

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22428Orig1s000

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-428
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	12/15/08
PRODUCT:	Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution
INTENDED CLINICAL POPULATION:	Adult and Pediatric Patients with bacterial conjunctivitis
SPONSOR:	Alcon
DOCUMENTS REVIEWED:	Vol. 1.1, 2.1-2.2, 4.1-4.2
REVIEW DIVISION:	Division of Anti-Infective and Ophthalmology Products
PHARM/TOX REVIEWER:	Amy L. Ellis
SUPERVISORY PHARMACOLOGIST:	Wendelyn Schmidt
ACTING DIVISION DIRECTOR:	Wiley Chambers
PROJECT MANAGER:	Lori Gorski

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The pharmacologist has no objection to the approval of this NDA.

B. Recommendation for nonclinical studies

No additional nonclinical studies are recommended.

C. Recommendations on labeling

(b) (4)

The *Pregnancy* section (8.1) and the remainder of the *Carcinogenesis, Mutagenesis, Impairment of Fertility* section (13.1) are consistent with the Vigamox® label and are appropriate. The dose multiples proposed by the Sponsor are close to those calculated by the reviewer.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Daily topical application of 0.5% Moxifloxacin AF to rabbits for up to one month was not associated with ocular inflammation, irritation, or toxicity. Higher concentrations of moxifloxacin (1%, 1.5%) in the same AF vehicle did not cause inflammation, but microscopic evaluation indicated signs of minor irritation in the lower conjunctiva and third eyelid. Ophthalmic examination (biomicroscopy/slit lamp, indirect ophthalmoscopy) did not reveal any changes associated with Moxifloxacin AF treatment at concentrations up to 1.5%. Moxifloxacin AF, 0.5%, did not impede wound healing in rabbits when applied following a keratectomy.

B. Pharmacologic activity

Moxifloxacin exerts its activity against Gram-positive and Gram-negative bacteria by inhibiting DNA gyrase and DNA topoisomerase IV, enzymes involved in DNA replication, transcription, repair, and recombination.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-428

Review number: 1

Sequence number/date/type of submission: N-000/15-DEC-2008/orig NDA submission; updated versions of the nonclinical PK reports were submitted in N-000/05-MAY-2009/BP

Information to sponsor: Yes (X) No ()- labeling comments- see Recommendations Section

Sponsor and/or agent: Alcon (Fort Worth, TX)

Manufacturer for drug substance: Bayer AG, Wuppertal, Germany

Reviewer name: Amy L. Ellis

Division name: Anti-Infective and Ophthalmology Products

Review completion date: 4/15/09

Drug:

Trade name: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution

Generic name: moxifloxacin hydrochloride ophthalmic solution 0.5% in alternative vehicle formulation

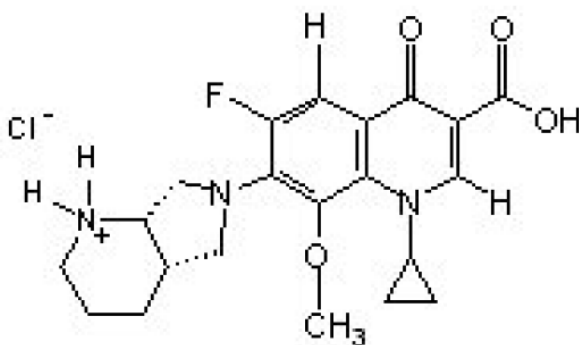
Code name: n/a

Chemical name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride

CAS registry number: 151096-09-2

Molecular formula/molecular weight: $C_{21}H_{24}FN_3O_4$ / 437.9

Structure:



Relevant INDs/NDAs/DMFs: NDA 21-598 (0.5% moxifloxacin hydrochloride ophthalmic solution, Vigamox®) owned by the Sponsor; NDA 21-085 (moxifloxacin oral tablets, Avelox®) Sponsor has obtained a letter from Bayer providing a right to cross reference the Avelox® NDA.

Drug class: Fluoroquinolone anti-infective

Intended clinical population: Adult and pediatric patients (≥ 1 month of age) with bacterial conjunctivitis

Clinical formulation: Moxifloxacin AF Ophthalmic Solution contains:

Moxifloxacin HCl	0.545% (equivalent to 0.5% base)
Xanthan Gum	(b) (4)
NaCl	
Boric Acid	
Sorbitol	
Tyloxapol	
HCl/NaOH	adjust to pH 7.4
Purified Water	(b) (4)

This solution contains the same amount of moxifloxacin as Vigamox®. The inactive ingredients can all be found in other approved ophthalmic products at concentrations not less than those above.

