concentration ± SD (mcg/mL)	Sample Size
1	366 ± 214	3
2	74.2 ± 70.6	3
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 mcg/mL/2 = 0.5 mcg/mL).

Human Pharmacokinetics

Plasma concentrations were studied in 21 healthy male and female subjects who were administered moxifloxacin 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.

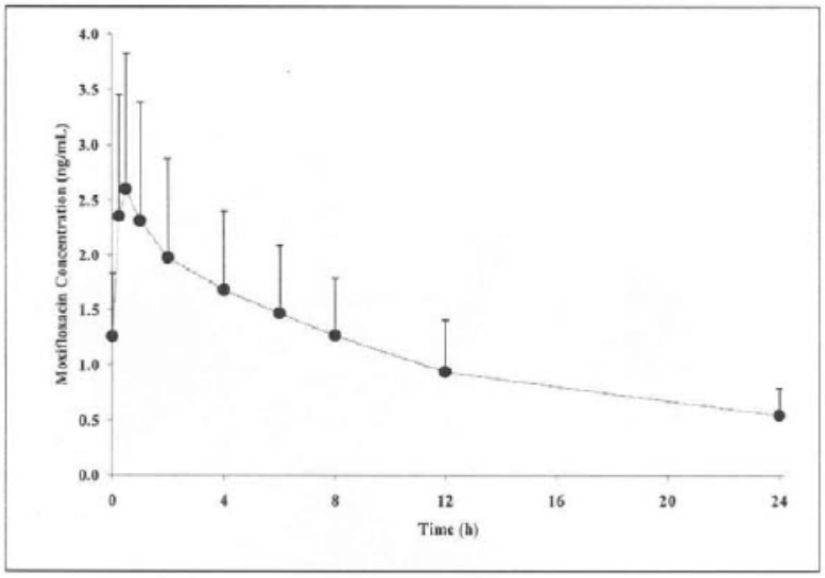


Figure 1: Mean (+ SD) Moxifloxacin Plasma Profile Following the Last Topical Ocular Dose of Moxifloxacin in healthy Subjects

Tear film concentrations of moxifloxacin were studied in 31 healthy male and female adult volunteers who were administered 1 drop of moxifloxacin 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 mcg/mL, respectively. Thereafter, mean tear concentrations rapidly declined in a biphasic manner with means ranging from approximately 1 to 4 mcg/mL over the 1 to 8-hour sampling period. Pre-dose morning tear concentrations on Days 2 to 4 averaged over 4 mcg/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 ophthalmic solution. Given the low systemic exposure observed for moxifloxacin after topical ocular administration of moxifloxacin 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^{++}, Al^{+++}, 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 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 pms-MOXIFLOXACIN 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 pms-MOXIFLOXACIN 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 4), both *in vitro* and in clinical infections from the US and India (see INDICATIONS AND CLINICAL USE).

Table 4: Moxifloxacin *In Vitro* Activity Against Clinical Isolates

Pathogen	N	MIC Range (mcg/mL)	MIC50 (mcg/mL)	MIC90 (mcg/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 5) are also 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. 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 5) 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 breakpoint susceptibility) against most (greater than or equal to 90%) strains of the following ocular isolates:

Table 5: Susceptibility of Bacterial Conjunctivitis Isolates to Moxifloxacin

Bacterial Species	N	MIC Range (mcg/mL)	MIC50 (mcg/mL)	MIC90 (mcg/mL)
Aerobic Gram-positive Microorganisms				
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
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 6).

Table 6: 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 mcL 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 mcL 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 7). The daily dosages of moxifloxacin evaluated in this study are significantly higher than the recommended daily dose of moxifloxacin ophthalmic solution.

Table 7: 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 1,300 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 8, and repeat-dose systemic studies that included ocular evaluations are summarized in Table 9. The daily dose levels of moxifloxacin evaluated in these studies are significantly higher than the recommended daily dose of moxifloxacin ophthalmic solution.

Table 8: Single-Dose Systemic Studies

Species	Strain/Sex	No./Group	Route of Administration	LD50 mg/kg B.W. (Conf. Int. for 95%)
Mouse	NMRI/male	5	p.o.	Approx. 435
	NMRI/female		p.o.	Approx. 758 (440-1,305)
	NMRI/male		IV	Approx. 105 (84-132)
	NMRI/female		IV	Approx. 130 (116-145)
	WU/male		p.o.	Approx. 1,320
	WU/female		p.o.	Approx. 1,320
	WU/male		IV	Approx. 112
	WU/female		IV	Approx. 146
Monkey	Cynomolgus/ Male	2	p.o.	Approx. 1,500

Table 9: 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; 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

Species/No. per Group	Dose/Route	Duration of Treatment	Findings
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. 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.

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 at100 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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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]pms-MOXIFLOXACIN
Moxifloxacin Ophthalmic Solution, USP
0.5% w/v (as moxifloxacin hydrochloride)

Read this carefully before you start taking **pms-MOXIFLOXACIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **pms-MOXIFLOXACIN**.

What is pms-MOXIFLOXACIN used for?
pms-MOXIFLOXACIN is an antibiotic used to treat bacterial infection of the eye (pink eye).

How does pms-MOCIFLOXACIN work?
pms-MOXIFLOXACIN is an antibiotic that stops the growth of bacteria. This kills the bacteria and reduces eye infections.

