CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-308

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: February 20, 2009

To: NDA 22-308

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-308 Besivance ™, besifloxacin HCL ophthalmic suspension.

I have assessed the ONDQA review of NDA 22-308 Besivance ™, besifloxacin HCL ophthalmic suspension. Adequate data, manufacturing process information and controls have been submitted to produce a quality product. The overall Office of Compliance site recommendation is acceptable. ONDQA is recommending approval from a CMC perspective. I concur with the ONDQA recommendation.

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/s/

Elaine Morefield
2/20/2009 11:57:33 AM
CHEMIST

Addendum to NDA 22-308 review #1- CMC comments

1. B & L proposed to add the product release test (method 23-T197or C-1774) for leachable with an acceptance criteria of NMT [redacted] for unidentified leachable in response to IR#2 in review#1. The proposal was emailed to FDA on 1/29/09 and already reviewed and accepted in CMC review #1. The amendment to the NDA dated 2/4/09 was a delayed submission of the emailed proposal by B&L. b(4)

2. [redacted] is an alternate analytical site for compendial testing for drug substance. This site is now acceptable by Office of Compliance on 2/11/09 by profile. The EER is attached in the next 3 pages. All facilities are acceptable for NDA 22-308 as listed in review #1 already. b(4)

12-FEB-2009

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application	: NDA 22308/000	Sponsor:	BAUSCH AND LOMB
Org Code	: 520		NO CITY, , XX
Priority	: 1S		
		Brand Name :	BESIFLOXACIN HCL
Stamp Date	: 02-JUN-2008	Estab. Name:	
PDUFA Date	: 02-APR-2009	Generic Name:	BESIFLOXACIN
Action Goal	:	Dosage Form:	(SUSPENSION)
District Goal:	01-FEB-2009	Strength :	0.6%

FDA Contacts: A. YU Review Chemist
301-796-1488

L. NG Team Leader
301-796-1426

Overall Recommendation: ACCEPTABLE on 22-JAN-2009by H. KIEL (HFD-323)
301-796-3246

ACCEPTABLE on 06-SEP-2008by S. ADAMS (HFD-325) 301-796-3193

Establishment : CFN : 1313525 FEI : 1313525

BAUSCH AND LOMB INC

1400 NORTH GOODMAN ST

ROCHESTER, NY 14609

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

FINISHED DOSAGE STERILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-FEB-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 1052807 FEI : 1000113778

BAUSCH AND LOMB PHARMACEUTICALS INC

8500 HIDDEN RIVER PKY

TAMPA, FL 33637

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

FINISHED DOSAGE STERILITY TESTER

Profile : SNI OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-FEB-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI : [redacted]

[redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-FEB-09

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI : [redacted]

b(4)

[redacted]

DMF No: AADA:

b(4)

Responsibilities: [redacted]

Profile	: CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	22-JAN-09		
Decision	: ACCEPTABLE		
Reason	: BASED ON PROFILE		

4

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/s/

Andy Yu
2/12/2009 01:37:32 PM
CHEMIST
Please sign for Norman

Stephen Paul Miller
2/17/2009 12:10:40 PM
CHEMIST
I concur, as acting Branch Chief

Addendum- CMC comments on label

Label edits are marked in "red" color below. Other changes regarding name and label were implemented by B &L and reflected in the current label and carton already.

11 DESCRIPTION

Besivance™ (besifloxacin ophthalmic suspension) 0.6%, is a sterile ophthalmic suspension formulated from besifloxacin HCl. It contains 6mg of besifloxacin base per mL. It is an 8-chloro fluoroquinolone anti-infective for topical ophthalmic use.

$C_{19}H_{21}ClFN_3O_3 \cdot HCl$
Mol Wt 430.30

Chemical Name: (+)-7-[(3R)-3-aminohexahydro-1H-azepin-1-yl]-8-chloro-1-cyclopropyl-6 fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid monohydrochloride.

Besifloxacin hydrochloride is a white to pale yellowish-white powder. Each mL of Besivance™ contains 6.63 mg besifloxacin hydrochloride equivalent to 6 mg besifloxacin base.

STERILE

Each mL Contains:

Active: besifloxacin 0.6% (6 mg/mL);

Preservative: benzalkonium chloride 0.01%

Inactives: polycarbophil, mannitol, poloxamer 407, sodium chloride, edetate disodium dihydrate, sodium hydroxide and water for injection.

