CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204251Orig1s000

CHEMISTRY REVIEW(S)

NDA 204-251

Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension

Alcon Research, Ltd.

Maotang Zhou, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V

ADDENDUM 1 TO CMC REVIEW #1

For the Division of Transplant and Ophthalmology Products

CMC Review Data Sheet

1. NDA 204-251

2. REVIEW #: Addendum 1 to Review #1

3. REVIEW DATE: 17-Apr-2013

4. REVIEWER: Maotang Zhou, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND (b) (4) submission	23-May-2001
Original IND (b) (4) CMC review	23-July-2001
End-of-phase-2 meeting (No CMC issues discussed)	24-Aug-2009
Pre-NDA meeting	13-Aug-1010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	19-JUN-2012	
Amendment (Labeling/Package insert draft)	0001	03-JUL-2012	
Amendment (Labeling/container-carton draft)	0006	04-OCT-2012	
Amendment (Response to 11/19/2012 CMC IR)	0008	14-DEC-2012	
Amendment (Response to 11/19/2012 CMC IR)	0009	14-DEC-2012	
Amendment (Response to 12/14/2012 CMC IR)	0011	04-JAN-2013	
Amendment (Response to 01/11/2013 CMC IR)	0013	18-JAN-2013	
Amendment (Response to 01/15/2013 CMC IR on Methods Validation Package)	0014	22-JAN-2013	
Amendment (Revised container and carton labeling)	0017	04-MAR-2013	
Amendment (Revised container and carton labeling)			

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon Research Ltd.
Address:	6201 South Freeway, Fort Worth, TX 76134
Representative:	Katherine Rath
Telephone:	817-302-5912

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SIMBRINZA®
b) Non-Proprietary Name: Brinzolamide/Bromonidine Ophthalmic Suspension
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 4
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Ophthalmic

11. DOSAGE FORM: Ophthalmic suspension

12. STRENGTH/POTENCY: 1%/0.2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

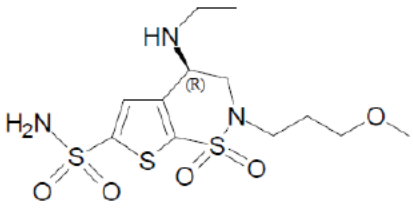
_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

Brinzolamide (USP)
Chemical Name: (R)-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno-[3,2,-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide
Molecular Formula: $C_{12}H_{21}N_3O_5S_3$
Molecular Weight: 383.51

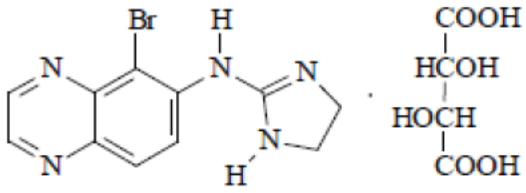
Chemical Structure:



Brimonidine Tartarate
Chemical Name: 5-Bromo-6-(2-imidazoline-2-ylamino) quinoxaline L-tartarate
Molecular Formula: $C_{11}H_{10}BrN_5.C_4H_6O_6$

Molecular Weight: 422.23

Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	10/10/2012	By R. Chang
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	V			4	N/A	N/A	

[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
IND	106293	Original IND
ANDA	76254	Bromonidine Tartrate
NDA	21764	Bromonidine Tartrate
NDA	20816	Brinzolamide

18. STATUS:

ONDQA: Approvable pending resolution of microbiology deficiencies.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Adequate	3/15/2013	Cheryl Dixon
EES	Acceptable	4/17/2013	T. Sharp
Pharm/Tox	N/A		
Biopharm			Tapash Ghosh
LNC	N/A		
Methods Validation	Acceptable	3/14/2013	Michael Trehy
DMEPA*	Proprietary name acceptable	08-AUG-2012	Jung Lee
EA	Categorical exclusion (see review)	11-FEB-2012	Maotang Zhou
Microbiology	Recommend approval	20-DEC-2012	Vinayak Pawar

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 202-514

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as revised in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product.

Labels and labeling contain adequate CMC information. Minor labeling comments from ONDQA were conveyed to the review team.

An "Acceptable" site recommendation from the Office of Compliance was made on April 17, 2013.

Therefore, this NDA is recommended for approval from the CMC perspective.

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

None

II. Summary of CMC Assessments

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

(1) General

Alcon's NDA 204-251 provides for SIMBRINZA™ (brinzolamide /Brimonidine Tartrate ophthalmic suspension) 1%/0.2%, a fixed dose combination product composed of two individual active ingredients: brinzolamide and brimonidine Tartrate. Alcon currently holds NDA/ANDAs for both active ingredients: NDA 20-816 for brinzolamide ophthalmic suspension; NDA 21-764 and ANDA 76-254 for brimonidine tartrate ophthalmic solutions 0.15% and 0.20%, respectively. These drug products have been approved for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

(2) Drug Substance

Brimonidine tartrate is manufactured by two drug substance manufacturers: [redacted] (b) (4) and [redacted] (b) (4) Both are the approved manufacturers for Alcon's Brimonidine Tartrate Ophthalmic Solution (ANDA 76-

254). The CMC information for brimonidine tartrate produced in [redacted] facility is being referred to the relevant sections of ANDA 76-254 while the CMC information for brimonidine tartrate produced in [redacted] is being referred to DMF [redacted] which is adequate without any pending CMC issues.

