

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204822Orig1s000

CHEMISTRY REVIEW(S)

NDA 204822

IZBATM
Travoprost Ophthalmic Solution, 0.003%

Alcon Research Ltd.

Addendum 1 to Review 1

Fuqiang Liu, Ph.D.
Branch V
Office of New Drug Quality Assessment
for the Division of Transplant and Ophthalmology Products

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Chemistry Review Data Sheet

1. NDA 204822
2. REVIEW #: addendum 1 to Review #1
3. REVIEW DATE: 07-May-2014
4. REVIEWER: Fuqiang Liu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original: New NDA	15-Jul-2013
SDN 002: Quality/Response to Information Request	28-Aug-2013
SDN 007: Quality/Response to Information Request	18-Dec-2013
SDN 008: Quality/Response to Information Request	31-Jan-2014
SND 009: Labeling/Package Insert Draft	30-Apr-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon Research Ltd.
Address: 6201 South Freeway
Fort Worth, TX 76134-2099
Representative: Naj Sharif, Ph.D.

Chemistry Review Data Sheet

Telephone: 817-568-6494

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: IZBA
- b) Non-Proprietary Name (USAN): Travoprost
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Reduction of elevated intraocular pressure

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.003%

13. ROUTE OF ADMINISTRATION: Topical (ocular)

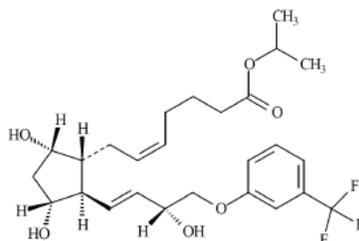
14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

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

Chemistry Review Data Sheet

Chemical Name: [1R-[1 α (Z),2 β (1E,3R*),3 α ,5 α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester

Structural Formula:



Molecular Formula: C₂₆H₃₅F₃O₆

Molecular Mass: 500.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate		Reviewed by A. Fenselau for NDA- (b) (4) in Chemistry Review #2
	II		3	Adequate		Reviewed by Z. J. Tang for NDA (b) (4)	
	III		4	Adequate			
	III		4	Adequate			
	III		3	Adequate		Reviewed by L. Rodriguez for NDA (b) (4)	
	V		7	Adequate		See Quality Micro review by V. Pawar	

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")

Chemistry Review Data Sheet

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: (for internal use only)

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21257	Different formulation of the same drug with different preservative
NDA	21994	Different formulation of the same drug with different preservative
NDA	(b) (4)	(b) (4)
NDA	21764	The use of POLYQUAD as preservative
NDA	20809	The use of POLYQUAD as preservative

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	4-Apr-2014	
Pharm/Tox	Approval	3-Apr-2014	Andrew McDougal
Biopharm			
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Not required		
Microbiology	Approval	28-Oct-2013	VINAYAK B PAWAR

The Chemistry Review for NDA 204822

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 204822 has provided adequate CMC information to assure the identity, strength, purity and quality of the drug product. The Drug Master Files (DMF (b) (4) and DMF (b) (4) for the Travoprost drug substance supporting this NDA are adequate. The labeling has adequate CMC information and will be finalized during OND team review of the labeling. The overall recommendation from the Office of Compliance is “acceptable” as of Apr. 4, 2014 for the establishment evaluation. Therefore, from the CMC perspective, NDA 204822 is recommended for approval at this time.

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

None

II. Summary of Chemistry Assessments

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

Drug Substance

All drug substance information is referenced to (b) (4) Drug Master File (DMF) (b) (4) and (b) (4) DMF (b) (4). Letters of Authorization (LOA) to refer to these DMFs are provided. Both DMF (b) (4) and DMF (b) (4) are currently being used for NDA (b) (4) and NDA (b) (4) and they were found to be adequate. Since the last reviews of these DMFs, they have been updated in several annual reports and administrative changes. The changes made to the DMFs are minor and mostly editorial. Therefore, both DMF (b) (4) and DMF (b) (4) are adequate to support NDA 204822.