Besivance™ is an isotonic suspension with an osmolality of approximately 290 mOsm/kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

Besivance™ (besifloxacin ophthalmic suspension) 0.6%, is supplied as a sterile ophthalmic suspension in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and tan polypropylene cap. Tamper evidence is provided with a shrink band around the cap and neck area of the package.

5 mL in 7.5 mL bottle
NDC 24208-446-05

Storage: Store at 15°- 25°C (59° - 77°F). Protect from Light.

Invert closed bottle and shake once before use.

Rx Only

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/s/

Andy Yu
2/9/2009 10:12:36 AM
CHEMIST

Norman Schmuff
2/9/2009 11:51:19 AM
CHEMIST

Chemistry Review Data Sheet

1. NDA: 22-308

2. REVIEW: #1

3. REVIEW DATE: 1/29/09

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	12/21/07
Amendment (Facility information)	3/27/08
Amendment (Quality Amendment)	5/30/08
Amendment (Quality Microbiology)	8/22/08
Amendment (CMC IR response to)	11/14/08
Amendment (Quality Amendment)	1/14/08
Amendment (Stability update)	12/17/08 (12/23/08 CDER date)
Amendment (Leachable update)	1/23/09
Amendment (Leachable update)	1/29/09

7. NAME & ADDRESS OF APPLICANT:

Name:	Bausch & Lomb Inc.,
Address:	1400 North Goodman St Rochester, NY 14609-3547
Representative:	Jennifer S. Knicley
Telephone:	585-338-6307
Fax:	585-338-0700

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Besivance™
b) Non-Proprietary Name (USAN):Besifloxacin HCl
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: NME
- Submission Priority:1S

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

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Ophthalmic suspension

12. STRENGTH/POTENCY: 0.6%

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: x___Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

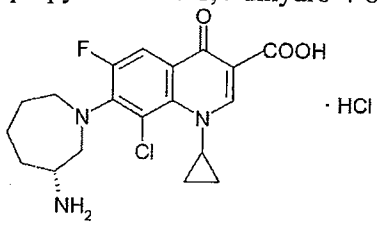
_____SPOTS product – Form Completed

__x__Not a SPOTS product

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

Molecular Formula: C19H21ClFN3O3 HCl Molecular Weight: 430.30

3-Quinolinecarboxylic acid, 7-[(3*R*)-3-aminohexahydro-1*H*-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-, monohydrochloride.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	1	Adequate	8/1/08	A. Yu
	III			3	Adequate	8/15/2000	Yong-de Lu
	III			3	Adequate	2/4/91	Tim Anderson
	III			3	Adequate	2/3/94	Tim Anderson
	III			3	Adequate	7/11/03	Milton Sloan
	III			3,4	Adequate	6/12/08	See rev. for [redacted] from B/L by J.R. Wetzel

b(4)

b(4)

[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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	1/22/09	H. Kiel
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not needed	12/02/08	A. Yu
OPDRA			
EA	Acceptable	12/02/08	A. Yu
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			

Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for 22-308

The Executive Summary

I. Recommendations

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval. All deficiencies have been adequately responded by the sponsor (pages 153-166). The CDER Office of Compliance has issued an overall acceptable recommendation on Jan 22, 2009.

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)

Drug Substance

Besifloxacin is an 8-chlorofluoroquinolone anti-infective for topical ophthalmic use. The ophthalmic product is indicated for the treatment of bacterial conjunctivitis caused by aerobic and facultative Gram-positive microorganisms and aerobic and facultative Gram-negative microorganisms as described in the besifloxacin package insert. The structure of besifloxacin has been established by its route of synthesis and elemental analysis, UV, FTIR, MS, ^{1}H NMR and ^{13}CNMR analysis. Impurities (related substances) introduced during synthesis or degradation products formed during synthesis and /or storage have been adequately studied. The synthetic processes as well as controls of starting materials, reagents, process intermediate, and the final drug substance are acceptable. The commercial batches will be manufactured at [redacted] Stability of the drug substance has been evaluated on 3 batches at long-term conditions (25°C/60%RH) for [redacted] and accelerated conditions (40°C/75%RH) for [redacted] The stability data support a [redacted] retest period for the drug substance. The quality of the drug substance is adequately controlled by identification tests, potency assay [redacted] moisture level, residual solvents, particle size distribution and heavy metals tests. [redacted] drug substance impurities, [redacted] are identified and controlled at NMT [redacted] each. [redacted] is also present in the drug substance and controlled at NMT [redacted] Unidentified

b(4)

b(4)

b(4)

individual impurities of the drug substance are controlled at NMT [redacted] and total impurities at NMT [redacted] respectively. Two low level residual solvents present are adequately controlled well below the Q3C limits. b(4)