Brinzolamide is also manufactured by two drug substance manufacturers: [redacted] and [redacted] the same manufacturers of brinzolamide for Alcon's approved AZOPT® (brinzolamide ophthalmic suspension) in NDA 20-816. The CMC information in the current NDA (NDA 204-251) is being referred to the relevant sections of NDA 20-816.

(3) Drug Product

The drug product, Brinzolamide 1% and Brimonidine Tartrate 0.2% Ophthalmic Suspension (i.e., Brinzolamide/Brimonidine Suspension), is a sterile, preserved, multi-dose ophthalmic suspension formulation containing 1% brinzolamide and 0.2% brimonidine tartrate. The formulation is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The formulaton is developed based on Alcon's marketed products AZOPT (NDA 20-816) and Brimonidine Tartrate Ophthalmic Solution, 0.2% (ANDA 76-254).

The drug product is a multi-dose product with 0.003% benzalkonium chloride added for antimicrobial preservation. The formulation, an isotonic topical suspension, also contains carbomer 974P as a [redacted] tyloxapol as a [redacted] boric acid as a [redacted] mannitol as a [redacted] propylene glycol and sodium chloride as [redacted] and purified water as [redacted] The formulation is adjusted to a pH of 6.5 with sodium hydroxide and/or hydrochloric acid. This drug product will be packaged in an opaque, white, low density polyethylene (LDPE) bottle with a natural LDPE dispensing plug and white polypropylene (PP) closure filled with either 8 mL in 10 mL (for trade) [redacted] of the suspension.

The drug product is manufactured by Alcon Laboratories Inc., Fort Worth, TX. The manufacturing process consists of [redacted]

(b) (4)

The specification for the drug product was finalized after negotiation with the Agency and they are as follows: brinzolamide & brimonidine tartrate identity (by TLC and HPLC), brinzolamide & brimonidine tartrate assay (by HPLC; (b) (4)), limits for five specified impurities, any single unspecified impurity (NMT (b) (4) total impurities (NMT (b) (4) benzalkonium chloride identity, benzalkonium chloride assay (b) (4) boric acid identity, boric acid assay (b) (4)), pH (b) (4) osmolality (b) (4) appearance of suspension, redispersibility (NMT (b) (4) viscosity (b) (4) particle size distribution, endotoxin content (b) (4) and sterility (meets USP). The limit of NMT (b) (4) for any individual unspecified impurity is deemed acceptable as it is based on the minor component bromonidine tartrate and it would be NMT (b) (4) if based the major component brinzolamide. Analytical method description was provided for all the methods and method validation was provided for non-compendial methods.

Two production scale (b) (4) primary stability batches were produced in Alcon's ASPEX Manufacturing Facility using the above process. At the time of NDA submission, 9 months long-term stability data and 6 months accelerated stability data were provided for both the trade size (8.0 mL/10 mL) (b) (4) This is deemed to acceptable as per ICH Q1C as the drug product is considered as a new dosage form manufactured by the same manufacturer of the approved dosage forms. Furthermore, the company submitted the 12 months long term data during the review process. On the basis of the available stability data, the applicant requested an expiration dating period of 18 months for the drug product stored at 2 to 25 °C, which is acceptable. The post-approval stability commitment to placing the commercial lots on stability is acceptable.

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

SIMBRINZA™ (brinzolamide /Brimonidine Tartrate ophthalmic suspension) 1%/0.2% is a fixed dose combination of a carbonic anhydrase inhibitor and an alpha 2-adrenergic agonist. The product is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. The intended dosing is to instill one drop of SIMBRINZA™ in the affected eye(s) three times daily. The requested expiration dating period of 18 months for product stored at 2 to 25 °C (36 to 77 °F) is adequately supported by the drug product stability data.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The

NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

In CMC review #1 dated March 12, 2013, this NDA was recommended for approval contingent upon the following pending issues being satisfactorily resolved: (1) Overall site recommendation: Office of Compliance has not yet issued an overall acceptable site recommendation in EES; (2) Labeling: The review team has not yet initiated labeling negotiations.

On April 17, 2013, the Office of Compliance made an overall recommendation of "Acceptable" for the facilities related to the NDA (See the attached establishment evaluation report). The labeling changes recommended by ONDQA have now been forwarded to the applicant by the FDA review team (See CMC Assessment in this review). Labels and labeling contain adequate CMC information. Therefore, this NDA is recommended for approval from the CMC perspective.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

C. CC Block: entered electronically in DARRTS

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

MAOTANG ZHOU
04/17/2013

RAPTI D MADURAWE
04/17/2013

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

pplication:	NDA 204251/000	Action Goal:	
amp ate:	19-JUN-2012	District Goal:	18-FEB-2013
eg	19-APR-2013		
pplicant:	ALCON RES LTD	Brand Name:	Brinzolamide 1% / Brimonidine Tartrate 0
	6201 SOUTH FREEWAY	Estab. Name:	
	FORT WORTH, TX 761342099	Generic Name:	Brinzolamide 1% / Brimonidine Tartrate 0
iority:	4	Product Number; Dosage Form; Ingredient; Strengths	
g. Code:	590	001; SUSPENSION; BRINZOLAMIDE; 1% 001; SUSPENSION; BRIMONIDINE TARTRATE; .2%	

pplication Comment:

