CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-598

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: —— 21-598
Review number: 1
Sequence number/date/type of submission: 000/October 16, 2002/Commercial
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Alcon, Inc., P.O. Box 62, Bosch 69, CH-6331 Hunenberg, Switzerland
Alcon Research, Ltd., 6201 S. Freeway, Fort Worth, TX 71634-2099
Manufacturer for drug substance:

1) Bayer AG
   Friedrich-Ebert Strasse, D-42096 Elberfeld, Wuppertal, Germany
2) Bayer AG
   D-51368 Leverkusen, Germany

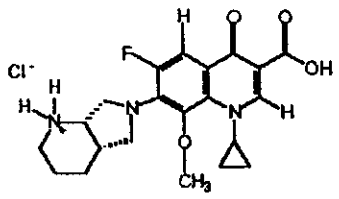
Reviewer name:	Jinhui Dou, Ph.D. (HFD-105)
Division name:	Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD #:	HFD-550
Review completion date:	February 10, 2003

Drug:

Trade name: ——
Generic name: 0.5% Moxifloxacin Hydrochloride Ophthalmic Solution
Code name: AL-15469A, BAY-12-8039
Chemical name:

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

CAS registry number: 186826-86-8
151096-09-2 (base)
Mole file number: Not indicated
Molecular formula/molecular weight: $C_{21}H_{24}FN_3O_4 \cdot HCl$, MW 437.9
Structure:



Relevant INDs/NDAs/DMFs: ——, NDA 21-085
Drug class: Fluoroquinolone antimicrobial, DNA gyrase inhibitor

Indication: Treatment of bacterial conjunctivitis

Clinical formulation:

Ingredient	Concentration (w/v %)
Moxifloxacin HCl	0.545 (= 0.5% of base)
Boric Acid	—
Sodium Chloride	—
Sodium Hydroxide	Adjust pH to 6.8
Hydrochloric Acid	Adjust pH to 6.8
Purified Water	—

Route of administration: Ocular, topical

Proposed use: 1 drop (~ 38 µL) in the affected eye, tid x —. (for a 50 kg adult, the total dose can reach 1.14 mg/patient/day or 0.023 mg/kg/day, or 0.85 mg/m^2/day).

Disclaimer: Information in this review is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

There are no pharmacology/toxicology objections to the approval of this NDA.

B. Recommendation for Nonclinical Studies

No recommendation is necessary.

C. Recommendations on Labeling

Minor modifications of labeling in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy" sections are recommended (See Labeling Review).

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

The drug product, 0.5% Moxifloxacin Ophthalmic Solution, was well tolerated and produced low ocular and systemic toxicity in rabbits and monkeys. Moxifloxacin HCl solutions (0.5%, 1.0%, and 3.0%) were tested (the right eye, 2 drops, qid) in rabbits with or without pigmented eyes for up to 4 weeks and one month, respectively. No adverse clinical signs were noted. Ocular examinations and measurements performed revealed no treatment-related findings, except a few testing animals showed signs of minimal ocular irritation (conjunctival congestion, discharge and aqueous flare). Clinical pathology data and histopathological evaluations did not indicate any significant changes attributed to topical ocular administration of moxifloxacin HCl solutions. Very similar results were observed in the third study of administrating the same moxifloxacin ophthalmic solutions to monkeys for three months (2 drops, six times per day during Days 1-16, tid, for the remainder of the three months). In addition, 1.0% moxifloxacin ophthalmic solution showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

The huge differences between the approved 400 mg/day oral dose (AVELOX®) and the proposed 1.14 mg/day maximum ophthalmic dose further indicate a very good safety margin of moxifloxacin ophthalmic solution. Results from oral toxicity studies in NDA 21-085 also found no drug-related ocular changes by ophthalmic examination in rats (500 mg/kg, 28 weeks), dogs (30 mg/kg, 4 weeks), and monkeys (135 mg/kg, 26 weeks). The drug concentrations in ocular tissues and in tear film were relative high, while the plasma drug concentrations were very low following a single administration of 0.3% moxifloxacin ophthalmic solution. The plasma drug concentrations measured from repeated dosing of up to 3.0% moxifloxacin

ophthalmic solutions were still much lower than those measured in clinical studies at an oral dose of 400 mg/day.

Based on the nonclinical study results and previous human experience with systemic use of moxifloxacin (AVELOX®), it is concluded that there are no safety concerns over this new drug product. No toxicological issues are indicated.

B. Pharmacologic Activity

Moxifloxacin HCl, a fourth generation fluoroquinolone currently being marketed in about 30 countries, has enhanced activity against Gram-positive bacteria while maintains the activity against Gram-negative bacteria as compared to the older fluoroquinolones.

The drug product, 0.5% moxifloxacin ophthalmic solution, is a new formulation of moxifloxacin hydrochloride. In the few studies submitted by the sponsor, moxifloxacin ophthalmic solutions generally performed better *in vitro* and *in vivo* against Gram-positive pathogens that may cause bacterial conjunctivitis than the approved drug, ciprofloxacin. For Gram-negative bacteria, moxifloxacin ophthalmic solutions were comparable to ciprofloxacin or slightly less effective.

Moxifloxacin ophthalmic solutions were well absorbed and distributed in the eye of rabbits following topical ocular administration. A few hours post ocular administration, moxifloxacin concentrations in ocular tissues and tear film were found to be higher than the MIC (minimum inhibition concentration) values of a group of common ocular pathogens tested.

C. Nonclinical Safety Issues Relevant to Clinical Use

There are no nonclinical safety issues in this NDA relevant to the clinical use of the drug product.

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

Moxifloxacin HCl, a fourth generation fluoroquinolone, has been developed by Bayer in tablet and intravenous formulations and gained FDA's approval in 1999 and late 2001, respectively. Currently, moxifloxacin hydrochloride tablets are marketed in about 30 countries. The nonclinical pharmacology, toxicology and pharmacokinetic studies of moxifloxacin following systemic administrations have been previously reviewed in NDA 21-085. The drug product in this NDA application, 0.5% moxifloxacin ophthalmic solution, is a new formulation of moxifloxacin hydrochloride. The sponsor only submitted several nonclinical studies related to the new formulation. For the information of other nonclinical studies, the sponsor asked for the reference of NDA 21-085 (BAY 12-8038, Moxifloxacin hydrochloride).

I. PHARMACOLOGY:

Five studies were submitted in this NDA. For other pharmacology studies, please refer to the Pharmacology/Toxicology review for NDA 21-085.

Studies submitted and reviewed:

1. In Vitro Evaluation of Moxifloxacin (AL-15469). V1, M4, TR# 020:38540:0399
2. Kinetics of Kill by Moxifloxacin (AL-15469) of Ciprofloxacin-Susceptible and Ciprofloxacin-Resistant *Staphylococcus aureus*. V1, M4, TR# 024:38540:0399
3. Kinetics of Kill of Moxifloxacin and Ciprofloxacin of Ocular Isolates. V1, M4, TR# 098:50:0802
4. In Vivo Evaluation of Moxifloxacin (AL-15469) in Rabbit Keratitis Model. V1, M4, TR# 023:38540:0399
5. Evaluation of Moxifloxacin Efficacy in *Staphylococcus aureus*-Induced Rabbit Keratitis Model. V1 , M4, TR# 160:50:1101

In Vitro Evaluation of Moxifloxacin (AL-15469). V1, M4 (4.2.1 Pharmacology)
Study Report Number: TR# 020:38540:0399

In vitro agar dilution and broth dilution MIC testing of moxifloxacin were conducted against several ocular and otic isolate test panels of the following species: *Staphylococcus aureus*, *S. epidermidis*, *S. pneumoniae*, *S. sanguis*, *Enterococcus faecalis*, *E. faecium*, *Corynebacterium spp.*, *Turicella otitidis*, *Microbacterium spp.*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Haemophilus influenzae*, *Acinetobacter spp.*, *Klebsiella pneumoniae*, *Escherichia coli*, *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, and *Citrobacter freundii*.