Drug product:
Besivance™ (besifloxacin suspension 0.6%) is a sterile, preserved ophthalmic suspension formulated for topical application. The inactive components include polycarbophil, mannitol, poloxamer 407, sodium chloride, and edetate disodium. Benzalkonium chloride is present as a preservative. The product is packaged in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and a tan polypropylene cap. Besivance™ is manufactured as a sterile ophthalmic suspension and filled in two configurations. The quality tests include Besivance™ identification, assay, physical appearance, pH, osmolality, drug impurities, benzalkonium chloride, leacheables and compendial tests. No leacheable has been reported above [redacted] in the tested stability batches by a validated GC/MS method after two years of long term storage. The issue of leachable was discussed with the applicant and an acceptance criteria of NMT [redacted] was added to the product/stability specification for unidentified leachable. Other product quality tests include preservative effectiveness, endotoxin, sterility container/closure integrity, particle size distribution, and compendial tests appropriate for ophthalmic suspensions. Besifloxacin impurities and degradation products are tested by a validated stability indicating method. The acceptance criteria are NMT [redacted] for the photo degradation product [redacted] the only degradation product found. The acceptance criteria for any individual unspecified impurity is NMT [redacted] and total impurities is NMT [redacted] in the product. The acceptance criteria for besifloxacin assay is [redacted] at release and [redacted] during its shelf life. Besivance™ has an expiration dating period of 24 months in the carton protected container. The physician sample (2 mL) has an expiration dating period of 18 months. The product should be protected from light. b(4) b(4)

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

Besivance™ (besifloxacin ophthalmic suspension) 0.6%, is supplied as 5 mL sterile ophthalmic suspension in a 7.5-mL a white low density polyethylene (LDPE) bottle with a controlled dropper tip and tan polypropylene cap. Tamper evidence is provided with a shrink band around the cap and neck area of the package.
Storage: Store at 15°- 25°C (59° - 77°F). Protect from Light. The expiration dating period is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided adequate information on the chemistry, manufacturing and controls for Besivance™ ophthalmic suspension 0.6%, and all facilities were judged acceptable by the CDER Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

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

C. CC Block

168 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-1

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/s/

Andy Yu
1/29/2009 01:15:29 PM
CHEMIST

Norman Schmuff
1/29/2009 06:11:33 PM
CHEMIST

Initial Quality Assessment
Branch __IV__
Pre-Marketing Assessment Division __II__

OND Division:	Division of Anti-Infective and Ophthalmology Produ
NDA:	22-308
Applicant:	Bausch and Lomb
Stamp Date:	May 30, 2008
PDUFA Date:	March 30, 2009
Trademark:	Optura
Established Name:	Besifloxacin HCl Ophthalmic suspension
Dosage Form:	Ophthalmic Suspension 0.6% as base
Route of Administration:	topical
Indication:	Bacterial conjectivitis
PAL:	Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

Summary

The pre-submission for this eCTD NDA dated December 21, 2007 included the non-clinical and chemistry. The official NDA was submitted May 30, 2008 and was accepted as a 1S submission. It is noted that the submission BZ as well as the amendment dated May 30, 2008 contain stability protocol and testing data and updated stability data respectively.

b(4)

Besifloxacin HCl, an antibiotic and new molecular entity, is manufactured in [redacted] It is a salt and express as 0.6% free base for the drug product in the label. Though this is not manufactured by the NDA holder, all information related to the drug substance was submitted in the NDA without a DMF. The primary reference standard was characterized by the NDA holder with assay using potentiometric titration of the amine group at [redacted]

b(4)

The drug product is formulated as a preserved opaque suspension by Bausch and Lomb, Tampa, Florida. The firm of multiple sites is also responsible for release and stability testing. Benzalkonium chloride and edentate disodium are in the formulation. Poloxamer 407, a surfactant, was used as [redacted]

b(4)