DA Contacts:	M. ZHOU	Prod Qual Reviewer		3017962163
	V. PAWAR	Micro Reviewer	(HFD-805)	3017961587
	A. CUFF	Product Quality PM	(HF-01)	3017964061
	J. MILSTEIN	Regulatory Project Mgr	(HFD-590)	3017960763
	D. MATECKA	Team Leader		3017961415

erall Recommendation:	ACCEPTABLE	on 17-APR-2013	by T. SHARP	()	3017963208
	PENDING	on 28-DEC-2012	by EES_PROD		
	ACCEPTABLE	on 11-OCT-2012	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 20-JUL-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

tablishment: CFN: 1610287 FEI: 1610287

ALCON LABORATORIES INC

6201 SOUTH FWY
FORT WORTH, TX 761342001

MF No: AADA:

esponsibilities: FINISHED DOSAGE MANUFACTURER

tablishment omment: DRUG PRODUCT MANUFACTURER - QBD ELEMENTS FOR THE (b) (4) - CMC REVIEWER WOULD LIKE TO PARTICIPATE IN THE INSPECTION IF ONE IS SCHEDULED FOR THIS FACILITY (on (b) (4) by A. CUFF (HF-01) 3017964061)

ofile: (b) (4) **OAI Status:** NONE

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
JBMITTED TO OC	20-JUL-2012				CUFFA
JBMITTED TO DO	23-JUL-2012	10-Day Letter			SAFAAIJAZIR
D RECOMMENDATION	03-AUG-2012			ACCEPTABLE	JMARTIN1
APPROVAL RECOMMENDATION BASED ON PREVIOUS INSPECTION OF ALCON IN MARCH 2012.				BASED ON FILE REVIEW	
C RECOMMENDATION	03-AUG-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	
JBMITTED TO DO	28-DEC-2012	Product Specific			SMITHDE
UPDATING THE RECORD FOR THE PS COVERAGE TO BE PERFORMED FEBRUARY 2013 PER [redacted] MARTINEZ OF DAL-DO AND LINDA NG OF CDER					
SS[redacted] INSPECTION TO IB	10-JAN-2013	Product Specific			JMARTIN1
D RECOMMENDATION	16-APR-2013			ACCEPTABLE	JMARTIN1
THE FIRM (ALCON) INSPECTION IS STILL OPEN; HOWEVER, THE PAI PORTION OF THE INSPECTION WAS COMPLETED. A FDA-483 WILL BE ISSUED WHEN THE INSPECTION IS CONCLUDED BUT IT WILL ONLY BE CLASSIFIED "VAI". DAL-DO RECOMMENDS APPROVAL OF NDA 204251/000.				INSPECTION	
C RECOMMENDATION	17-APR-2013			ACCEPTABLE	SHARPT
				DISTRICT RECOMMENDATION	

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

MF No: AADA:

esponsibilities: DRUG SUBSTANCE MANUFACTURER

stablishment omment: DRUG SUBSTANCE MANUFACTURER (on (b) (4) by A. CUFF (HF-01) 3017964061)

ofile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
JBMITTED TO OC	20-JUL-2012				CUFFA
C RECOMMENDATION	23-JUL-2012			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: CFN: (b) (4) FEI: (b) (4)

MF No: (b) (4) AADA:

esponsibilities: DRUG SUBSTANCE MANUFACTURER

stablishment omment:

ofile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
JBMITTED TO OC	20-JUL-2012				CUFFA
C RECOMMENDATION	23-JUL-2012			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

stablishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

MF No: AADA:

esponsibilities: DRUG SUBSTANCE MANUFACTURER

stablishment omment: DRUG SUBSTANCE MANUFACTURER (on (b) (4) by A. CUFF (HF-01) 3017964061)

ofile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
JBMITTED TO OC	20-JUL-2012				CUFFA
C RECOMMENDATION	23-JUL-2012			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

tablishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

MF No: AADA:

esponsibilities: FINISHED DOSAGE PACKAGER

tablishment (b) (4) (on (b) (4) by A. CUFF (HF-01) 3017964061)
omment:
ofile: OAI Status: NONE

ilestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
JBMITTED TO OC	20-JUL-2012				CUFFA
JBMITTED TO DO	23-JUL-2012	GMP Inspection			SAFAAIJAZIR
D RECOMMENDATION	26-SEP-2012			ACCEPTABLE	JMARTIN1
				BASED ON FILE REVIEW	
C RECOMMENDATION	11-OCT-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

NDA 204-251

Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension

Alcon Research, Ltd.