The results demonstrated that moxifloxacin, MIC of 0.03-16 µg/mL, was about 10 to 20 times more active than ciprofloxacin against Gram-positive bacteria. Moxifloxacin was comparable to ciprofloxacin against Gram-negative bacteria, with the exception of *P. aeruginosa*, where ciprofloxacin (MIC = 0.06-0.5 µg/mL) was about 8 times more active than moxifloxacin (MIC = 0.5-4 µg/mL). Moxifloxacin was generally more active than ofloxacin against most of the bacteria strains tested. The MIC values were not specified in the sponsor's report. However, the same MIC value, 0.06 µg/mL, for *S. aureus* was specified as MIC_{50} in another study (TR#: 015:38570:0299). Thus, all the MIC values in this review were treated as MIC_{50} values if not specified otherwise.

Kinetics of Kill by Moxifloxacin (AL-15469) of Ciprofloxacin-Susceptible and Ciprofloxacin-Resistant *Staphylococcus aureus*. V1, M4 (4.2.1 Pharmacology)
Study Report Number: TR# 024:38540:0399

The purpose of this *in vitro* study was to compare moxifloxacin's kinetics of kill with those of ciprofloxacin against ciprofloxacin susceptible and resistant strains of *S. aureus*, one of the few common ocular pathogens for bacterial keratitis. The studies were conducted by exposing *S. aureus* cells (10^6 - 10^7 colony forming unit/mL or CFU/mL) to different concentrations of moxifloxacin and ciprofloxacin for different periods of time. The surviving cells (CFU/mL) were determined after the exposure of the cells to moxifloxacin or ciprofloxacin. The results indicated that moxifloxacin killed both *S. aureus* strains more rapidly than did ciprofloxacin at the same concentrations.

Summary of Kinetics of Kill Results

S. aureus strain	Ciprofloxacin Susceptible		Ciprofloxacin Resistant	
	Moxifloxacin	Ciprofloxacin	Moxifloxacin	Ciprofloxacin
MIC (µg/mL)	0.06	0.25	4	128
Concentration				
300 (µg/mL)	> 3 logs in 120 min	< 1 log in 180 min	> 2 logs in 120 min	No Kill in 180 min
30 (µg/mL)	> 3 logs in 75 min	> 2 logs in 180 min	< 1 log in 180 min	
3 (µg/mL)	> 3 logs in 150 min	>3 logs in 180 min		

Kinetics of Kill of Moxifloxacin and Ciprofloxacin of Ocular Isolates.
V1, M4 (4.2.1 Pharmacology)
Study Report Number: TR# 098:50:0802

The purpose of this *in vitro* study was to compare kinetics of kill of 0.5% moxifloxacin and 0.3% ciprofloxacin ophthalmic solutions against the selected isolates of ocular pathogens, *S. aureus*, *S. epidermidis* and *P. aeruginosa*. Both ciprofloxacin susceptible and resistant strains of *S. aureus* and *S. epidermidis* were tested. One ciprofloxacin susceptible *P. aeruginosa* strain was also tested. Both the 0.5 % moxifloxacin and 0.3% ciprofloxacin ophthalmic solutions were diluted at factors of 1:10 and 1:100. The results showed that the kinetics of kill of selected isolates by moxifloxacin was faster than those of ciprofloxacin for all five tested bacteria strains at either dilution (1:10 or 1:100). Moxifloxacin and ciprofloxacin were able to kill the ciprofloxacin susceptible *P. aeruginosa* rapidly, in 5 min at the regular test temperature of 35 °C. Even at reduced temperature of 25 °C, no viable organisms of *P. aeruginosa* were recovered after 60 min by moxifloxacin and after 180 min by ciprofloxacin.

The Kinetics of Kill by Two Quinolone Products

Product	Quinolone Concentration (µg/mL)	Time (min) to achieve 99.9% kill			
		S. aureus		*S. epidermidis*	
		Susceptible	Resistant	Susceptible	Resistant
Moxifloxacin	500	45	180	85	>180
	50	30	nd	50	>180
Ciprofloxacin	300	>180	>180	>180	>180
	30	>180	nd	>180	>180

nd: Not determined

In Vivo Evaluation of Moxifloxacin (AL-15469) in Rabbit Keratitis Model. V1, M4 (4.2.1 Pharmacology)
Study Report Number: TR# 023:38540:0399

Three different concentrations of moxifloxacin (0.2, 0.3, and 0.5% ophthalmic solutions) were evaluated for its ability against *S. aureus* and *P. aeruginosa* in rabbit models of keratitis. In the case of *S. aureus* keratitis, the dosing was a single drop of moxifloxacin solution applied topically 9 hr postinfection. The corneas were harvested 1 hr after dosing. In the case of *P. aeruginosa* keratitis, the dosing was a single drop of moxifloxacin solution every 30 min from 16 to 19 hr postinfection. The corneas were harvested 20 hr postinfection. The results were given in the table below. Ciprofloxacin (0.3%) was tested as the control under the same conditions. The sponsor claims that 0.3% moxifloxacin was equally active as 0.3% ciprofloxacin in killing *S. aureus* and *P. aeruginosa* in rabbit's cornea. However, no ciprofloxacin data were submitted.

Treatment Results from Infected Rabbit Corneas

Treatment Group	*S. aureus*	*P. aeruginosa*	
	Log CFU at 10 hr	Log CFU at 20 hr	SLE Score at 20 hr
Untreated	6.8 ± 0.13	7.4 ± 0.07	11.1 ± 0.58
Vehicle Control	6.7 ± 0.21	7.4 ± 0.04	11.4 ± 0.68
Moxifloxacin (0.2%)	3.8 ± 0.45*	5.5 ± 0.28*	11.1 ± 0.67
Moxifloxacin (0.3%)	4.1 ± 0.23*	3.8 ± 0.69*	11.7 ± 0.53
Moxifloxacin (0.5%)	3.9 ± 0.79*	2.1 ± 0.31*	11.5 ± 0.39

* Results significantly different from the Untreated and Vehicle Control groups; SLE = Slit-Lamp Examination

Evaluation of Moxifloxacin Efficacy in *Staphylococcus aureus*-Induced Rabbit Keratitis Model. V1, M4 (4.2.1 Pharmacology)
Study Report Number: TR# 160:50:1101

Moxifloxacin 0.5% ophthalmic solution was compared to QUIXIN® (0.5% levofloxacin) and CILOXAN® (0.3% ciprofloxacin) in rabbit models of keratitis caused by four different strains of *S. aureus*. Two models, "early" and "late", were used in this study.

For the "early" model, the dosing schedule was every 30 min from 4 to 9 hr postinfection (total 11 doses, 45 µL each). The surviving bacteria (CFU) in the cornea were determined at 1 hr after the last dose. The dosing schedule for the "late" model was started late, 10 hr postinfection. Eleven doses, 45 µL each, were applied every 30 min from 10 to 15 hr postinfection. The surviving bacteria (CFU) in the cornea were determined at 1 hr after the last dose.

The results from the "early" model indicated that 0.5% moxifloxacin was significantly more effective than 0.5% levofloxacin and 0.3% ciprofloxacin against the *S. aureus* strains, which were resistant to either quinolone only or both quinolone and β-lactam. Moxifloxacin was not as effective as the two comparator quinolones against the two quinolone sensitive strains of *S. aureus*. All three quinolones were generally much less effective against the *S. aureus* infections in the "late" model than in the "early" model. Moxifloxacin though was more effective than levofloxacin and ciprofloxacin in the "late" model.

