

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22428Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-428

**Moxifloxacin Alternative Formulation (AF)
Ophthalmic Solution, 0.5%**

Alcon Pharmaceuticals Ltd.

Lin Qi
Division of Anti-Infective and Ophthalmology Product

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Chemistry Review Data Sheet

1. NDA 22-428
2. REVIEW #: 2
3. REVIEW DATE: October 1, 2009
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

12/15/2008

Amendment

2/11/2009

Amendment

6/11/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon Pharmaceuticals Ltd.

Route des Arsenaux 41

Address: 1700 Fribourg

Switzerland

US Agent:

Representative: Alcon Research Ltd.

6201 South Freeway

Fort Worth, TX 76134-2099

Telephone: 817-568-6494 (Karen Lankow)

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution

b) Non-Proprietary Name (USAN): Moxifloxacin Hydrochloride

c) Code Name/# (ONDC only):

Company or Laboratory Code: AL-15469A (Alcon), BAY 12-8039 (Bayer)

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Antibacterial agent

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 0.5% as base

13. ROUTE OF ADMINISTRATION: Topical/ocular, one drop in affected eye two times a day

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

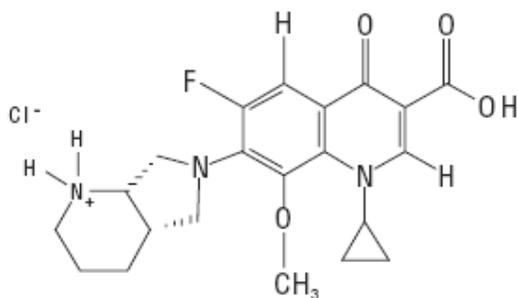
Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s):

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

Chemical structure:

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

Relative Molecular Mass: 437.9; 401.4 (base)

Recommended International Nonproprietary Name (INN): Moxifloxacin

Compendial Name (USAN): Moxifloxacin Hydrochloride

Other Non-Proprietary Name(s):

1-Cyclopropyl-7-[(*S,S*)-2,8-diazabicyclo[4.3.0] non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro 4-oxo-3-quinoline carboxylic acid, monohydrochloride

Chemical Abstracts Service (CAS) Registry Number

186826-86-8 (salt)

151096-09-2 (base)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	Not reviewed	LOA: 5/20/08
	III			1	Adequate	8/25/09	LOA: 8/11/08
	III			4	N/A	Not reviewed	LOA: 8/6/08

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 21-085	NDA 21-085	Same drug substance, LOA dated 8/27/08
NDA 21-598	NDA 21-598	Same drug substance, Alcon

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	Oct 1, 2009	Marisa Stock
Methods Validation	Acceptable	Jul 30, 2009	Lin Qi
Microbiology	Acceptable	Sep 30, 2009	Robert Mello

The Chemistry Review for NDA 22-428

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval from the quality perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, moxifloxacin hydrochloride, is a slightly yellow to yellow powder or crystalline solid. Its solubility in water is (b) (4). Moxifloxacin hydrochloride has a pKa1 of (b) (4) and (b) (4). It has a partition coefficient of log P_{O/W} of (b) (4) and (b) (4). Moxifloxacin hydrochloride is used as the drug substance in the approved NDA 21-085 and NDA 21-598. Moxifloxacin hydrochloride is manufactured and supplied by Bayer AG, Wuppertal, Germany. Drug substance manufacturing and control information is referenced in NDA 21-085 and NDA 21-598.