Maotang Zhou, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V

CMC REVIEW OF NDA 204-251
For the Division of Transplant and Ophthalmology Products (DTOP)

Table of Contents

CMC Review Data Sheet

1. NDA 204-251

2. REVIEW #: 1

3. REVIEW DATE: 11-FEB-2013

4. REVIEWER: Maotang Zhou

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 106,293 submission	31-AUG-2009
Original IND 106,293 CMC review (A. Yu)	26-SEP-2009
CMC end-of-phase-2 meeting	15-NOV-2010
CMC only pre-NDA meeting	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	19-JUN-2012	
Amendment (Labeling/Package insert draft)	0001	03-JUL-2012	
Amendment (Labeling/container-carton draft)	0006	04-OCT-2012	
Amendment (Response to 11/19/2012 CMC IR)	0008	14-DEC-2012	
Amendment (Response to 11/19/2012 CMC IR)	0009	14-DEC-2012	
Amendment (Response to 12/14/2012 CMC IR)	0011	04-JAN-2013	
Amendment (Response to 01/11/2013 CMC IR)	0013	18-JAN-2013	
Amendment (Response to 01/15/2013 CMC IR on Methods Validation Package)	0014	22-JAN-2013	
Amendment (Revised container and carton labeling)	0017	04-MAR-2013	
Amendment (Revised container and carton labeling)			

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon Research Ltd.
Address:	6201 South Freeway, Fort Worth, TX 76134
Representative:	Katherine Rath
Telephone:	817-302-5912

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SIMBRINZA®
b) Non-Proprietary Name: Brinzolamide/Bromonidine Ophthalmic Suspension
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 4
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Ophthalmic

11. DOSAGE FORM: Ophthalmic suspension

12. STRENGTH/POTENCY: 1%/0.2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed

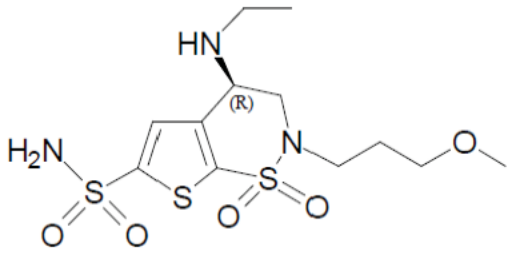
__√__Not a SPOTS product

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

Brinzolamide (USP)
Chemical Name: (R)-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno-[3,2,-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide
Molecular Formula: $C_{12}H_{21}N_3O_5S_3$

Molecular Weight: 383.51

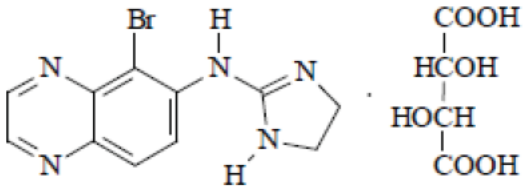
Chemical Structure:



Brimonidine Tartarate
Chemical Name: 5-Bromo-6-(2-imidazoline-2-ylamino) quinoxaline L-tartarate
Molecular Formula: $C_{11}H_{10}BrN_5.C_4H_6O_6$

Molecular Weight: 422.23

Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)				
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	V			4	N/A	N/A	

[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
IND	106293	Original IND
ANDA	76254	Bromonidine Tartrate
NDA	21764	Bromonidine Tartrate
NDA	20816	Brinzolamide

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		Cheryl Dixon
EES			
Pharm/Tox	N/A		
Biopharm			Tapash Ghosh
LNC	N/A		
Methods Validation	Consult sent		
DMEPA*	Proprietary name acceptable	08-AUG-2012	Jung Lee
EA	Categorical exclusion (see review)	11-FEB-2012	Maotang Zhou
Microbiology	Recommend approval	20-DEC-2012	Vinayak Pawar

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 204-251

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as revised in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product.

Labels and labeling contain adequate CMC information. Minor labeling comments were conveyed to the review team. Labels and labeling are pending team review as of the date of this review.

An "Acceptable" site recommendation from the Office of Compliance has not been made as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval until an Acceptable site recommendation is made by the Office of Compliance.

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

None

II. Summary of CMC Assessments

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

Alcon's NDA 204-251 provides for SIMBRINZA™ (brinzolamide /Brimonidine Tartrate ophthalmic suspension) 1%/0.2%, a fixed dose combination product composed of two individual active ingredients: brinzolamide and brimonidine Tartrate. Alcon currently holds NDA/ANDAs for both active ingredients: NDA 20-816 for brinzolamide ophthalmic suspension; NDA 21-764 and ANDA 76-254 for brimonidine tartrate ophthalmic solutions 0.15% and 0.20%, respectively. These drug products have been approved for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

(1) Drug Substance

Brimonidine tartrate is manufactured by two drug substance manufacturers: [redacted (b) (4)] and [redacted (b) (4)] Both are the approved manufacturers for

Alcon's Brimonidine Tartrate Ophthalmic Solution (ANDA 76-254). The CMC information for brimonidine tartrate produced in [redacted] facility is being referred to the relevant sections of ANDA 76-254 while the CMC information for brimonidine tartrate produced in [redacted] is being referred to DMF [redacted] which is adequate without any pending CMC issues.

Brinzolamide is also manufactured by two drug substance manufacturers: [redacted] and [redacted] the same manufacturers of brinzolamide for Alcon's approved AZOPT® (brinzolamide ophthalmic suspension) in NDA 20-816. The CMC information in the current NDA (NDA 204-251) is being referred to the relevant sections of NDA 20-816.