Route of administration: Topical ocular

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Pharmacokinetics/Toxicokinetics:

Moxifloxacin in tear film of pigmented rabbit concentration after a single topical ocular administration of moxifloxacin ophthalmic solutions (Report No. EM:005:00735:1104)

Moxifloxacin in aqueous humor of pigmented rabbit concentration after a single topical ocular administration of moxifloxacin ophthalmic solutions (Report No. EM:002:00735:0804)

Repeat-dose Toxicity:

Comparison of wound healing in New Zealand White rabbits receiving various topical ocular fluoroquinolones following microkeratome anterior keratectomy (Protocol No. E-04-012)

One month ocular irritation study in the albino rabbit (Report No. EM:002:00735:1004)

Studies not reviewed within this submission:

All nonclinical pharmacology/toxicology studies submitted under the NDA were reviewed.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Moxifloxacin inhibits bacterial DNA gyrase and topoisomerase IV and has a broad spectrum of bactericidal activity against strains commonly isolated from patients with bacterial conjunctivitis.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Moxifloxacin exerts its activity against Gram-positive and Gram-negative bacteria by inhibiting DNA gyrase and DNA topoisomerase IV, enzymes involved in DNA replication, transcription, repair, and recombination.

Drug activity related to proposed indication: Antibacterial

2.6.2.3 Secondary pharmacodynamics

There are no nonclinical data on the secondary pharmacodynamics of moxifloxacin in this NDA.

2.6.2.4 Safety pharmacology

Safety pharmacology data are not relevant to the topical ophthalmic use of moxifloxacin because systemic exposure following clinical ocular dosing is very low.

2.6.2.5 Pharmacodynamic drug interactions

Nothing relevant reported in the nonclinical data.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable for this submission.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

When administered systemically, moxifloxacin is widely distributed with tissue concentrations often exceeding those found in plasma. Approximately half of the dose is metabolized via glucuronide and sulfate conjugation. The remainder of the dose is excreted unchanged. Moxifloxacin is excreted in both urine (unchanged drug, glucuronide conjugate) and feces (unchanged drug, sulfate conjugate). Systemic availability of moxifloxacin was very low in human subjects when Moxifloxacin AF was applied to both eyes twice daily for 4 days, then once on Day 5 (C_{max} 0.977 ± 0.673 ng/ml; AUC 8.17 ± 5.31 ng·hr/ml). In rabbits, moxifloxacin levels in tear film decreased more slowly when Moxifloxacin AF was applied to

the eye than they did when Vigamox® was applied. Both products contain moxifloxacin hydrochloride as an active ingredient (0.5% as base). The AUC in tear film and the C_{max} and AUC in aqueous humor of rabbits were greater following the topical ocular application of Moxifloxacin AF compared to Vigamox®.

2.6.4.2 Methods of Analysis

No new analytical methods were developed. An HPLC method with fluorescence detection was used to measure the concentration of moxifloxacin in samples collected for the nonclinical pharmacokinetic studies conducted to support the current NDA. An HPLC method with tandem MS detection was used in some PK/TK studies conducted to support the Vigamox® NDA.

2.6.4.3 Absorption

The absorption of moxifloxacin is low in humans following topical ocular application of Moxifloxacin AF. When this product was applied to both eyes of human subjects twice daily for 4 days, then once on Day 5, the mean C_{max} was 0.977 ± 0.673 ng/ml and the mean AUC was 8.17 ± 5.31 ng·hr/ml. Plasma levels of moxifloxacin were not measured in animals following topical ocular application of Moxifloxacin AF, but one would expect them to be low as well. Studies in rabbits (reviewed below) showed that the C_{max} for moxifloxacin in tear film was similar when either Moxifloxacin AF or Vigamox® was applied topically to the eyes, but the concentration of drug fell more slowly following application of Moxifloxacin AF. This led to higher C_{max} and AUC values for moxifloxacin in aqueous humor after Moxifloxacin AF was applied compared to those observed after application of Vigamox®.