The drug product, Vigamox AF (moxifloxacin hydrochloride ophthalmic solution) 0.5%, is a sterile, (b) (4) - (b) (4) ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride, equivalent to 0.5% moxifloxacin. The product is greenish yellow solution with an osmolality of 300-370 mOsm/kg and a pH of approximately 7.4 (b) (4). This product is developed using the same drug substance and for the same indication as Vigamox (moxifloxacin HCl ophthalmic solution) 0.5% as base (NDA 21-598). However, this proposed formulation has been modified with (b) (4) with similar efficacy to marketed Vigamox but with a less frequent dosing regimen from TID to BID. The excipients used in the proposed product include sodium chloride, xanthan gum, boric acid, sorbitol, tyloxapol, purified water, and hydrochloride acid and/or sodium hydroxide to adjust pH (See page 14 of quality review #1 for composition). No (b) (4) is used in the proposed formulation because Moxifloxacin AF ophthalmic solution has been observed to maintain adequate (b) (4) to meet USP (b) (4) effectiveness requirements in the absence of a (b) (4) agent.

Executive Summary Section

The product will be packaged with a labeled fill volume of [REDACTED] (b) (4) and 3 mL (Trade size) in a 4 mL natural, low density polyethylene (LDPE) bottle with a polyethylene (LDPE) natural dispensing plug and a tan polypropylene (PP) closure. The drug product will be manufactured and tested at Alcon Research, Ltd., Fort Worth, TX (See page 23 of quality review #1 for the proposed regulatory specification for the drug product).

B. Description of How the Drug Product is Intended to be Used

The proposed indication for this product is to treat bacterial conjunctivitis. The proposed dosing regimen is “Instill 1 drop in the affected eye(s) 2 times daily for 7 days.”

The proposed shelf-life is 24 months for the 3 mL trade size product [REDACTED] (b) (4) at the proposed storage condition, 2°C-25°C (36°F-77°F).

C. Basis for Approvability or Not-Approval Recommendation

In quality review #1, this application is recommended for approval pending a satisfactory quality microbiological review and an “Acceptable” recommendation from the Office of Compliance on the GMP status of facilities. An “Acceptable” recommendation was provided by the Office of Compliance in September 30, 2009 (See Attachment). Dr. Robert J Mello recommended approval in his product quality microbiological review dated September 29, 2009 with the following two comments:

“Quality Microbiological Comments: (The following are **not** deficiencies but are comments, only, to be provided to the Applicant.)

1. The specification for bacterial endotoxin (NMT [REDACTED] (b) (4) while similar to some other Alcon topical ophthalmic drug products containing xanthan gum, is higher than the expected limit of [REDACTED] (b) (4) for such drug products. The applicant is advised, as part of the product’s continual process improvement life cycle, to establish a program to lower the acceptance criteria to NMT [REDACTED] (b) (4).

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

{See signature and date in DARRTS.}

Lin Qi, Ph.D.

Review Chemist

Date

Norman Schmuff, Ph.D.

Branch Chief

Date

B. Endorsement Block

Filed in DARRTS.

C. CC Block

See CC list filed in DARRTS.

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(4) CCI/TS immediately following this
page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22428	ORIG-1	ALCON PHARMACEUTICA LS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

LIN QI
10/05/2009

NORMAN R SCHMUFF
10/05/2009

NDA 22-428

Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution, 0.5%

Alcon Pharmaceuticals Ltd.

Lin Qi
Division of Anti-Infective and Ophthalmology Product

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Chemistry Review Data Sheet

1. NDA 22-428
2. REVIEW #: 1
3. REVIEW DATE: Aug 5, 2009
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

12/15/2008

Amendment

2/11/2009

Amendment

6/11/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon Pharmaceuticals Ltd.

Route des Arsenaux 41

Address: 1700 Fribourg

Switzerland

US Agent:

Representative: Alcon Research Ltd.

6201 South Freeway

Fort Worth, TX 76134-2099

Telephone: 817-568-6494 (Karen Lankow)

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution

b) Non-Proprietary Name (USAN): Moxifloxacin Hydrochloride

c) Code Name/# (ONDC only):

Company or Laboratory Code: AL-15469A (Alcon), BAY 12-8039 (Bayer)

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Antibacterial agent

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13. ROUTE OF ADMINISTRATION: Topical/ocular, one drop in affected eye two times a day