All the ingredients [redacted]

The particle size distribution of besifloxacin is proposed to be controlled at [redacted] and volume mean diameter by [redacted] The mean is around [redacted] and [redacted] around [redacted] One stability batch of the drug product used the drug substance from the commercial site [redacted]. b(4)

The 2 fill sizes, 2 mL and 5 mL, are stored in 4 and 7.5 mL respectively white, round [redacted] LDPE bottle, white [redacted] dropper tip, and beige polypropylene cap and clear [redacted] neck band. All first three components are [redacted] before filling. Residuals after sterilization were evaluated. b(4)

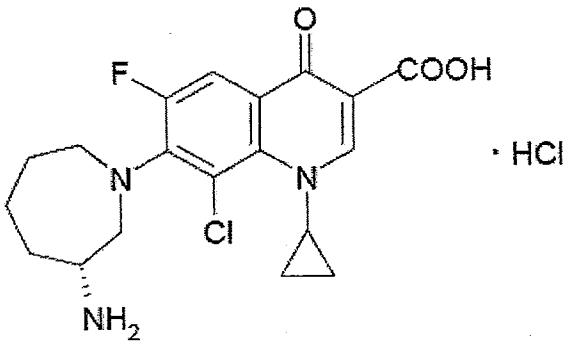
Three batches of stability testing for 18 months were submitted and testing is expected to continue to 36 months. One batch of the commercial drug substance was included in the submitted drug product stability. Regression analysis was performed on the 18 months stability. Freeze-thaw, stress to include acid, base, thermal and photolytic, droplet size and water loss studies were also provided. Water loss is less than [redacted] per year. b(4)

Mock-up labels are provided.

A microbiology consult was submitted by the OND PM, Alison Rodgers. Ms. Rodgers submitted the trade name request on March 3, 2008 and the labeling consult to DDMAC on June 11, 2008. Dr Andrew Yu submitted EES request and all have been found acceptable on September 6, 2008.

The structure and properties of the drug substance are listed:

Structure



Molecular Formula: $C_{19}H_{21}ClFN_3O_3 \cdot HCl$

Molecular Weight: 430.30

Critical issues for review

- The residual solvents in the drug substance specification meet ICH criteria. However, actual levels are much lower. The applicant should consider manufacturing capability of the product for setting acceptance criteria.
- Summary information for the drug product container closure and secondary packaging are provided in Table 2.3.P.7-2 and Table 2.3.P.7-3. A beige cap is noted for the drug product. This should be checked to meet the AAO requirement.
- Polycarbophil is claimed t [redacted] Reviewer should confirm. b(4)
- The uniformity of the drug substance in the bottle and particle size distribution of the suspension formulation should be evaluated. For particle sizing, testing at three levels is recommended. Appropriate test and acceptance criteria included in the drug product specification as needed.
- Weight loss is needed only in 1 batch and not necessary for stability. With future cc change, then the need exists to repeat a water loss study.
- It is suggested that a system suitability test to include a standard at the quantitation limit to ensure detectability of impurities at that level. The system suitability test should be included for both drug substance and drug product impurities test. In this NDA, a s/n ratio was proposed in the drug substance testing. Reviewer can consider a revised system suitability testing.
- The acceptance criteria of tests should be reviewed for meaningful conditions and criteria. The any individual unspecified impurity for the drug product is expected to be NMT [redacted] in the ophthalmic drug product. b(4)
- The stability protocol does not contain an adequate commitment. It should state to inform the division and to reference the CFR for FDA contact in case of failure.
- The established name is a HCl salt and labeling is corrected as the base. Appropriate naming should be used.

• Comments for 74-Day Letter

None recommended.

D. Review, Comments and Recommendation:

The NDA is acceptable for filing. No team review is recommended. Dr. Andrew Yu has been assigned to review the NDA.

_____Linda Ng, Ph.D._____ _____
Pharmaceutical Assessment Lead Date

___Norman Schmuff, Ph.D._____ _____
Branch Chief Date

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X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Linda Ng
9/30/2008 03:33:36 PM
CHEMIST

Norman Schmuff
10/1/2008 09:07:44 AM
CHEMIST