What are the ingredients in pms-MOXIFLOXACIN?
Medicinal Ingredients: Moxifloxacin 0.5% w/v (as moxifloxacin hydrochloride)
Non-medicinal ingredients: Boric Acid, Sodium Chloride, and Purified Water. May also contain Hydrochloric Acid/Sodium Hydroxide, used to adjust pH.

pms-MOXIFLOXACIN comes in the following dosage forms:
pms-MOXIFLOXACIN is supplied in a plastic dispenser bottles containing 3 mL.

Do not use pms-MOXIFLOXACIN if:
- You are allergic to moxifloxacin or any of the ingredients in pms-MOXIFLOXACIN (see What are the ingredients in pms-MOXIFLOXACIN?)
- You are allergic to other quinolones.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-MOXIFLOXACIN. Talk about any health conditions or problems you may have, including if you:
- Develop an allergic reaction (see Serious side effects and what to do about them). Stop taking pms-MOXIFLOXACIN and get immediate medical help.
- Notice your infection gets worse. Stop taking pms-MOXIFLOXACIN and get immediate medical help. As with any antibiotic, use of pms-MOXIFLOXACIN for a long time may lead to other infections. Do NOT use pms-MOXIFLOXACIN longer than your doctor tells you to.

- Develop pain or swelling in your tendons. Stop taking pms-MOXIFLOXACIN and get immediate medical help. This is more likely to happen if you are elderly or taking corticosteroids at the same time as pms-MOXIFLOXACIN.

Other warnings you should know about:

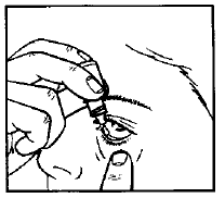
- pms-MOXIFLOXACIN can be used in children as young as 1 year of age. pms-MOXIFLOXACIN should not be used in children younger than 1 year of age.
- Do NOT wear contact lenses if you have an eye infection.
- Your vision may be temporarily blurry after using pms-MOXIFLOXACIN. Wait until your vision clears before driving or using machinery.
- If you are pregnant or planning to become pregnant or are breast-feeding or planning to breastfeed, talk to your doctor or pharmacist before using pms-MOXIFLOXACIN.
- Antibacterial drugs like pms-MOXIFLOXACIN treat only bacterial infections. They do not treat viral infections, such as the common cold. Although you may feel better early in treatment, pms-MOXIFLOXACIN should be taken exactly as directed. Misuse or overuse of pms-MOXIFLOXACIN could lead to the growth of bacteria that will not be killed by pms-MOXIFLOXACIN (resistance). This means that pms-MOXIFLOXACIN may not work for you in the future. Do not share your medicine.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with pms-MOXIFLOXACIN:

- Tell your doctor or pharmacist if you are:
  - taking or have recently taken any prescription or non-prescription medicines,
  - using any other eye products,
  - taking corticosteroids as this may increase your chance of developing pain or swelling of your tendons.

How to take pms-MOXIFLOXACIN:



1. Get the bottle of pms-MOXIFLOXACIN and a mirror.
2. Wash your hands.
3. Twist off the cap. After cap is removed: if security snap collar is loose, remove before using pms-MOXIFLOXACIN.
4. Hold the bottle, pointing down, between your thumb and fingers.
5. Tilt your head back.
6. Pull down your eyelid with a clean finger, until there is a “pocket” between your eyelid and eye. The drop will go in there.
7. Bring the bottle close to the eye. Use the mirror if it helps.

8. **Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper.** It could contaminate the drops.
9. Gently squeeze the bottle to release one drop of pms-MOXIFLOXACIN solution.
10. If the drop misses you eye, wipe it up and try again.
11. If you need drops in both eyes, repeat the steps for your other eye.
12. Keep the bottle tightly closed when not in use.

Usual dose:
Apply one drop in the affected eye(s) three times a day (morning, afternoon and at night) unless your doctor tells you otherwise.

Use pms-MOXIFLOXACIN for seven days or as long as your doctor tells you to.

Overdose:
If you use too much pms-MOXIFLOXACIN, rinse it out of your eyes with warm water. Do not put any more drops of pms-MOXIFLOXACIN in until it's time for your next dose.

If you accidentally swallow pms-MOXIFLOXACIN, talk to your doctor or pharmacist.

If you think you have taken too much pms-MOXIFLOXACIN, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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

What are the possible side effects from using pms-MOXIFLOXACIN?
These are not all the possible side effects you may feel when taking pms-MOXIFLOXACIN. If you experience any side effect not listed here, contact your healthcare professional.

Common eye side effects while using pms-MOXIFLOXACIN include:
- mild temporary burning or stinging,
- itching or redness.

Other less common eye side effects include:
- dryness,
- sensation of pressure, discomfort, corneal inflammation, 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 or eyelid, tired eyes, redness of the eyelid,
- watery eyes, sensitivity to light, eye discharge.

You may also experience reactions in other areas of your body, including:
- bad taste,
- headache,

- throat pain,
- abnormal liver blood tests,
- abnormal skin sensation,
- vomiting,
- nose discomfort,
- dizziness,
- irregular heart rhythm,
- shortness of breath,
- nausea,
- allergic reaction,
- skin redness or itching,
- rash or hives.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN Severe allergic reaction: • swelling of hands • feet • ankles • face • lips • mouth or throat • difficulty breathing • fever • rash or hives • large fluid-filled blisters • sores			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:
Store between 2°C and 25°C. Keep out of the reach and sight of children.

Do not use pms-MOXIFLOXACIN after the expiry date (shown as EXP on the package). Discard 28 days after opening.

If you want more information about pms-MOXIFLOXACIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (www.pharmascience.com), or by calling Pharmascience Inc. at 1-888-550-6060.

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Pharmascience Inc.
Montréal, Québec
H4P 2T4

www.pharmascience.com

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