(2) Drug Product

The drug product, Brinzolamide 1% and Brimonidine Tartrate 0.2% Ophthalmic Suspension (i.e., Brinzolamide/Brimonidine Suspension), is a sterile, preserved, multi-dose ophthalmic suspension formulation containing 1% brinzolamide and 0.2% brimonidine tartrate. The formulation is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The formulaton is developed based on Alcon's marketed products AZOPT (NDA 20-816) and Brimonidine Tartrate Ophthalmic Solution, 0.2% (ANDA 76-254).

The drug product is a multi-dose product with 0.003% benzalkonium chloride added for antimicrobial preservation. The formulation, an isotonic topical suspension, also contains carbomer 974P as a [redacted] tyloxapol as a [redacted] boric acid as a [redacted] mannitol as a [redacted] propylene glycol and sodium chloride as [redacted] and purified water as [redacted] The formulation is adjusted to a pH of 6.5 with sodium hydroxide and/or hydrochloric acid. This drug product will be packaged in an opaque, white, low density polyethylene (LDPE) bottle with a natural LDPE dispensing plug and white polypropylene (PP) closure filled with either 8 mL in 10 mL (for trade) [redacted] of the suspension.

The drug product is manufactured by Alcon Laboratories Inc., Fort Worth, TX. The manufacturing process consists of [redacted]

The specification for the drug product was finalized after negotiation with the Agency and they are as follows: brinzolamide & brimonidine tartrate identity (by TLC and HPLC), brinzolamide & brimonidine tartrate assay (by HPLC; (b) (4)), limits for five specified impurities, any single unspecified impurity (NMT (b) (4) total impurities (NMT (b) (4) benzalkonium chloride identity, benzalkonium chloride assay (b) (4) boric acid identity, boric acid assay (b) (4) pH (b) (4) osmolality (b) (4) appearance of suspension, redispersibility (NMT (b) (4) viscosity (b) (4) particle size distribution, endotoxin content (b) (4) and sterility (meets USP). The limit of NMT (b) (4) for any individual unspecified impurity is deemed acceptable as it is based on the minor component bromonidine tartrate and it would be NMT (b) (4) if based the major component brinzolamide. Analytical method description was provided for all the methods and method validation was provided for non-compendial methods.

Two production scale (b) (4) primary stability batches were produced in Alcon's ASPEX Manufacturing Facility using the above process. At the time of NDA submission, 9 months long-term stability data and 6 months accelerated stability data were provided for both the trade size (8.0 mL/10 mL) (b) (4) This is deemed to acceptable as per ICH Q1C as the drug product is considered as a new dosage form manufactured by the same manufacturer of the approved dosage forms. Furthermore, the company submitted the 12 months long term data during the review process. On the basis of the available stability data, the applicant requested an expiration dating period of 18 months for the drug product stored at 2 to 25 °C, which is acceptable. The post-approval stability commitment to placing the commercial lots on stability is acceptable.

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

SIMBRINZA™ (brinzolamide /Brimonidine Tartrate ophthalmic suspension) 1%/0.2% is a fixed dose combination of a carbonic anhydrase inhibitor and an alpha 2-adrenergic agonist. The product is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. The intended dosing is to instill one drop of SIMBRINZA™ in the affected eye(s) three times daily. The requested expiration dating period of 18 months for product stored at 2 to 25 °C (36 to 77 °F) is adequately supported by the drug product stability data.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

Labels and labeling contain adequate CMC information. Minor labeling comments were conveyed to the review team. Labels and labeling are pending team review as of the date of this review.

An "Acceptable" site recommendation from the Office of Compliance has not been made as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval until an Acceptable site recommendation is made by the OC.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Maotang Zhou, Ph.D., Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Balajee Shanmugam, Ph.D., CMC Lead, Division of New Drug Quality Assessment II, Office of New Drug Quality Assessment (ONDQA)

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II (DNDQA II), ONDQA

C. CC Block: entered electronically in DARRTS

101 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

MAOTANG ZHOU
03/13/2013

RAPTI D MADURAWE
03/13/2013

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Product Quality and Manufacturing Memo

Memo Date: September 27, 2012
From: Maotang Zhou, Ph.D.
on behalf of the CMC Review Team

Through: Rapti Madurawe, Ph.D. Branch Chief

NDA Number: 204-251 GRMP Date: March 15, 2013
Applicant: Alcon Research Labs PDUFA Date: April 19, 2013

Drug Product Name and Strength: Brinzolamide/Brimonideine Tartrate Ophthalmic Suspension, 1%/0.2%

Introduction:

This memo is prepared according to ONDQA's IQP 5705 – *Product Quality and Manufacturing PQM) Memo*. The PQM memo is prepared because certain QbD elements have been identified in NDA 204-251, which is currently under review. This memo is intended to apprise the extended review team (including OC and ORA) of potential risks from a review perspective to product quality pertaining to the manufacturing facilities listed in the application. ***However, this memo is not intended to provide inspectional instructions for the inspection team.***

Drug Substances:

The application involves two drug substances: brinzolamide and brimonidine tartrate. The manufacturing processes and manufacturing facilities for both drug substances remain the same as those used in previous NDA applications that have been previously approved by the Agency. Since no QbD elements have been identified in the manufacturing processes for either drug substance, information concerning the drug substance manufacture facilities is not included in the memo.