Moxifloxacin in Tear Film of Pigmented Rabbit: Concentration after a Single Topical Ocular Administration of Moxifloxacin Ophthalmic Solutions (Report No. EM:005:00735:1104)

Summary: One 50 µl application of 0.5% Moxifloxacin AF or Vigamox® was applied to each eye of male Dutch-Belted rabbits (3-4 per time point). Tear samples were collected from each eye 1, 5, 10, 30, and 60 minutes after dosing using capillary pipettes. The moxifloxacin concentration in tear film decreased more rapidly in the eyes treated with Vigamox® than in the eyes treated with Moxifloxacin AF.

Mean Tear Film Concentration of Moxifloxacin (µg/mL, ± SD) After Administration of Test Articles

Time (min)	Moxifloxacin AF	Vigamox®
1	3656 ± 1292	3621 ± 1000
5	2035 ± 273	258 ± 153
10	122 ± 120	18 ± 9
30	14 ± 9	3.6 ± 2.5
60	5.0 ± 4.0	3.0 ± 2.8

The AUC₀₋₆₀ ($\pm$ SEM) for Moxifloxacin AF in tear film was higher ($p \leq 0.01$) than that for Vigamox®, 20240 ± 1376 vs. 10571 ± 1161 $\mu\text{g} \cdot \text{min}/\text{mL}$.

Moxifloxacin in Aqueous Humor of Pigmented Rabbit: Concentration after a Single Topical Ocular Administration of Moxifloxacin Ophthalmic Solutions (Report No. EM:002:00735:0804)

Summary: One 50 μl application of 0.5% Moxifloxacin AF or Vigamox® was applied to each eye of male Dutch-Belted rabbits (2-5 per time point). Animals were sacrificed and samples of aqueous humor were collected from each eye 15, 30, 60, and 120 minutes after dosing. The moxifloxacin concentrations in aqueous humor were higher in the eyes treated with Moxifloxacin AF than in the eyes treated with Vigamox®.

Mean Concentration of Moxifloxacin ($\mu\text{g}/\text{mL}$, $\pm$ SD) in Aqueous Humor After Administration of Test Articles

Time (min)	Moxifloxacin AF	Vigamox®
15	2.21 ± 0.69	0.89 ± 0.37
30	4.74 ± 0.70	1.61 ± 0.71
60	2.54 ± 0.77	1.18 ± 0.49
120	0.78 ± 0.30	0.49 ± 0.03

The AUC₀₋₁₂₀ ($\pm$ SEM) for Moxifloxacin AF in aqueous humor was higher ($p \leq 0.01$) than that for Vigamox®, 277 ± 17 vs. 118 ± 11 $\mu\text{g} \cdot \text{min}/\text{mL}$.

2.6.4.4 Distribution

Systemic distribution of moxifloxacin is not relevant for this product due to limited total body exposure following ocular administration. After systemic administration, moxifloxacin is widely distributed with tissue levels frequently exceeding plasma levels.

2.6.4.5 Metabolism

Metabolism of moxifloxacin is not relevant for this product due to limited total body exposure following ocular administration. From the Avelox® label: “Approximately 52% of an oral or intravenous dose of moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. The sulfate conjugate (M1) accounts for approximately 38% of the dose, and is eliminated primarily in the feces. Approximately 14% of an oral or intravenous dose is converted to a glucuronide conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.”

2.6.4.6 Excretion

Moxifloxacin excretion is not relevant for this product due to limited total body exposure following ocular administration. From the Avelox® label: “Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites.”

2.6.4.7 Pharmacokinetic drug interactions

Not relevant for this product.

2.6.4.8 Other Pharmacokinetic Studies

None.

2.6.4.9 Discussion and Conclusions

C_{max} and AUC values for moxifloxacin in the aqueous humor of rabbits were higher following topical ocular application of Moxifloxacin AF compared to Vigamox®. Tear film C_{max} values for moxifloxacin were similar for both products, but tear film concentration fell more rapidly after dosing with Vigamox®, suggesting that the formula of Moxifloxacin AF promoted longer residence time for moxifloxacin in the eye, allowing increased ocular penetration. The clinical dosing regimen for Moxifloxacin AF will be twice daily, in contrast to 3 times daily for Vigamox®. Clinical pharmacology data showed lower plasma levels following multiple doses of Moxifloxacin AF compared to Vigamox®.

2.6.4.10 Tables and figures to include comparative TK summary

Not relevant for this product.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable for this submission.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Topical ocular application of Moxifloxacin AF (0.5%) did not cause inflammation, irritation, or toxicity when applied to rabbit eyes at least 4 times daily for one month. When the same AF formulation contained 1% or 1.5% moxifloxacin, there were microscopic signs of minor irritation of the lower conjunctiva and third eyelid, but still no inflammation or other ocular changes. Moxifloxacin AF did not impede corneal wound healing after anterior keratectomy was performed in rabbits.