Efficacy of Various Ophthalmic Quinolone Solutions in "Early" and "Late" Models

Stain *S. aureus*	Log CFU/Cornea							
	Early Model				Late Model			
	Moxifloxacin	CILOXAN	QUIXIN	Untreated	Moxifloxacin	CILOXAN	QUIXIN	Untreated
β-lactam^{sens} quinolone^{sens}	0.68 ± 0.21	0.40 ± 0.20	0.51 ± 0.35	6.73 ± 0.13	1.68 ± 0.32	3.99 ± 0.27	2.96 ± 0.30	7.12 ± 0.09
β-lactam^{sens} quinolone^{res}	1.25 ± 0.31	4.57 ± 0.21	2.35 ± 0.73	5.69 ± 0.21	5.63 ± 0.25	6.41 ± 0.21	6.26 ± 0.06	6.53 ± 0.16
β-lactam^{res} quinolone^{sens}	1.29 ± 0.45	0.55 ± 0.29	0.17 ± 0.17	6.58 ± 0.16	1.93 ± 0.40	4.68 ± 0.21	2.79 ± 0.42	6.66 ± 0.14
β-lactam^{res} quinolone^{res}	0.82 ± 0.37	5.75 ± 0.20	2.15 ± 0.45	5.89 ± 0.08	3.44 ± 0.63	6.32 ± 0.21	6.01 ± 0.10	6.53 ± 0.08

Pharmacology summary and conclusions:

Three *in vitro* and two *in vivo* pharmacology studies were conducted.

The *in vitro* results indicated that moxifloxacin was generally about 10-20 times more active and could kill more rapidly than ciprofloxacin against a group of Gram-positive bacteria which are common ocular pathogens. Moxifloxacin was comparable to ciprofloxacin against Gram-negative bacteria, with the exception of one case where ciprofloxacin was more active.

In rabbit models of keratitis induced by different *S. aureus* or *P. aeruginosa* strains, 0.5% moxifloxacin ophthalmic solution was more effective than or comparable to 0.3% ciprofloxacin.

II. SAFETY PHARMACOLOGY:

Please refer to the Pharmacology/Toxicology review for NDA 21-085.

III. PHARMACOKINETICS/TOXICOKINETICS:

Please refer to the Pharmacology/Toxicology review for NDA 21-085 for systematic PK/TK studies. Two analytical method validation reports and five new PK/TK studies related to ocular administrations of moxifloxacin ophthalmic solutions were reviewed.

Studies reviewed:

1. Validation of an HPLC method for the determination of moxifloxacin in rabbit plasma. V1, M4 (4.2.2 Pharmacokinetics). TR#: 014:33:0301
2. Validation of an HPLC (HPLC method for the determination of moxifloxacin in cynomologus monkey plasma V1, M4 (4.2.2 Pharmacokinetics), TR#: 004:33:0102
3. Distribution of moxifloxacin and ofloxacin in ocular tissues and plasma following topical ocular administration to male Dutch belted rabbits. V1, M4 (4.2.2 Pharmacokinetics), TR#: 015:38570:0299
4. Distribution of radioactivity in ocular tissues and plasma following a single topical ocular administration of ^{14}C-moxifloxacin in male Dutch belted rabbits. V1, M4 (4.2.2 Pharmacokinetics), TR#: 022:33:0502
5. Tear film concentrations of moxifloxacin and ofloxacin following topical ocular administration to Dutch belted rabbits. V1, M4 (4.2.2 Pharmacokinetics), TR#: 006:38570:0299
6. Moxifloxacin plasma concentrations from a one-month topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in pigmented rabbits (Protocol N-00-120). V1, M4 (4.2.2 Pharmacokinetics), TR#: 047:33:1001

7. Moxifloxacin plasma concentrations from a three-month topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in primates (Protocol N-00-081). V1, M4 (4.2.2 Pharmacokinetics), TR#: 055:33:11015

Analytical Method Development:

Validation of an HPLC method for the determination of moxifloxacin in rabbit plasma. V1, M4 (4.2.2 Pharmacokinetics)
Report Number: TR# 014:33:0301

A — HPLC with fluorescence detection of the determination of moxifloxacin in rabbit plasma was developed and validated. This method was developed to support TK studies in rabbits. The method was demonstrated to have a quantitation limit of — Samples at concentrations of 4 ng/mL (low), —.g/mL (medium), and — g/mL (high) in rabbit plasma were analyzed with acceptable precision and accuracy.

Validation of an HPLC — (HPLC —) method for the determination of moxifloxacin in Cynomologus monkey plasma — V1, M4 (4.2.2 Pharmacokinetics)
Report No.: TR# 004:33:0102

An HPLC — method was developed. This method was capable for detecting moxifloxacin in cynomologus monkey plasma at a working range of g/mL.

ADME:

The following five studies were conducted to determine the absorption and distribution behaviors of moxifloxacin ophthalmic solutions in ocular tissues and plasma.

Distribution of moxifloxacin and ofloxacin in ocular tissues and plasma following topical ocular administration to male Dutch belted rabbits. V1, M4 (4.2.2 Pharmacokinetics)

Study No: N-99-013
Report No: 015:38570:0299
Study Site: —
Study initiation: February 3, 1999
Date of final report: May 13, 1999.
GLP compliance: Yes
QA report: Yes
Animal: Male Dutch belted rabbits, 1.43-1.83 kg
Route: Ocular (both eyes), topical
Drug: 0.3 % Moxifloxacin ophthalmic solution (pH = 7.36 with benzalkonium chloride, NaCl and a phosphate buffer, different from the clinical formula of 0.5 % Moxifloxacin at pH = 6.8)
Dosage: Single administration, 1 drop (30 µL) per eye

The distribution of moxifloxacin was determined in ocular tissues of male Dutch belted rabbits following a single topical ocular dose of a 0.3% ophthalmic solution of moxifloxacin.

The formulation in this study is different from the clinical formulation, which contains 0.5% moxifloxacin. A marketed ofloxacin product, Ocuflox® Ophthalmic Solution 0.3%, was used as a control in this study. The drug concentrations in aqueous humor, cornea, iris-ciliary body (ICB), and plasma were determined using an HPLC method. Moxifloxacin was well absorbed into the eye and its C_{max} values in all the tissues analyzed were typically 2-fold higher than those found for ofloxacin (See the table below).

Maximal Concentrations of Moxifloxacin and Ofloxacin

Drug	Maximal Concentrations (μg/g)			
	Aqueous Humor	Cornea	Iris-Ciliary Body	Plasma
Ofloxacin	0.507 ± 0.489	6.02 ± 2.27	5.42 ± 2.88	0.0080 ± 0.0010
Moxifloxacin	1.78 ± 0.39	12.5 ± 3.8	10.4 ± 5.6	0.0130 ± 0.0016

Concentrations of both moxifloxacin and ofloxacin declined in parallel in their respective tissues. However, moxifloxacin concentrations were generally higher than ofloxacin concentrations in all tissues during the course of 48 hr study, especially in cornea and ICB. After 48 hr of dosing, moxifloxacin cornea concentration of 0.25 μg/g was 4-fold above its MIC_{50} value of 0.06 μg/mL for methicillin susceptible *S. aureus*, a common ocular pathogen. Mean concentrations of moxifloxacin and ofloxacin were given in the table below.