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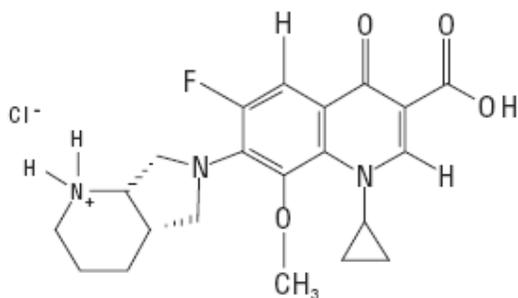
Chemistry Review Data Sheet

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Chemical structure:

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

Relative Molecular Mass: 437.9; 401.4 (base)

Recommended International Nonproprietary Name (INN): Moxifloxacin

Compendial Name (USAN): Moxifloxacin Hydrochloride

Other Non-Proprietary Name(s):

1-Cyclopropyl-7-[(*S,S*)-2,8-diazabicyclo[4.3.0] non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro 4-oxo-3-quinoline carboxylic acid, monohydrochloride

Chemical Abstracts Service (CAS) Registry Number

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Chemistry Review Data Sheet

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6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 21-085	NDA 21-085	Same drug substance, LOA dated 8/27/08
NDA 21-598	NDA 21-598	Same drug substance, Alcon

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	Acceptable	July 30, 2009	Lin Qi
Microbiology	Pending		

The Chemistry Review for NDA 22-428

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not recommended for approval as there are pending issues related to the GMP status of facilities and a satisfactory quality microbiological review. All other drug product quality (CMC) issues are satisfactory.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, moxifloxacin hydrochloride, is a slightly yellow to yellow powder or crystalline solid. Its solubility in water is (b) (4). Moxifloxacin hydrochloride has a pKa1 of (b) (4) and pKa2 of (b) (4). It has a partition coefficient of log P_{O/W} of (b) (4) and (b) (4). Moxifloxacin hydrochloride is used as the drug substance in the approved NDA 21-085 and NDA 21-598. Moxifloxacin hydrochloride is manufactured and supplied by Bayer AG, Wuppertal, Germany. Drug substance manufacturing and control information is referenced in NDA 21-085 and NDA 21-598.

The drug product, Vigamox AF (moxifloxacin hydrochloride ophthalmic solution) 0.5%, is a sterile, (b) (4) ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride, equivalent to 0.5% moxifloxacin. The product is greenish yellow solution with an osmolality of 300-370 mOsm/kg and a pH of approximately 7.4 (b) (4). This product is developed using the same drug substance and for the same indication as Vigamox (moxifloxacin HCl ophthalmic solution) 0.5% as base (NDA 21-598). However, this proposed formulation has been modified with (b) (4) similar efficacy to marketed Vigamox but with a less frequent dosing regimen from TID to BID. The excipients used in the proposed product include sodium chloride, xanthan gum, boric acid, sorbitol, tyloxapol, purified water, and hydrochloride acid and/or sodium hydroxide to adjust pH (See page 14 for composition). No (b) (4) is used in the proposed formulation because Moxifloxacin AF ophthalmic solution has been observed to maintain adequate (b) (4) to meet USP (b) (4) effectiveness requirements in the absence of a (b) (4) agent.

Executive Summary Section

The product will be packaged with a labeled fill volume of 1 mL (Sample size) and 3 mL (Trade size) in a 4 mL natural, low density polyethylene (LDPE) bottle with a polyethylene (LDPE) natural dispensing plug and a tan polypropylene (PP) closure. The drug product will be manufactured and tested at Alcon Research, Ltd., Fort Worth, TX (See page 23 for the proposed regulatory specification for the drug product).

B. Description of How the Drug Product is Intended to be Used

The proposed indication for this product is to treat bacterial conjunctivitis. The proposed dosing regimen is “Instill 1 drop in the affected eye(s) 2 times daily for 7 days.”

The proposed shelf-life is 24 months for the 3 mL trade size product (b) (4) at the proposed storage condition, 2°C-25°C (36°F-77°F).