The genotoxic profile of moxifloxacin is comparable to other fluoroquinolones. It was mutagenic in one of 5 bacterial strains used for the Ames test (TA 102) and clastogenic in a chromosome aberration assay using cultured cells. It did not induce unscheduled DNA synthesis *in vitro* and was negative in a mouse micronucleus test *in vivo*.

Moxifloxacin had no effect on fertility in rats at systemic doses far above those that can be achieved using a topical ophthalmic route. It was not teratogenic in rats and monkeys given oral doses far above the highest recommended total daily human ophthalmic dose.

2.6.6.2 Single-dose toxicity

No single dose toxicity studies were performed with Moxifloxacin AF.

2.6.6.3 Repeat-dose toxicity

Comparison of Wound Healing in New Zealand White Rabbits Receiving Various Topical Ocular Fluoroquinolones Following Microkeratome Anterior Keratectomy

Protocol No.: E-04-012

Module 4, Vol. 1.1

Conducting laboratory and location: Alcon Research, Fort Worth, TX

Date of report: 11/19/07

GLP compliance: not GLP

QA report: yes () no (X)

Drug, lot #, and % purity: Lot Nos. are below; % purity not provided

Summary: New Zealand White rabbits (approximately 3.5 months old, 2.5-2.9 kg, mixed gender groups of 5) underwent microkeratome anterior keratectomy. Animals were assigned to one of the following 7 treatment groups:

1. BSS® (balanced salt solution, control); Lot No. 45068F
2. Vigamox® (0.5% moxifloxacin); Lot Nos. 66138F and 66739F
3. Zymar® (0.3% gatifloxacin); Lot Nos. 26862 and 29621
4. 0.5% Moxifloxacin AF FID EM 107022, 0.6% xanthan; Lot No. 04-36877-1
5. Moxifloxacin AF FID EM 107283 (0.4% xanthan); Lot No. 04-36967-1
6. 1.5% Levofloxacin Ophthalmic Solution FID 106897; Lot No. 04-36954
7. 0.5% Moxifloxacin Ointment (vehicle not reported); Lot No. 04-36990

On Day 1 (day of surgery), Groups 1-6 received 4 doses one hour apart and Group 7 received 2 doses 2 hours apart. On Day 2, Groups 1-6 received 8 doses one hour apart and Group 7 received 4 doses two hours apart. On Days 3 and 4, Groups 1-6 received 4 doses two hours apart and Group 7 received 2 doses 4 hours apart. Rabbits were observed at least twice daily for mortality and signs of toxicity. Detailed examinations occurred and animals were weighed prior to the initiation of the study and prior to sacrifice. Slit lamp examinations were conducted at screening, immediately after surgery, and 24, 48, and 72 hours after surgery. A 96 hour examination had been scheduled, but was not able to be conducted. Photographs (biomicroscopic images) of the wound areas were taken at all post-surgical time points.

No clinical signs of toxicity were observed in any of the animals. Test article-related ocular irritation was not observed and none of the treatments significantly inhibited or enhanced corneal wound healing under the conditions of this study. Wound healing exceeded 96% in all animals by the end of the study.

One Month Ocular Irritation Study in the Albino Rabbit

Key study findings: No signs of inflammation were observed in the eyes of rabbits after topical ocular application of moxifloxacin at concentrations up to 1.5% several times daily for one month. Microscopic examination of ocular tissues revealed signs of minor irritation in the lower conjunctiva at concentrations of moxifloxacin $\geq 1\%$ (minimal to slight focal loss of goblet cells and replacement with squamous epithelium). Ophthalmoscopy (slit lamp and indirect) did not show any treatment-related changes.