Mean Concentrations of Moxifloxacin and Ofloxacin in Ocular Tissues and Plasma Following a Single Topical Ocular Dose of 0.3% Moxifloxacin and 0.3% Ocuflox Ophthalmic Solutions to Male Dutch Belted Rabbits

	Ofloxacin Concentrations (μg/g)							
	Aqueous Humor		Cornea		Iris-Ciliary Body		Plasma	
Time	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5	0.507	0.489	6.02	2.27	0.800	0.360	0.0069	0.0037
1	0.267	0.134	2.34	0.99	0.653	0.423	0.0080	0.0010
2	0.229	0.031	2.41	0.46	4.43	1.99	0.0038	0.0003
4	0.0933	0.0389	1.05	0.39	5.42	2.88	BLQ	BLQ
8	BLQ	BLQ	0.493	0.123	4.36	1.57	BLQ	BLQ
12	BLQ	BLQ	0.150	0.042	2.92	0.07	BLQ	BLQ
24	BLQ	BLQ	0.270	0.240	3.33	1.01	BLQ	BLQ
48	BLQ	BLQ	0.0967	0.0839	2.78	0.33	BLQ	BLQ
	Moxifloxacin Concentrations (μg/g)							
	Aqueous Humor		Cornea		Iris-Ciliary Body		Plasma	
Time	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5	1.78	0.39	12.5	3.8	6.26	2.07	0.0130	0.0016
1	0.993	0.075	5.89	0.78	10.4	5.6	0.0109	0.0010
2	0.304	0.059	2.02	0.13	8.54	1.45	0.0065	0.0003
4	0.0589	0.0071	0.650	0.082	11.0	1.7	BLQ	BLQ
8	0.0353	0.0232	0.990	0.288	13.5	4.7	BLQ	BLQ
12	0.0207	0.0002	0.437	0.225	9.42	3.76	BLQ	BLQ
24	0.0182	0.0029	0.253	0.119	10.7	6.2	BLQ	BLQ
48	0.0172	*	0.247	0.015	7.68	2.14	BLQ	BLQ

BLQ - Below the Limit of Quantitation;

A longer half-life in the pigmented irisciliary tissue was observed for both drugs. It was suggested that melanin binding, a characteristic known for fluoroquinolones, be responsible for

this phenomenon. The concentrations of moxifloxacin and ofloxacin in plasma were low indicating minimal systemic exposure.

Distribution of radioactivity in ocular tissues and plasma following a single topical ocular administration of ^{14}C-moxifloxacin in male Dutch belted rabbits. V1, M4 (4.2.2 Pharmacokinetics)

Study No: N-01-250
Report No: 022:33:0502
Study Site: Alcon Research, Ltd., 6201 South Free Way, Fort Worth, TX 76134
Study initiation: January 14, 2002
Date of final report: September 04, 2002.
GLP compliance: Yes
QA report: Yes
Animal: Male Dutch belted rabbits, 1.98 ± 0.07 kg
Route: Ocular (the right eye only), topical
Drug: 0.3 % Moxifloxacin ophthalmic solution (0.164% ^{14}C-moxifloxacin and 0.150% unlabeled moxifloxacin at pH = 7.2)
Dosage: Single administration, 1 drop (30 µL) to the right eye

Following a single topical ocular administration of a 0.3% ^{14}C-moxifloxacin ophthalmic solution into the right eye of male Dutch belted rabbits, the pharmacokinetics and distribution of radioactivity in ocular tissues and plasma were determined. Concentrations of radioactivity for the following ocular tissues from both eyes were determined by liquid scintillation counting: aqueous humor, bulbar conjunctiva, cornea, ICB, lens, vitreous humor, retina, choroid, optic nerve, anterior sclera, and posterior sclera. For the dosed right eye, ocular tissues were collected up to 2184 h (91 days), while for the undosed left eye tissues were collected up to 24 h.

The results demonstrated that ^{14}C-moxifloxacin was well absorbed into the eye following a single topical ocular administration to Dutch belted rabbits. Radioactivity maximum concentration (C_{max}) levels were reached within 0.5 h to 2 h (T_{max}) in most of the ocular tissues, except for choroid (T_{max} = 8 h). The levels of radioactivity in viterous humor and optic nerve tissues were below the limit of quantitation (BLQ). Highest concentrations of radioactivity were found in cornea, ICB, anterior sclera, and conjunctiva. The half-lives ($t_{1/2}$) of ^{14}C-moxifloxacin ranging from 5.6 h in aqueous humor to 1080 h in anterior sclera. The unexpected long $t_{1/2}$ of the non-pigmented tissue anterior sclera, longer than the pigmented tissues ICB ($t_{1/2}$ = 649 h) and choroid ($t_{1/2}$ = 872 h), was suspected to be caused by contamination during dissection.

PK Parameters of Radioactivity in Tissues from the Dosed Eye Following a Single Topical Ocular Dose of 14C-Moxifloxacin to Male Dutch Belted Rabbits

Parameter	Aqueous Humor	Conjunctiva	Cornea	ICB	Lens	Anterior sclera	Choroid	Retina	Posterior Sclera
T_{max} (hr)	0.5	0.5	0.5	2.0	2.0	0.5	8.0	2.0	2.0
C_{max} (µg eq/g)	1.36	2.54	10.6	7.54	0.0851	2.86	0.441	0.0663	0.090
$T_{1/2}$ (hr)	5.6	43.4	92.3	649	36.6	1080	872	48	92.1
$AUC_{(0\text{-}Inf)}$ (hr*µg eq/g)	2.09	15.2	27.4	2440	1.10	243	349	1.86	3.11

In the undosed eye, radioactivity was generally much lower than the dosed eye and only detected from three ocular tissues: ICB (C_{max} = 0.25 µg eq/g, T_{max} = 24 h), choroid (C_{max} = 0.111 µg eq/g, T_{max} = 1 h), and retina (C_{max} = 0.07 µg eq/g, T_{max} = 2 h).

Minimal systemic exposure was indicated by the low radioactivity in the plasma (C_{max} = 0.005 µg eq/g, T_{max} = 0.5 h).

Tear film concentrations of moxifloxacin and ofloxacin following topical ocular administration to Dutch belted rabbits. V1, M4 (4.2.2 Pharmacokinetics)

Study No: N-99-014
Report No: 006:38570:0299
Study Site: Alcon Laboratories, Inc., 6201 South Free Way, Fort Worth, TX 76134
Study initiation: February 1, 1999
Date of final report: April 29, 1999.
GLP compliance: Yes
QA report: Yes
Animal: Female Dutch belted rabbits, 2.12 ± 0.17 kg
Route: Ocular (the right eye only), topical
Drug: 0.3 % Moxifloxacin ophthalmic solution (pH = 7.36 with benzalkonium chloride, NaCl and a phosphate buffer, different from the clinical formula of 0.5 % Moxifloxacin at pH = 6.8)
Dosage: Single administration, 1 drop (30 µL) to the right eye

The purpose of this study was to determine tear film concentrations of moxifloxacin in Dutch Belted Rabbits following a single topical ocular administration of 0.3% moxifloxacin ophthalmic solution. Tear film samples were collected at 1, 2, 3, 5, 10, 20, 30, and 45 min and at 1, 1.5, 2, 3, 4, and 6 hr after dosing, and analyzed by an HPLC. The limit of quantitation was — with concentration limits of — for a 1 µL tear volume and — for a 0.5 µL tear volume.

The result showed that moxifloxacin tear film concentrations, similar to those of ofloxacin, dropped rapidly during the first 5-10 min. One minute after dosing, the mean concentration measured in three test animals was 366 ± 214 µg/mL. The study also found that 4-6 hr after dosing, moxifloxacin tear film concentrations were still well above its MIC_{50} of 0.06 µg/mL against *S. aureus*, a common pathogen involved in ocular bacterial keratitis. However, the data collected at and after 3 hr postdosing may not be very reliable. The detected concentrations were below or slightly above the quantitation limit. There were also unexplained significant decreases of tear film moxifloxacin concentrations between 30 min to 45 min and then increases between 45 min to 60 min. The mean concentrations reported for 30, 45, and 60 min were 10.3 ± 3.64, 1.21 ± 0.65, and 7.14 ± 6.12 µg/mL, respectively. The mean concentration calculated at 45 min (1.21 ± 0.65 µg/mL) was actually lower than the mean concentration calculated at 6 hr (1.73 ± 1.50 µg/mL).