C. Basis for Approvability or Not-Approval Recommendation

The purpose of current application is to develop a formulation similar to Vigamox with the (b) (4) to provide similar efficacy to marketed Vigamox with reduced dosing regimen. Both drug products have the same concentration (0.5%) of the active ingredient moxifloxacin. (b) (4)



The applicant proposed acceptance criteria for the release and stability tests based on pharmacopoeial standards, batch release data, and the results from the accelerated and long-term stability studies on three primary stability batches for trade size of moxifloxacin AF ophthalmic solution. The acceptance criteria are consistent with those for Vigamox (approved NDA 21-598) except for the acceptance criteria for (b) (4) “Product” and “Total Impurities”. The proposed acceptance criterion for (b) (4) “Product” is decreased from (b) (4) for Vigamox to (b) (4) for current product because this impurity has not been observed to date (through 104 weeks) in stability studies with moxifloxacin AF ophthalmic solution. The proposed acceptance criterion for “Total Impurities” was also decreased from (b) (4) for Vigamox to (b) (4) for the current product. The acceptance criteria are adequately justified. The tests and acceptance criteria for bacterial endotoxins, sterility, and (b) (4) effectiveness will be evaluated by the quality microbiological reviewer.

The stability data for the primary lots of moxifloxacin AF ophthalmic solution are available up to 104 weeks at 25°C/40% RH. All test results through the proposed (b) (4)

Executive Summary Section

for samples at 25°C/40% RH meet the proposed regulatory specification. (b) (4)

Therefore the proposed shelf-life is 24 months for the
3 mL trade size product (b) (4).

This application is recommended for approval pending a satisfactory quality microbiological review and an “Acceptable” recommendation from the Office of Compliance on the GMP status of facilities.

III. Administrative

A. Reviewer’s Signature

[See signature in DARRTS.](#)

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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(4) CCI/TS immediately following this
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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22428	ORIG 1	ALCON PHARMACEUTICA LS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP
NDA 22428	ORIG 1	ALCON PHARMACEUTICA LS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

LIN QI
08/24/2009

NORMAN R SCHMUFF
08/26/2009

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division: Division of Anti-Infective and Ophthalmology Products
NDA: 22-428
Applicant: Alcon Research Ltd
Stamp Date: December 12, 2008
PDUFA Date: October
Trademark: Moxifloxacin alternate formulation AF Ophthalmic Solution (To be confirmed)
Established Name: Moxifloxacin HCl oph soln 0.5% as base
Dosage Form: Ophthalmic Solution
Route of Administration: Topical
Indication: Treatment of bacterial conjunctivitis

PAL: Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

Summary

In general, this NDA, 3S, dated December 12, 2008, is straightforward. The product is a (b) (4) multi-use ophthalmic solution formulated with moxifloxacin HCl. This is a 505(b)(1) NDA, submitted in CTD format and was accepted as a standard NDA. No priority name was identified in the NDA.

A microbiology consult was submitted by the OND PM, Lori Gorski and Dr. Robert Mello was assigned. Ms. Gorski stated she will submit the labeling consult to DDMAC.

The drug substance is manufactured by Bayer Healthcare AG, Wuppertal, Germany. Moxifloxacin has (b) (4) An LOA was submitted, referencing the synthesis, controls and stability information to NDA 21-085. This is the same source as Alcon's Vigamox, moxifloxacin ophthalmic solution product.

The current product (b) (4) The drug product with pH of 7.4 is manufactured, packaged, labeled, release and stability tested at Alcon Research Ltd, Fort Worth, Texas. The pH and osmolality are higher for this product than for Vigamox.