Drug Product:

The drug product is a sterile ophthalmic suspension containing two drug substances. As shown in the process flow diagram in the Appendix of the memo, the drug product manufacturing involves (b) (4) During the process development, the company has applied QbD principles to determine the potential critical variables, including material attributes and process parameters. In the application, the company has provided extensive information on the establishment of Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs), the initial risk screening, process risk assessment, development of acceptable ranges to establish design space, final risk assessment (FMEA), and process control strategy. The operating ranges proposed for process control are typical as shown in Table 1 through 3 in the Appendix of this memo.

The key process variables and control strategy (QbD) for the manufacture of the drug product is summarized in Alcon's Technical Report TDOC-0015342. In the report, a failure mode effect analysis (FMEA) was performed for material attributes/process parameters that have a range of acceptable values. The objective of the FMEA was to assess the risks of the process variable deviating from the established acceptable ranges in a commercial production set-up and to determine what additional actions could be taken to avoid out of specification (OOS) product quality. Based on FMEA, one process parameter, (b) (4) was identified as a critical process parameter with a risk priority number (RPN) scores of (b) (4) As shown in Table 4 in the Appendix of this memo, additional controls should be implemented based on local plant procedures. The inspection team is recommended to verify the implementation of the proper control strategy concerning this process parameter through local procedures.

Analytical Procedures:

QbD principles were also applied to evaluate method robustness of the HPLC method for assay and identification of the drug substances and related impurities (PROC-0004824). A multivariate design of experiments was used. However, the lower and upper boundaries for each method operating parameters were determined by the allowable criteria defined by USP <621>. As such, these studies do not seem to warrant any special attentions during the inspection.

Conclusion:

In this particular application, the company has applied the QbD principles in the development of the drug product manufacturing process as well as in the validation of an HPLC method. However, there are no claims of RTRT or model-based in-process controls in the application. Even though the term "design space" is used in the NDA, no regulatory flexibility is requested for manufacturing process in Section 3.3.P.3.3: *Description of Manufacturing Process and Process Control.* Therefore, in spite of the QbD approaches applied during the process development, no unusually high level of potential risks from a review perspective to product quality is identified pertaining to the manufacturing facilities listed in the NDA.

APPENDIX

Drug Product Tables and Figures

Figure 1: Drug Product Process Flow Diagram

Exhibit 3.2.P.3.3–1 Manufacturing Process Flowchart for Brinzolamide/Brimonidine Suspension

(b) (4)

[redacted]

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Site Specific Information:

Table 1: Drug Product Manufacturing Site A: Alcon Laboratories Inc

Name of Site A: Alcon Laboratories Inc
FEI/CFN Number: 1610287
Address of Site: 6201 South Freeway, Fort Worth, TX 76134-2001
Function of Site: Finished dosage manufacturer
Reviewer name as contact person for site A in case the inspector has questions: Maotang Zhou

Site Specific High Risk Elements of the Manufacturing Process and Control Strategy	**Site Specific Considerations for Inspection**
(b) (4)	

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

/s/

MAOTANG ZHOU
10/01/2012

RAPTI D MADURAWE
10/01/2012

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER:204251

2. SUBMISSION TYPE :Original

3. SUBMISSION NUMBER: 0

4. PRODUCT PROPERTIES: Sterile, preserved, multi-dose ophthalmic suspension

Trade or Proprietary Name:	Simbrinza (request under review)
Established or Non-Proprietary Name (USAN):	Brinzolamide/brimonidine tartarate
Dosage Form:	Ophthalmic Suspension

5. NAME & ADDRESS OF APPLICANT:

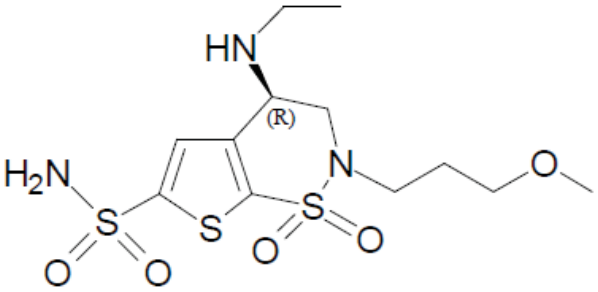
Name:	Alcon Research Ltd
Address:	6201 South Freeway, Fort Worth, TX
Representative:	

6. SUBMISSION PROPERTIES:

Review Priority :	Standard
Classification (Chem. Code and Type):	4
Property (Legal Basis):	505 (b) 1
Responsible Organization:	CDER

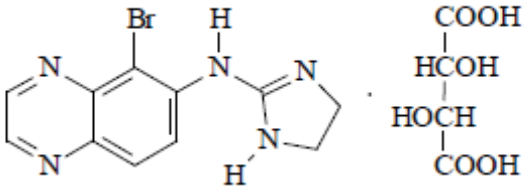
Review Information

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
   Brinzolamide: (R)-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno [3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide.



$C_{12}H_{21}N_3O_5S_3$
383.51

Brimonidine tartarate: 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline L-tartarate



$C_{11}H_{10}BrN_5.C_4H_6O_6$
442.23

2. INDICATION: Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

3. PHARMACOLOGICAL CATEGORY: Fixed combination carbonic anhydrase inhibitor and alpha-agonist agent

4. ROUTE OF ADMINISTRATION: Topical

5. STRENGTH/POTENCY: 1%/0.2%

6. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

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

   Is this a SPOTS product? ☐ Yes ☒ No ☐ Not evaluated at time of IQA.