Report No.: EM:002:00735:1004; **Protocol No.:** EM-N-04-012

Module 4, Vol. 1.1

Conducting laboratory and location:

(b) (4)

Date of study initiation: 7/12/04

GLP compliance: OECD and French GLPs

QA report: yes (X) no ()

Drugs, lot #, and % purity: 0.5% Moxifloxacin Ophthalmic Solution, EM 107022 V.1, Lot No. 04-36793-2; 1.0% Moxifloxacin Ophthalmic Solution, EM107190 V.1, Lot No. 04-36818-1; 1.5% Moxifloxacin Ophthalmic Solution EM105709 V.2, Lot No. 04-36845-1; % purity not provided, but the Certificates of Analysis for each Lot of solution listed several impurities as being below the threshold of quantification; Zymar (gatifloxacin 0.3%) Batch No. 30618

Methods

Doses: Vehicle (AF with 0.6% xanthan gum), 0.5%, 1.0%, 1.5% moxifloxacin; 0.3% gatifloxacin; an additional control group was a sham control (left eye manipulated, but no test article applied)

Species/strain: New Zealand White rabbits (KBL strain)

Number/sex/group (main study): 4

Route, formulation, volume, and infusion rate: Topical ophthalmic drugs in the intended clinical vehicle, 80 μ l (2 drops) per application

Satellite groups used for toxicokinetics or recovery: None

Age: 12-15 weeks old

Weight: 2.52-2.89 kg (males); 2.50-2.91 kg (females)

Unique study design or methodology: The right eyes were treated and the left eyes were untreated. Dosing solutions were applied 8 times daily for the first 3 days (1 hour between applications) and 4 times daily for the remainder of the study (2 hours between applications). Rabbits were treated for 31 days and sacrificed and necropsied the day after the final application of test articles occurred. Animals were fasted prior to sacrifice.

Results

Mortality: Rabbits were observed at least twice daily. All animals survived until scheduled sacrifice.

Clinical signs: During the dosing period, rabbits were observed prior to each administration of test article. Detailed clinical examinations were conducted prior to the initiation of dosing, weekly during the dosing period, and before sacrifice. No clinical signs of systemic toxicity were observed.

Body weights: Rabbits were weighed twice during the acclimation period, before the initiation of dosing (Day 0), and on Days 7, 14, 21, and 28. Ocular application of moxifloxacin did not appear to affect body weight.

Food consumption: Measured weekly. Ocular application of moxifloxacin did not appear to affect food consumption.

Ophthalmology: Slit lamp/biomicroscopy evaluations were conducted prior to the initiation of dosing then weekly during the study on Days 3, 7, 14, 21, and 29 or 30. This included evaluation of pupillary reflex and fluorescein staining. Indirect ophthalmoscopy was performed prior to the initiation of dosing and on either Day 29 or 30. Corneal thickness was measured prior to the initiation of dosing and on Day 30.

Neither biomicroscopy nor indirect ophthalmoscopy revealed any treatment-related changes in the eyes. A small, but statistically significant decrease in corneal thickness ($p \leq 0.05$) was observed in the drug-treated (right) eyes compared to the untreated (left) eyes. This was observed in the vehicle control group as well as the moxifloxacin and gatifloxacin groups. The finding was not considered of toxicological significance because there were no other findings in the treated eyes (based on both ophthalmologic examinations and histopathology) that were suggestive of an adverse treatment effect. Additionally, the corneal thickness in the majority of drug treated eyes was still within the range of values seen in the controls and the mean thickness of the right eyes was generally lower than those of the left eyes even before treatment was initiated.

EKG: Not done.

Hematology/Clinical chemistry/Urinalysis: Not done.

Gross pathology: No treatment-related macroscopic findings were observed at necropsy.

Organ weights: Not done.

Histopathology: Adequate Battery: yes (X), no ()
Peer review: yes (X), no ()

The eyes and adnexae (upper and lower eyelids, third eyelid, lachrymal glands, Harderian gland), optic nerve, and all gross lesions were removed from all animals, preserved, and fixed as

appropriate for microscopic examination. For this ocular study, it was acceptable to limit the histopathology evaluation to ocular tissues.

There was a minimal focal loss of goblet cells in the lower eyelid of the treated (right) eye observed in most rabbits from the 1.0% (7/8) and 1.5% (5/8) moxifloxacin AF groups. Minimal to slight focal loss of goblet cells was also observed in the third eyelid for most of these rabbits and one male from the 0.5% moxifloxacin AF group. The goblet cells were replaced with squamous epithelium and this finding was considered indicative of minor local irritation. There were no signs of inflammation in any of the treated eyes.

Toxicokinetics: Not done.

2.6.6.4 Genetic toxicology

The labels for approved moxifloxacin products state that it was not mutagenic in 4 bacterial strains used in the Ames assay, but it was positive in *S. typhimurium* strain TA 102. This pattern of response has been observed with other fluoroquinolones and is believed to be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in Chinese Hamster ovary cells at the HGPRT locus, although mutagenicity results were equivocal when v79 cells were used in this assay. Moxifloxacin was clastogenic in v79 cells in the chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. In mice (*in vivo*), a dominant lethal test was negative, and micronuclei were not detected in bone marrow PCEs following treatment with moxifloxacin.