Individual and Mean Moxifloxacin and Ofloxacin Concentrations in Tear Film Following a Single Topical Ocular Dose to Dutch Belted Rabbits

Moxifloxacin (µg /mL)					
Time (minutes)	Animal 124993	Animal 124994	Animal 124995	Mean	STD
1				366	214
2				74.2	70.6
3				60.9	11.9
5				23.7	17.2
10				19.4	4.03
20				23.4	11.6
30				10.3	3.64
45				1.21	0.65
60				7.14	6.12
90				2.69	1.32
120				7.27	9.96
180				1.67	1.06
240				0.693	0.335
360				1.73	1.50
Ofloxacin (µg /mL)					
Time (minutes)	Animal 124996	Animal 124997	Animal 124998	Mean	STD
1				437	137
2				178	135
3				114	49
5				34.6	19.1
10				7.34	4.32
20				5.21	3.59
30				2.84	1.12
45				1.00	0.05
60				0.790	0.087
90				0.440	0.329
120				0.710	0.564
180				1.04	1.37
240					
360					

STD: Standard Deviation
LS: Lost Sample (due to technical error)
BLQ: Below Quantitation Limit (Moxifloxacin -

Moxifloxacin plasma concentrations from a one-month topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in pigmented rabbits. V1, M4 (4.2.2 Pharmacokinetics)

Study No: N-00-120
Report No: 047:33:1001
Study Site: Alcon Research, Ltd., 6201 South Free Way, Fort Worth, TX 76134
Study initiation: February 12, 1999
Date of final report: April 29, 1999.
GLP compliance: Yes
QA report: Yes
Animal: New Zealand F_1 Cross (NZW x NZR) rabbits, 2.5-3.1 kg
Route Ocular (the right eye only), topical
Drug: 0.5, 1.0, or 3.0% Moxifloxacin ophthalmic solution

Dosage: 2 drops (80 µL), qid at 2.5-3 hr intervals

The purpose of this study was to assess systemic exposure to moxifloxacin by measuring plasma concentrations of moxifloxacin in pigmented rabbits treated topically with 0.5, 1.0, or 3.0% moxifloxacin ophthalmic solution qid for 35 days. Blood samples from 3 male and 3 female animals per treatment group were collected on days 1, 17, and 35 and analyzed by an HPLC method with fluorescence detection.

Quantifiable exposure to moxifloxacin was demonstrated across all three treatments. A dose-proportional increase in plasma exposure was observed in both sexes. Results indicated no significant accumulation of moxifloxacin in plasma. The $AUC_{0\text{-}2\ hour}$ values were given in the table below.

$AUC_{0\text{-}2\ hour}$ Values (ng*hour/mL) for Study N-00-120

Moxifloxacin	Gender	Day 1	Day 17	Day 35
0.5 %	Male	19.4 ± 2.0	19.0 ± 1.1	18.2 ± 0.8
	Female	15.1 ± 1.3	16.1 ± 1.8	16.6 ± 1.1
1.0 %	Male	33.3 ± 2.4	41.7 ± 3.5	37.3 ± 1.8
	Female	32.5 ± 5.1	24.6 ± 3.0	35.6 ± 4.1
3.0 %	Male	92.2 ± 13.5	98.1 ± 12.6	102± 14
	Female	68.1 ± 2.1	70.5 ± 11.2	81.4 ± 7.8

Moxifloxacin plasma concentrations from a three-month topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in primates. V1, M4 (4.2.2 Pharmacokinetics)

Protocol No:	N-01-081
Report No.:	055:33:1101
Conducting laboratory:	Alcon Research, Ltd., 6201 South Freeway, Fort Worth, TX 76134
Date of study initiation:	June 20, 2001
Study Completion Date:	January 30, 2002
GLP compliance:	Yes
QA reports:	Yes
Animal:	Cynomolgus monkeys (2.5-3.6 kg for male, 2.8-5.7 kg for female)
Route	Ocular (the right eye only), topical
Drug:	0.5, 1.0, or 3.0% Moxifloxacin ophthalmic solution
Dosage:	2 drops (80 µL) Six times per day (Days 1-16) at 2 hr intervals or tid (Days 17-86) at 3.5-4 hr intervals

The purpose of this study was to assess systemic exposure to moxifloxacin by measuring the plasma concentrations in Cynomolgus monkeys treated with 0.5, 1.0, or 3.0% moxifloxacin ophthalmic solution. Blood samples from 3 male and 3 female animals per treatment group were collected on days 1, 14, 62, and 86 and analyzed by an HPLC — method.

Quantifiable exposure to moxifloxacin was demonstrated across all three dose levels. A dose-proportional increase in plasma exposure was observed in both sexes. Only slight accumulation of moxifloxacin in plasma was observed between days 1 and 14. The AUC values indicated an approximately dose-proportional increase in plasma exposure over the dose range. No sex-related differences in systemic exposure in plasma were observed. The animals in the low dose (0.5%) group and the high dose (3.0%) group showed a significant decrease in AUC values on Day 86 relative to Day 62. The cause of this phenomenon was not identified. The $AUC_{0\text{-}2\ hour}$ values were given in the table below.

$AUC_{0\text{-}2\ hour}$ Values (ng*hour/mL) for Moxifloxacin Plasma Concentrations (Study N-01-081)

Moxifloxacin	Gender	Day 1	Day 14	Day 62	Day 86
0.5 %	Male (M)	37.0 ± 3.2	47.0 ± 4.8	23.5 ± 2.4	5.76 ± 0.58
	Female (F)	39.0 ± 5.3	46.8 ± 3.4	21.8 ± 3.3	8.82 ± 1.58
	M and F	38.0 ± 2.8	46.9 ± 2.7	22.6 ± 1.8	7.29 ± 0.83
1.0 %	Male (M)	69.8 ± 2.3	75.5 ± 3.2	43.4 ± 7.9	43.1 ± 3.6
	Female (F)	60.4 ± 5.1	69.7 ± 5.5	34.2 ± 1.8	31.4 ± 6.1
	M and F	65.1 ± 2.8	72.6 ± 3.0	38.8 ± 3.8	37.2 ± 3.5
3.0 %	Male (M)	198 ± 23	286 ± 38	137 ± 20	93.9 ± 15.6
	Female (F)	207 ± 18	244 ± 35	144 ± 20	88.8 ± 18.6
	M and F	203 ± 13	265 ± 24	140 ± 13	91.4 ± 10.9

PK/TK summary and conclusions:

Five PK/TK studies following topical ocular administration of moxifloxacin ophthalmic solutions (0.3%, 0.5%, 1.0%, or 3.0%) were reviewed.

These studies with a single topical ocular dose of 0.3% moxifloxacin ophthalmic solution demonstrated that the drug was well absorbed. Even though the drug concentrations in ocular tissues and tear films dropped rapidly after dosing, meaningful concentrations (i.e., above the MIC_{50} against one *S. aureus* strain) could be maintained for more than 4 hr in rabbits. Low plasma drug concentrations indicated minimum systemic exposure.

Systemic exposure to moxifloxacin were further studied by repeated dosing of 0.5, 1.0, or 3.0% moxifloxacin ophthalmic solution to pigmented rabbits (35 days) and monkeys (3 month). A dose-proportional increase in plasma concentrations and no significant accumulations of moxifloxacin were observed in both studies.

IV. GENERAL TOXICOLOGY:

Three studies conducted by Alcon Research, Ltd. to characterize the repeated-dose toxicity following topical ocular administration of moxifloxacin ophthalmic solutions were reviewed. For additional toxicology studies, the sponsor asked to reference NDA 21-085.

Studies Reviewed:

1. Four-week topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in rabbits. V1, M4 (4.2.3 Toxicology), TR #: 036:30:0100.
2. One-month topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in pigmented rabbits. V1, M4 (4.2.3 Toxicology), TR #: 233:30:1100.
3. Three-month topical ocular irritation and systemic toxicity evaluation of

Four-week topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in rabbits. V1, M4 (4.2.3 Toxicology)

Key study findings:

Moxifloxacin ophthalmic solutions (0.5, 1.0, and 3.0%) produced a low ocular irritation potential and did not elicit noticeable ocular or systemic toxicity.

Report No: 036:30:0100
Protocol No: N-99-366

Conducting laboratory:	Alcon Research, Ltd., 6201 South Freeway, Fort Worth, TX 76134
Date of study initiation:	December 15, 1999
GLP compliance:	Yes
QA reports:	Yes
Animal:	New Zealand White rabbits, 2.1-2.5 kg
Route	Ocular (the right eye only), topical
Drug:	0.5, 1.0, or 3.0 % Moxifloxacin ophthalmic solution
Dosage:	2 drops (80 µL), qid at 2.5-3 hr intervals

The purpose of this study was to determine the ocular irritation and systemic toxicity of moxifloxacin following ocular administrations (qid x 4 weeks) to rabbits. The study design and toxicity assessment procedures were summarized in the tables below.