8. RELATED REVIEW DOCUMENTS:

   a. Drug Master Files listed on 356h form:

DMF	TYPE		ITEM	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	May-11-2009	
	III			Oct-19-2011	
	III			Oct-07-2010	
	V			Apr-12-2010	

   b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☒	
Clin Pharm	☐	☐	
EES	☐	☐	
Pharm/Tox	☐	☐	
Methods Validation	☐	☐	
EA	☐	☐	
New Drug Micro	☒	☐	
CDRH	☐	☐	
Other	☐	☐	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND		106293	
ANDA		76254	Brimonidine tartarate
NDA		21764	Brimonidine tartarate
NDA		20816	Brinzolamide

d. Previous Communications with the Applicant to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
EOP2 meeting	Nov-15-2010	IND 106293	CMC, non-clinical & clinical

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
☒	☐	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	CMC Comments for 74 Day Letter
☐	☒	1.

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☒	☐	1.

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	Biopharmaceutics Comments for 74 Day Letter
☐	☐	1.

CMC Summary:
Critical Issues and Complexities

CMC Critical Issues or Complexities

The two drug substances are manufactured by two different manufacturers. Brinzolamide manufactured by (b) (4) [redacted]

The drug product manufacturing involves (b) (4) [redacted] **and Alcon has applied QbD principles to determine the potential critical variables, including material attributes and process parameters. The company has provided extensive information on the initial risk screening, rank scoring to detailing the Design of Experiment and has established design space range based on these studies. They do not seem to claim regulatory flexibility and this should be verified. A PQM should be drafted by the reviewer.**

Office of Compliance has been notified of the QbD component in this application.

Additional non-critical quality issues are listed in the summary section of this review for further evaluation during the review of the NDA.

Does the submission contain any of the following elements?

Nanotechnology	QbD Elements	PET	Other, please explain
☐	☒	☐	

Is a team review recommended?

Yes	No	Suggested expertise for team
☒	☐	Assigning a QbD liaison will be helpful in evaluating the QbD component.

Summary or Highlights of the Application ***(not already mentioned in other sections)***

- Each of the two drug substances will be manufactured in two different manufacturing facilities. Brinzolamide will be manufactured by (b) (4) and (b) (4) Brimonidine tartarate will be manufactured by (b) (4) and (b) (4)
- DMF (b) (4) is referenced for brimonidine tartarate and a LOA has been provided. This DMF was last reviewed by Chong Ho Kim and found adequate in the review dated Feb-2-2011. *Since this review, one Annual Report has been submitted which requires to be reviewed.*
- Brimonidine tartarate from the referenced DMF was also used in the approved ANDA 76254 and NDA 21764.
- Alcon's approved NDA 20816 also uses brinzolamide manufactured by (b) (4)
- Alcon proposes a (b) (4)
- *Please note that the proposed retest date for brinzolamide manufactured by (b) (4) and (b) (4) is different. Based on (b) (4) of stability data, (b) (4) is proposing a retest date of (b) (4) while (b) (4) is proposing a retest date of (b) (4) based on (b) (4) of stability data.*
- *While both drug substances have been approved in other marketed products individually, on review, the need for Pharm/Tox consult on the qualification of impurities may be evaluated.*
- The drug product formulated as a sterile, preserved, multi-dose suspension will be manufactured by Alcon Manufacturing Ltd (Texas).
- A biowaiver has been requested and the Biopharm group has been notified of the biowaiver request
- The manufacturing process is (b) (4)
- Brinzolamide is (b) (4)
- (b) (4)
- Though there is a USP monograph for brinzolamide, Alcon proposes testing per specification approved under NDA20816.
- The recommended dosing is one drop per eye three times daily.
- The product is supplied in opaque white LDPE plastic bottles as (b) (4) 8 mL in a 10 mL bottle. Storage is recommended at 2°-25°C.
- Long-term (39-weeks) and accelerated (26-weeks) stability data for the product

manufactured from Purrs (Belgium) and ASPEX (Texas) in the 8 mL (b) (4) fill volumes, in 10 (b) (4) mL containers, respectively, placed in horizontal orientation has been provided. *It should be determined if this orientation represents the worst case scenario and if the data presented justify the proposed shelf-life of 78-weeks when stored at 2°C-25°C.*

- DMEPA has expressed concern that the (b) (4) cap is inconsistent with AAO and the proposed (b) (4) is prone to medication error (Jung Lee's email, July 10, 2012). However, the container closure section indicates using White closure. *Please confirm and communicate to DMEPA.*
- *Based on discussions provided in the Stability section (S.3.2.P.8.1) of the NDA, it appears that* (b) (4) *This discrepancy should be clarified with the company.*
- *Weight loss study is indicated to have been conducted only for developmental purposes. The impact of weight loss, if any, on other quality attributes should be assessed. An additional question to consider is, has Alcon conducted weight loss study over the shelf-life on the primary stability batches, if not, have they justified confining the study only for development and is the justification adequate.*
- *Stability results indicate observable trends for several quality attributes. How does this correlate with weight/moisture loss? Particle size is a critical quality attribute which appears to increase on stability and the impact of this observation on the quality of the product should be evaluated.*
- *Since the product is a suspension, please verify if any settling study has been conducted.*
- Package insert provides instruction to "Shake well before use". *Given the redispersability specification of NMT (b) (4) seconds, perhaps specifying time duration to shake in the label should be evaluated.*

Description of Facility Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.)