2.6.6.5 Carcinogenicity

The labels for approved moxifloxacin products state that long term carcinogenicity studies have not been performed with the compound. The sponsor has submitted data on an accelerated initiation/promotion assay in rats. They considered this study to be negative. Data from this study were erroneously permitted in the label for Vigamox®, which was approved after the systemic Avelox® products. These data had not been permitted in the labels for oral or IV Avelox® as they were not considered valid for determining the carcinogenic potential of moxifloxacin. The labels for the ophthalmic moxifloxacin products should be consistent with those for the systemic products.

2.6.6.6 Reproductive and developmental toxicology

Pregnancy Category C has been assigned to moxifloxacin. The labels for the approved moxifloxacin products state that the compound was not teratogenic when it was administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day, although decreased fetal body weights and slightly delayed fetal skeletal development were observed. Teratogenic effects were not observed in the offspring of pregnant monkeys that received oral doses of moxifloxacin as high as 100 mg/kg/day, although there was an increased incidence of smaller fetuses at 100 mg/kg/day.

2.6.6.7 Local tolerance

The repeat-dose ocular toxicity study conducted in rabbits with Moxifloxacin AF demonstrated that it was not an ocular irritant.

2.6.6.8 Special toxicology studies

No special toxicology studies were conducted with Moxifloxacin AF.

2.6.6.9 Discussion and Conclusions

This product is a reformulation of Vigamox® (b) (4) Both Moxifloxacin AF and Vigamox® contain 0.5% moxifloxacin. Vigamox® must be applied to the eye 3 times a day, but Moxifloxacin AF will be labeled for twice daily application. Ocular PK studies in rabbits showed that the concentration of moxifloxacin in tears fell more rapidly following application of Vigamox® than following application of Moxifloxacin AF. Additionally, the levels of moxifloxacin in the aqueous humor of rabbits was higher after application of Moxifloxacin AF compared to Vigamox®.

Moxifloxacin AF was well tolerated by rabbits when applied to the eyes several times daily for one month. Neither ocular irritation nor toxicity were observed with the formulation and concentration of active ingredient to be marketed. There were microscopic signs of slight irritation at higher moxifloxacin concentrations $\geq 1\%$ (same vehicle as Moxifloxacin AF), but no inflammation.

Moxifloxacin AF appears reasonably safe to use as directed in the proposed product label.

2.6.6.10 Tables and Figures

All tables and figures relevant to this NDA have been included in other sections of this review.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not relevant for this product

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Moxifloxacin AF appears reasonably safe to use as directed in the proposed product label. This product caused neither ocular irritation nor toxicity when applied to rabbit eyes several times daily for one month.

Unresolved toxicology issues (if any): None.

Recommendations: The pharmacologist has no objection to the approval of this NDA.

Suggested labeling: The sponsor is proposing to use the *Pregnancy* and *Carcinogenesis, Mutagenesis, Impairment of Fertility* sections from the Vigamox® label, which are mostly appropriate. They have recalculated the dose multiples for these sections to account for the reduced daily dose of moxifloxacin that will be applied when Moxifloxacin AF is used (twice daily dosing as opposed to three times daily for Vigamox®) and the new dose multiples are acceptable, although the pharmacologist would prefer rounding them to 25,000 and 5,000 (rather than 25,500 and 5,100). However, the second sentence in the *Carcinogenesis, Mutagenesis, Impairment of Fertility* section that refers to an initiation/promotion study in rats should be deleted. It should also be removed from the Vigamox® label. This statement was not permitted in the label for systemic moxifloxacin products (Avelox®) that were approved prior to Vigamox® and it should not be in the label for the ocular moxifloxacin products.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ____ No ____

APPENDIX/ATTACHMENTS

None.

**This is a representation of an electronic record that was signed electronically and
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/s/

Amy Ellis

7/14/2009 03:59:16 PM

PHARMACOLOGIST

The pharmacologist has no objection to the approval of
this NDA. Labeling recommendations can be found on
pg 15.

Wendy- You signed the paper copy of this review on 7/14/09.

Wendelyn Schmidt

7/14/2009 04:00:30 PM

PHARMACOLOGIST