Study Design

Group Number	Treatment	Moxifloxacin/Vehicle Batch No.	Animals	
			Male	Female
1	Untreated Control		4	4
2	Vehicle	99-25564	4	4
3	Moxifloxacin 0.5%*	99-25566	4	4
4	Moxifloxacin 1.0%*	99-25531	4	4
5	Moxifloxacin 3.0%*	99-25581	4	4

* Prestudy and poststudy tests demonstrated appropriate strength (97-100% of the target concentrations)

Toxicity Assessment

Parameter	Procedure
Clinical observation/examination	Twice daily
Body weights	Day 0 (the day of the 1st dosing), 7, 14, 21 and 28
Biomicroscopic examination	Pretest and Days 3, 7, 21, and 28
Indirect ophthalmoscopic examination	Pretest and Day 28
Corneal pachymetry	Pretest and Day 27
Hematology and clinical chemistry	Day 27
Necropsy	Day 29, eyes and adnexa
Histopathology	Eyes and adnexa

Results:

Clinical sings: One female animal (ID 140673) of Group 5 exhibited slight discharge in the right (treated) eye on Day 10. One female animal (ID 140677) of Group 4 was observed to have diarrhea on Day 17. The remaining animals in all the treatment Groups 2-5 had no remarkable clinical signs throughout the four-week study.

Body weight: No treatment-related differences were observed.

Biomicroscopic examinations: No moxifloxacin treatment-related light reflex changes, aqueous flare, iritis, corneal cloudiness, fluorescein staining, lenticular changes and neovascularization were observed. Treatment-related side effects were limited to the conjunctival congestion and discharge.

Moderate conjunctival congestion (score = 2 of maximum score of 3) was observed once in the treated eyes of a few animals in the three moxifloxacin treatment groups: Group 3 (1♂), Group 4 (2♂), and Group 5 (1♂ and 2♀). Minimal conjunctival congestion was noted for the treatment groups as well as the control group (score = 1).

A single instance of severe discharge (score = 3 of maximum score of 3) was noted in a Group 5 female animal (ID 140673) on Day 7 and was resolved by the next biomicroscopic evaluation on Day 21. The same animal developed a noticeable clinical sign described as slight discharge on Day 10.

Indirect ophthalmoscopic examinations: No treatment-related changes were observed.

Corneal pachymetry: Data revealed no significant treatment-related differences.

Clinical pathology: No toxicologically significant findings were observed in hematology, coagulation and clinical chemistry.

Gross pathology: No abnormalities or gross lesions were observed at necropsy.

Histopathology: No treatment-related lesions or evidence of ocular irritation were present in the eyes and adnexa. Only a few incidental and non-treatment-related changes were present in the ocular and nonocular tissues examined.

In summary, topical ocular treatment of rabbits with 0.5%, 1.0%, or 3.0% moxifloxacin ophthalmic solution qid for four-weeks was well tolerated. Treatment-related findings by ocular evaluations were limited to moderate conjunctival congestion in a few treated animals and a single instance of conjunctival discharge. No toxicologically significant findings were discovered in daily health observations, clinical pathological examinations, and post-mortem histopathological examinations. In conclusion, moxifloxacin ophthalmic solutions (0.5, 1.0, and 3.0%) produced a low ocular irritation potential and did not elicit noticeable ocular or systemic toxicity in rabbits.

One-month topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in pigmented rabbits. V1, M4 (4.2.3 Toxicology)

Key study findings:

Moxifloxacin ophthalmic solutions (0.5, 1.0 and 3.0%) produced a low ocular irritation potential and did not elicit noticeable ocular or systemic toxicity in pigmented rabbits.

Report No:	233:30:1100
Protocol No:	N-00120
Conducting laboratory:	Alcon Research, Ltd., 6201 South Freeway, Fort Worth, TX 76134
Date of study initiation:	May 17, 2000
GLP compliance:	Yes
QA reports:	Yes
Animal:	New Zealand F_1 Cross (NZW x NZR) rabbits, 2.5-3.1 kg
Route	Ocular (the right eye only), topical
Drug:	0.5, 1.0, or 3.0% Moxifloxacin ophthalmic solution
Dosage:	2 drops (80 µL), qid at 2.5-3 hr intervals

The purpose of this study was to determine the ocular irritation and systemic toxicity of moxifloxacin ophthalmic solution (0.5%, 1.0%, and 3.0%) following ocular administrations (qid, one month) to rabbits. The study design and toxicity assessment procedures were summarized in the tables below.

Study Design

Group Number	Treatment	Moxifloxacin/Vehicle Batch No.	Animals	
			Male	Female
1	Untreated Control		4	4
2	Vehicle	00-26523	4	4
3	Moxifloxacin 0.5%*	00-26520	4	4
4	Moxifloxacin 1.0%*	00-26521	4	4
5	Moxifloxacin 3.0%*	00-26522	4	4

* Prestudy and poststudy tests demonstrated appropriate strength (97-102% of the target concentrations)

Toxicity Assessment

Parameter	Procedure
Clinical observation/examination	Twice daily
Body weights	Day 0 (the day of the 1st dosing), 7, 14, 21, and 35
Biomicroscopic examination	Pretest and Days 3, 7, 14, 21, and 35
Indirect ophthalmoscopic examination	Pretest and Day 35
Corneal pachymetry	Pretest and Day 34
Hematology and clinical chemistry	Day 31
Blood drug concentration monitoring	Designated animals in Groups 3, 4, and 5 on Days 1, 17, and 35. Blood samples were taken immediately before the last dose and 0.5, 1, and 2 hr after the last dose of the day. (Reviewed separately)
Necropsy	Day 36, eyes and adnexa
Histopathology	Eyes and adnexa

Results:

Clinical sings: All the animals in the treatment Groups 2-5 had no remarkable clinical signs throughout the one-month study.

Body weight: No treatment-related differences were observed.

Biomicroscopic examinations: Treatment-related side effects were limited to conjunctival discharge and flare. Transient and sporadic instances of minimal conjunctival congestion (score = 1) were observed in all of the five groups. No moxifloxacin treatment-related conjunctival swelling, light reflex changes, iritis, corneal cloudiness, fluorescein staining, lenticular changes and neovascularization were observed.

A single instance of minimal conjunctival discharge (score = 1) was observed on Day 7 in the treated eye of one Group 5 male animal (ID 146060). Conjunctival discharge was not observed in the eyes of any other testing animals.

Minimal aqueous flare (score = 1) was observed on Day 35 in the treated eyes of three animals in the moxifloxacin treatment groups: Group 3 (1♂) and Group 5 (1♂ and 1♀). On the same day (Day 35), minimal aqueous flare was also observed in the left eyes of a Group 3 animal (♀) and a Group 1 (untreated control) animal. Flare was not observed in the eyes of any other testing animals.

Indirect ophthalmoscopic examinations: No treatment-related changes were observed.

Corneal pachymetry: Data revealed no significant treatment-related differences.

Clinical pathology: No toxicologically significant findings were observed in hematology, coagulation and clinical chemistry.

Gross pathology: No abnormalities or gross lesions were observed at necropsy.

Histopathology: No treatment-related lesions or evidence of ocular irritation were present in the eyes and adnexa.

In summary, topical ocular treatment of pigmented rabbits (F_1 Cross NZW x NZR) with 0.5%, 1.0%, or 3.0% moxifloxacin ophthalmic solution qid for one-month was well tolerated. Treatment-related findings by ocular evaluations were limited to minimal aqueous flares in a few treated animals and a single instance of conjunctival discharge. No toxicologically significant findings were discovered in daily health observations, clinical pathological examinations, and post-mortem histopathological examinations. In conclusion, 0.5, 1.0, and 3.0% moxifloxacin ophthalmic solutions produced a low ocular irritation potential and did not elicit noticeable ocular or systemic toxicity in rabbits with pigmented eyes.