See EES for complete list of facilities related to this application.

Biopharmaceutics Summary:
Critical Issues, and Complexities

Critical Issues or Complexities

General Summary:

The proposed drug product is an ophthalmic suspension applied topically in the eye and is intended only for local therapeutic effect. To support its approval, the Applicant conducted a PK study (C-10-010), which primary objective was to compare the steady-state pharmacokinetics (PK) of brimonidine in plasma and red blood cell (RBC) saturation of brinzolamide and N-desethyl brinzolamide following topical ocular

administration of Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension dosed 3 times per day (TID) or 2 times per day (BID) to the individual components (i.e., Brinzolamide or Brimonidine Tartrate) in healthy subjects. The Applicant concluded that the steady-state systemic exposure of brinzolamide, N-desethyl brinzolamide, and brimonidine following topical ocular administration of fixed combination Brinzolamide/Brimonidine dosed 3 times daily (TID) or 2 times daily (BID) was not meaningfully different compared to that observed following topical ocular administration of the individual components, Brinzolamide or Brimonidine alone, as statistically indicated by Least Squares Means Ratio confidence intervals bracketing unity. The only exception was the steady-state systemic exposure of brimonidine for the BID regimen on Day 21, where the combination Brinzolamide/Brimonidine showed lower exposure than Brimonidine dosed alone. A similar safety profile was observed comparing Brinzolamide/Brimonidine to the individual components, Brinzolamide and Brimonidine, and no additional risks were identified in healthy subjects dosed with Brinzolamide/Brimonidine TID or BID for 13 weeks, based upon the known risks of the individual components.

Based on the above information, Biopharmaceutics is of the opinion that the Applicant has characterized the systemic exposure of the fixed combination of Brinzolamide /Brimonidine. Note that the Clinical Pharmacology Reviewer from OCP will evaluate the PK information and provide a recommendation regarding its acceptability.

Biopharmaceutics Review Issues

In this submission, pursuant to 21CFR§320.22(b) (1) the Applicant is requesting a waiver from the requirements for the submission of in vivo bioavailability or bioequivalence data. However, based on the above PK information, ONDQA-Biopharmaceutics is of the opinion that the Applicant already characterized the BA/BE of the fixed combination of Brinzolamide /Brimonidine. In light of this, it is not clear why a biowaiver request was included in the NDA (*what is the specific reason behind the BA/BE waiver request*). Further clarification is needed. Once the reason of biowaiver is clear, the Biopharmaceutics Reviewer will address the biowaiver issue accordingly.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	☒	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	☒	☐	
3.	Are all the pages in the CMC section legible?	☒	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☒	☐	

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	☒	☐	
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☒	

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	☒	☐	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☒	☐	*See table on cover page.*

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☒	☐	The brimonidine tartarate drug substance is referenced to DMF (b) (4) and to Alcon's approved applications, ANDA 76-254 and NDA 21-764. The manufacturing process and controls for brinzolamide is provided in the NDA.
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	☒	☐	
15.	Does the section contain information on impurities?	☒	☐	
16.	Does the section contain information regarding the characterization of the DS?	☒	☐	
17.	Does the section contain controls for the DS?	☒	☐	
18.	Has stability data and analysis been provided for the drug substance?	☒	☐	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☒	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☒	
21.	Does the section contain container and closure information?	☒	☐	The DMFs referenced for container closure are: a) DMF (b) (4) b) DMF (b) (4) c) DMF (b) (4) LOA's have been provided in the NDA.

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	☒	☐	
23.	Does the section contain information on composition?	☒	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	☒	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☒	☐	
28.	Have any biowaivers been requested?	☒	☐	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	
30.	Does the section contain controls of the final drug product?	☒	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☒	☐	QbD team and OC have been notified.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?	☒	☐	

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☒	☐	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	☒	☐	
37.	Have the immediate container and carton labels been provided?	☒	☐	
38.	Does section contain tradename and established name?	☒	☐	

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
39.	Does the application contain dissolution data?		X	
40.	Is the dissolution test part of the DP specifications?		X	
41.	Does the application contain the dissolution method development report?		X	
42.	Is there a validation package for the analytical method and dissolution methodology?		X	
43.	Does the application include a biowaiver request?	X		
44.	Does the application include an IVIVC model?		X	
45.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	

46.	Is there any in *vivo* BA or BE information in the submission?	X		
FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
47.	**ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
48.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
49.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
50.	Are there any potential review issues identified?			Once the reason of biowaiver is clear, the Biopharmaceutics Reviewer will address the biowaiver issue accordingly.

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

See appended electronic signature page}
Balajee Shanmugam Ph.D.
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

{See appended electronic signature page}
Tapash Ghosh, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

{See appended electronic signature page}
Steve Miller, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

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

/s/

BALAJEE SHANMUGAM
08/21/2012

TAPASH K GHOSH
08/21/2012

ANGELICA DORANTES
08/21/2012

STEPHEN MILLER
08/21/2012
For R.Madurawe