The drug product is stored in Alcon's natural LDPE 'Drop-tainer' bottle, natural LDPE plug, and a tan LDPE cap with pressure sensitive label and shrink band around the neck and cap. The container and (b) (4) (b) (4) are described in DMF (b) (4) and the (b) (4) (b) (4) is in DMF (b) (4) the same (b) (4) as Vigamox. No manufacturer is mentioned in this NDA for the bottle, plug and cap

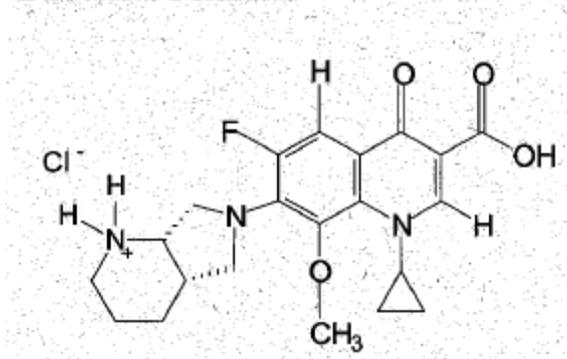
whereas Vigamox specified the manufacturers for the container closure. (b) (4) is the sterilization technique for the container closure used in both NDAs.

The average drop is claimed to be (b) (4) whereas Vigamox claimed (b) (4) for its trade size. Vigamox trade size is 3 mL in 6 mL container; this product trade size is 3 mL in 4 mL bottle, and the professional size is 1 mL in 4 mL bottle

Two new degradants, (b) (4) not mentioned for Vigamox, are listed in the drug product specification.

104 weeks, 3 batches each for both professional and trade sizes, stability data at 25C/40%RH and 26 weeks at 40C/25%RH were submitted. Upright and horizontal positions were studied. 156 weeks at refrigerator storage were also evaluated. Freeze thaw and light studies were provided. Expiration dating period is claimed to be 24 months for the trade size (b) (4)

Structural Formula:



Molecular Formula:



Molecular Weight: 437.9

Critical issues for review

- (b) (4)
- All tests should be evaluated for meaningful conditions and criteria. The endotoxin level is expressed on a per dose basis that converts to (b) (4) EU per mL. This is higher than products approved in the past. Micro will have to evaluate.
- The (b) (4) effectiveness test is missing in the drug product specification. Micro should be alerted to evaluate.
- Draft labels were submitted. The applicant should provide mock-up of the labels for evaluation.
- The (b) (4) (b) (4) information appears to be missing. Reviewer should follow up.

- The drop size is larger than the Vigamox product. Reviewer should check that number of drops per bottle is adequate for patient use period.

NDA 22-428
CMC IQA Review

Page 3

- **Comments for 74-Day Letter**
None recommended.

D. Review, Comments and Recommendation:

Acceptable for filing. No team review is recommended. A single reviewer can review this NDA due to the fairly straightforward issues. Dr. Lin Qi has been assigned to review this NDA.

Linda Ng, Ph.D.
Pharmaceutical Assessment Lead

May 19, 2009
Date

Norman Schmuff, Ph.D.
Branch Chief

Date

Cc: OND PM LGorshi
ONDQA PM JDavid

Appendix 1. Composition of the Drug Product

Composition of Moxifloxacin AF Ophthalmic Solution (FID^a 107022)

Component	Percent W/V	Compendial Designation	Purpose
Moxifloxacin Hydrochloride	0.545 ^b	Non-Compendial ^c	Active
Xanthan Gum	(b) (4)	NF	(b) (4)
Sodium Chloride		USP	
Boric Acid		NF	
Sorbitol		NF	
Tyloxapol		USP	
Hydrochloric Acid and/or Sodium Hydroxide	Adjust pH to 7.4	NF NF	pH Adjusters
Purified Water	(b) (4)	USP	(b) (4)

^a FID = formulation identification number

^b 0.545% moxifloxacin hydrochloride is equivalent to 0.5% moxifloxacin base

^c Although moxifloxacin hydrochloride has a Ph. Eur. Monograph, Alcon will continue to test the material to the specifications approved for VIGAMOX (NDA 21-598).

2 pages has been withheld in full as B (4) CCI/TS immediately following this page

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this page is the manifestation of the electronic signature.**

/s/

Linda Ng
5/19/2009 03:59:40 PM
CHEMIST

Norman Schmuff
6/8/2009 10:59:04 PM
CHEMIST