Three-month topical ocular irritation and systemic toxicity evaluation of Moxifloxacin Ophthalmic Solution in primates. V1, M4 (4.2.3 Toxicology)

Key study findings:

Moxifloxacin ophthalmic solutions (0.5, 1.0, and 3.0%) produced a low ocular irritation potential and did not elicit noticeable ocular or systemic toxicity in Cynomolgus monkeys.

Report No:	178:30:1001
Protocol No:	N-01-081
Conducting laboratory:	Alcon Research, Ltd., 6201 South Freeway, Fort Worth, TX 76134
Date of study initiation:	June 20, 2001
GLP compliance:	Yes
QA reports:	Yes
Animal:	Cynomolgus monkeys (2.5-3.6 kg for male, 2.8-5.7 kg for female)
Route	Ocular (the right eye only), topical
Drug:	0.5, 1.0, or 3.0% Moxifloxacin ophthalmic solution
Dosage:	2 drops (80 µL) Six times per day (Days 1-16) at 2 hr intervals or tid (Male: Days 17-91; Female: Days 17-92) at 3.5-4 hr intervals

The purpose of this study was to determine the ocular irritation and systemic toxicity of moxifloxacin following ocular topical administrations to Cynomolgus monkeys for three months. The study design and toxicity assessment procedures were summarized in the tables below.

Study Design

Group Number	Treatment	Moxifloxacin/Vehicle Batch No.	Animals	
			Male	Female
1	Vehicle	01-29039	4	4
2	Moxifloxacin 0.5%*	01-29035	4	4
3	Moxifloxacin 1.0%*	01-29036	4	4
4	Moxifloxacin 3.0%*	01-29038	4	4

* Prestudy and poststudy tests demonstrated appropriate strength (99-104% of the target concentrations).

Toxicity Assessment

Parameter	Procedure
Clinical observation/examination	Twice daily
Body weights	Day 0 (the day before the 1st dosing), 7, 16, 21, and 28, plus at times corresponding to biomicroscopic exams (Weeks 6, 8, and 10) and at necropsy.
Biomicroscopic examination	Pretest; Days 3, 7, 16, 21, and 28; Weeks 6, 8, and 10; and at study completion.
Indirect ophthalmoscopic examination	Three times (pretest, approximately 1 and 3 months of treatment)
Corneal pachymetry	Three times (pretest, approximately 1 and 3 months of treatment)
Specular microscopy	Twice (pretest and approximately 3 months of treatment)
Intraocular pressure	Three times (pretest, approximately 1 and 3 months of treatment)
Hematology and clinical chemistry	Twice (pretest and approximately 3 months of treatment)

Toxicity Assessment (continued)

Parameter	Procedure
Necropsy	End of the three-month study. List of observed tissues and organs: Eyes with Optic Nerve and Adnexa, Any Gross Lesion, Adrenals,* Aorta, Bone (long), Bone Marrow, Brachial Plexus, Brain,* Cecum, Cervical Lymph Nodes, Cervix/Vagina, Colon, Epididymis, Esophagus, Gall Bladder, Gonads,* Heart,* Kidneys,* Larynx, Liver,* Lungs, Mammary Gland, Mesenteric Lymph Nodes, Nasal-lacrimal Tissue, Oviduct, Pancreas with attached Duodenum, Parathyroid, Peripheral Nerve (Sciatic), Pituitary Gland, Prostate Gland, Rectum, Rib/Sternum, Salivary Glands, Seminal Vesicle, Skeletal Muscle, Skin, Small Intestine (ileum, jejunum, Peyer's patch), Spinal Cord (3 sections), Spleen,* Stomach (cardia, fundus, pylorus), Tattoo, Thymus, Thyroid, Tongue, Trachea, Ureters, Urethra, Urinary Bladder, and Uterus. (* Organ weights were measured)
Histopathology	Same as listed under Necropsy above.

Results:

Clinical sings: Two animals in the treatment groups had loose stool (1♂, Group 2, ID X1905, Day 7; 1♀, Group 4, ID X1929, Day 77). All but two animals in the treatment groups (Groups 2-4) and four animals in Group 1 (3♂, 1♀) experienced common mechanical injuries usually involving fingers, hands, arms, thighs and head. A high incidence of bruised thighs was noticed in the treatment groups that may be related to blood collections. The other injuries were considered not to be treatment-related.

Body weight: No treatment-related differences were observed.

Biomicroscopic examinations: No moxifloxacin treatment-related conjunctival congestion, conjunctival swelling, conjunctival discharge, light reflex changes, flare, iritis and neovascularization were observed.

Incidental instances of corneal cloudiness, fluorescein staining and lenticular changes were observed in a few animals of the treatment groups. These findings, however, were not considered as moxifloxacin treatment-related.

Minimal corneal cloudiness (score = 1) was observed in two animals of the treatment groups: 1♂, ID X1906, Group 2 (0.5% moxifloxacin), the right (treated) eye, Days 28 to 91; 1♀, ID X1927, Group 4 (3.0% moxifloxacin), the left (untreated) eye, Days 28 to 91.

Minimal fluorescein staining involving 1% to 25% of the area of the cornea was observed in the treated and untreated eye of one treated animal: ♂, ID X1910, Group 3 (1.0% moxifloxacin), Day 91.

An occurrence of granules was noted on the posterior lens capsule of the treated and untreated eye of one animal in Group 3 (1.0% moxifloxacin). The lens of each eye remained within normal range.

Indirect ophthalmoscopic examinations: No treatment-related changes were observed.

Corneal pachymetry: Data revealed no significant treatment-related differences.

Specular microscopy: Data revealed no significant treatment-related differences.

Intraocular pressure: Data revealed no significant treatment-related differences.

Clinical pathology: No toxicologically significant findings were observed in hematology, coagulation and clinical chemistry.

Gross pathology: No abnormalities or gross lesions were observed at the necropsy of control and treatment animals, except that one Group 2 animal had a gray nematode in its mesentery.

Organ weights: No significant differences were noted between the treatment groups and the Vehicle control group.

Histopathology: No treatment-related lesions or evidence of ocular irritation were present in the eyes, adnexa and nasal-lacrimal tissue.

In summary, topical ocular treatment of Cynomolgus monkeys with 0.5%, 1.0%, or 3.0% moxifloxacin ophthalmic solutions for three months was well tolerated. Ocular evaluations found only incidental and not moxifloxacin treatment-related instances of minimal corneal cloudiness and fluorescein staining in a few animals of the treatment groups. No toxicologically significant findings were discovered in daily health observations, clinical pathological examinations, and post-mortem gross pathological and histopathological examinations. In conclusion, 0.5, 1.0, and 3.0% moxifloxacin ophthalmic solutions produced a low ocular irritation potential and did not elicit noticeable ocular or systemic toxicity in Cynomolgus monkeys.

Toxicology summary and conclusions:

Repeated-dosing toxicity studies of 0.5, 1.0, and 3.0% moxifloxacin ophthalmic solutions in rabbits (with or without pigmented eyes) and Cynomolgus monkeys were conducted. Topical ocular treatments with moxifloxacin ophthalmic solutions were well tolerated in rabbits (qid, 4 weeks or 1 month) and monkeys (six times per day during Days 1-16, tid for the remainder of the three months). The very similar study results in rabbits with or without pigmented eyes indicated that moxifloxacin ophthalmic solutions did not cause extra harm to pigmented eyes in rabbits. Even though it was known that moxifloxacin may bind to melanin and have high concentrations and long half-lives in pigmented ocular tissues (e.g., ICB). Moxifloxacin ophthalmic solutions (0.5, 1.0, and 3.0%) produced a low ocular irritation potential and did not elicit noticeable ocular or systemic toxicity in rabbits and Cynomolgus monkeys.

V. GENETIC TOXICOLOGY:

Please refer to the Pharmacology/Toxicology review for NDA 21-085.

VI. CARCINOGENICITY:

Please refer to the Pharmacology/Toxicology review for NDA 21-085.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Please refer to the Pharmacology/Toxicology review for NDA 21-085.

VIII. SPECIAL TOXICOLOGY STUDIES:

One study conducted by to characterize the sensitization potential of 1.0% moxifloxacin HCl ophthalmic solution was reviewed.

Studies Reviewed:
Sensitization study in the guinea pig with moxifloxacin. V1, M4, TR #: 166:30:1001.

Sensitization study in the guinea pig with moxifloxacin
V1, M4 (4.2.3 Toxicology)

Key study findings:

Moxifloxacin ophthalmic solution (1.0%) showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

Report No:	166:30:1001
Protocol No:	N-00-219
Conducting laboratory:	
Date of study initiation:	August 22, 2000
GLP compliance:	Yes
QA reports:	Yes
Animal:	Female Guinea pigs (*Cavia porcellus*), 397-479 g
Route	Intradermal injection and Occlusive Patch
Drug:	1.0% Moxifloxacin ophthalmic solution

The study design, procedure, and sensitization assessment were summarized in the table below.

Study Design, Procedure, and Sensitization Assessment

	Control	Test
No. of Animals	5	10
Article	0.9% NaCl USP solution (C)	Moxifloxacin 1.0% (Batch no. 00-26521, T)
Induction I	Day 1: Three rows (two per row) intradermal injections within a 2 cm x 4 cm area. a: 0.1 mL of 50:50 (v/v) mixture of Freund's Complete Adjuvant and C (Mix)	
	b: 0.1 mL of C	0.1 mL of T
	c: 0.05 mL of C and 0.05 mL of Mix	0.05 mL of T and 0.05 mL of Mix
Induction II	Day 7: Topical application of 0.5-1.0 g sodium lauryl sulfate suspension in petrolatum. Removal of SLS after 24 hr. Apply a 2 cm x 4 cm paper saturated with C/T at the injection site of each animal and let it stay for 48 hr.	
	0.3 mL of C	0.3 mL of T
Challenge	Day 24: Apply a cotton disk saturated 0.3 mL of C to the left flank of each animal. Apply a cotton disk saturated 0.3 mL of T to the right flank of each animal. Each patch was secured to the skin for 24 hr. Observation of erythema (ER, score 0-4) and edema (ED, score 0-4) at 24, 48, and 72 hr after patch removal.	
Result	All 5 animals appeared clinically normal throughout the study and showed no ER and ED (score = 0).	No observed differences from the control group.

In summary, the study found that under the conditions tested, 1.0% moxifloxacin showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Moxifloxacin HCl, a fourth generation fluoroquinolone currently being marketed in about 30 countries, has enhanced activity against Gram-positive bacteria while maintains the activity against Gram-negative bacteria as compared to the older fluoroquinolones.

The drug product in this NDA application, 0.5% moxifloxacin ophthalmic solution, is a new formulation of moxifloxacin hydrochloride. In addition to the referenced systemic studies in NDA 21-085, a few ocular studies were submitted by the sponsor. Moxifloxacin ophthalmic solution 0.5% generally performed better *in vitro* and *in vivo* than or comparable to the approved drug ciprofloxacin against pathogens that could cause bacterial conjunctivitis. In animal PK studies, moxifloxacin ophthalmic solutions was well absorbed. The drug concentrations in ocular tissues and tear films were relatively high, while the plasma concentrations were very low.

In toxicity studies, moxifloxacin ophthalmic solutions up to 3.0% were well tolerated in rabbits (non-pigmented eyes, qid x 4 weeks; pigmented eyes, qid x 1 month) and monkeys (six times per day during Days 1-16, tid for the remainder of the three months). A very low ocular irritation potential was noted in the treated animals. No ocular and systemic toxicity was observed. Moxifloxacin ophthalmic solution 1.0% showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The huge differences between the approved 400 mg/day oral dose (AVELOX®) and the proposed 1.14 mg/day maximum ophthalmic dose further support the safety of the 0.5% moxifloxacin ophthalmic solution.

Based on the nonclinical study results, it is concluded that there are no safety concerns over this new drug product. No toxicological issues are indicated. No new nonclinical toxicology studies are necessary.

General Toxicology Issues:

No new nonclinical toxicology studies are necessary. No toxicological issues are indicated.

Recommendations:

There are no pharmacology/toxicology objections to the approval of this NDA.

Labeling with basis for findings:

Some minor modifications of labeling in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy" sections are recommended. Both revised and original labeling sections are listed below.

REVISED

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.

Pregnancy: Teratogenic Effects.
Pregnancy Category C: 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 [redacted] Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ORIGINAL

[redacted]

X. APPENDIX/ATTACHMENTS:

[redacted]

Reviewer Name: Jinhui Dou, Ph.D.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CDER/OFFICE OF DRUG EVALUATION V

Date: 01/23/2003
From: Jinhui Dou, Ph.D., Pharmacology Reviewer, ODE-V, HFD-105
Through: Josie Yang, Ph.D., Pharmacology Team Leader
To: Su Tso, Ph.D., Chemistry Reviewer

Subject: Safety and Toxicity Issues of — in Moxifloxacin Ophthalmic Solution

Your e-mail dated on January 22, 2003 informed me that — namely — were detected in samples of moxifloxacin ophthalmic solution. The maximum observed levels are: —. Your concern was whether there are any safety and toxicology issues regarding these —

Available published safety and toxicology data indicated that pure or concentrated solutions of — could cause mild to server ocular irritation when directly applied into the eyes of testing animals. Different degrees of ocular damage may also occur, but generally reversible in a few days. Eye irritation has been reported when animal or human eyes were exposed to vapors of one of the — —, at relative high concentrations.

The proposed daily maximum dose of moxifloxacin ophthalmic solution is 1 drop (~ 40 µL)/eye, three times a day. The calculated daily maximum volume is about 240 µL, which will contain calculated amounts of — µg. No data indicate that at low concentrations (up to — in aqueous solution, below — of any of the — could cause ocular or systemic toxicity.

This reviewer concluded that the — in the moxifloxacin ophthalmic solution at the levels reported should not cause ocular or systemic toxicity in humans. Supporting data are attached below for your reference.

—

In drinking water standard, the permitted level of —

—

In three different studies, testing of 4 mg to 80 mg of undiluted — on rabbit eyes indicates different degrees of irritation and injury (minimal to moderate, some severe). In all studies irritation disappeared or was markedly reduced by 7 days after treatment.

1

In humans, short-term exposure to caused headache and eye, nose, and throat irritation; caused mild irritation of the eyes; and caused slight nose and throat irritation. The OSHA's permissible exposure limit for in term of 8-hr time weighted average is

A drop of full-strength on rabbit eyes causes reversible injury graded 3 on a scale of 10 (10 most server) after 24 hr.

vapor exposure at sufficiently high concentration may cause prompt stinging and watering of the eyes, but there appear to be no reports of eye injury from industrial exposure to vapors. Human volunteers exposed to vapor concentration of 0.25% had no notable effect on the eyes. The OSHA's permissible exposure limit for in term of 8-hr time weighted average is

Exposure of rabbits to vapor at concentration which would be scarcely tolerable to humans caused no corneal damage despite exposure for 8 hr/day, 5 day a week, for up to 7 weeks. Standard testing on rabbit eyes, resulted in rating of 2 on scale of 10 (10 most server).

vapor is irritating to the eyes and respiratory passages of humans at concentrations above . The OSHA's permissible exposure limit for term of 8-hr time weighted average is

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jinhui Dou
1/23/03 04:13:43 PM
UNKNOWN

Josie Yang
1/23/03 05:00:11 PM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL

Other relevant materials (Studies not reviewed, appended consults, etc.): No

Any compliance issues: No

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jinhui Dou
2/11/03 03:18:45 PM
UNKNOWN

Josie Yang
2/11/03 03:48:38 PM
PHARMACOLOGIST