Drug Product

Travoprost Ophthalmic solution, 0.003% is a sterile, isotonic, buffered, preserved aqueous solution formulated for topical application. The inactive components include boric acid, hydrochloric acid, mannitol, polyoxyethylene hydrogenated castor oil 40 (HCO-40), Polyquaternium-1 (POLYQUAD), propylene glycol, sodium hydroxide, sodium chloride and purified water. HCO-40 excipient follows the JPE monograph which is of better quality than the HCO-40 USP Monograph. The applicant's NDA

Executive Summary Section

21257 and NDA 21994 also use JPE quality HCO-40. [REDACTED] (b) (4). POLYQUAD at the same concentration of 0.001% is used in some of Alcon's other commercial drug products including Brimonidine Tartrate Ophthalmic Solution, 0.15% (NDA 21764). The preservative, POLYQUAD, is tested according to the same specifications that have been approved for Travoprost 0.004% PQ in Europe which are [REDACTED] (b) (4) those approved for NDA 21764.

The drug concentration (0.003%) is slightly lower than that approved for NDA 21257 and NDA 21994 (each at 0.004%). The product is packaged in a natural [REDACTED] (b) (4) polypropylene [REDACTED] (b) (4) oval bottle with a polypropylene (PP) natural plug and a turquoise polypropylene (PP) closure. The pH of the solution is [REDACTED] (b) (4); the solution is sterile and isotonic. The major manufacturing steps are [REDACTED] (b) (4).

[REDACTED] (b) (4). Sufficient information was provided to assess safety and controls for leachables from the container closure. Drug product specifications include identification, assay and impurities for travoprost, leachates, assay for boric acid and POLYQUAD, and physical measurements, e.g., particulates, color, clarity, etc. The microbiological attributes include sterility and Bacterial Endotoxins. Travoprost 0.003% Solution are acceptable and the Product Quality Microbiology review has recommended approval of the NDA. All stability results at the long term storage conditions through 52 weeks, accelerated condition through 26 weeks, and stressed conditions through 6 weeks are acceptable for 2.5 mL/4mL and 5 mL/7.5 mL bottle configurations. Therefore, a shelf-life of 18 months (78 weeks) is granted for both container closure sizes (2.5 mL/4 mL and 5 mL/7.5 mL bottles) when stored at 2°C to 25°C.

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

Travoprost is a synthetic prostaglandin analog and a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure. The recommended dosage is one drop in the affected eye(s) once daily in the evening. The drug product (travoprost ophthalmic solution, 0.003%) is a sterile, isotonic, buffered, preserved aqueous solution of travoprost (0.03 mg/mL). The drug product is supplied as a 2.5 mL solution in a 4 mL bottle and a 5 mL solution in a 7.5 mL bottle. The dispenser bottles are made of natural [REDACTED] (b) (4) polypropylene and fitted with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package. The storage recommendation is "Store at 2° - 25°C (36° - 77°F)" and the expiration dating period granted is 18 months.

C. Basis for Approvability or Not-Approval Recommendation

Information provided for NDA 204822 regarding drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is adequate to support the quality of the drug product through a shelf-life of 18 months. The DMFs for the Travoprost drug substance are adequate.

Executive Summary Section

The labeling was reviewed and the CMC comments to the container/carton labels and packaging inset were incorporated by the applicant.

The overall recommendation from the Office of Compliance is “acceptable” as of Apr. 4, 2014 for the establishment evaluation. Therefore, NDA 204822 is recommended for approval from a CMC perspective.

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

Fuqiang Liu, Ph.D.
On file

B. Endorsement Block

Rapti Madurawe, Ph.D., Branch chief

C. CC Block

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/s/

FUQIANG P LIU
05/13/2014

RAPTI D MADURawe
05/13/2014

NDA 204822

**IZBATM
Travoprost Ophthalmic Solution, 0.003%**

Alcon Research Ltd.

**Fuqiang Liu, Ph.D.
Branch V
Office of New Drug Quality Assessment
for the Division of Transplant and Ophthalmology Products**

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Chemistry Review Data Sheet

1. NDA 204822
2. REVIEW #: 1
3. REVIEW DATE: 18-Mar-2014
4. REVIEWER: Fuqiang Liu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original: New NDA	15-Jul-2013
SDN 002: Quality/Response to Information Request	28-Aug-2013
SDN 007: Quality/Response to Information Request	18-Dec-2013
SDN 008: Quality/Response to Information Request	31-Jan-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon Research Ltd.
Address: 6201 South Freeway
Fort Worth, TX 76134-2099
Representative: Naj Sharif, Ph.D.
Telephone: 817-568-6494

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: IZBA
- b) Non-Proprietary Name (USAN): Travoprost
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Reduction of elevated intraocular pressure

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.003%

13. ROUTE OF ADMINISTRATION: Topical (ocular)

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

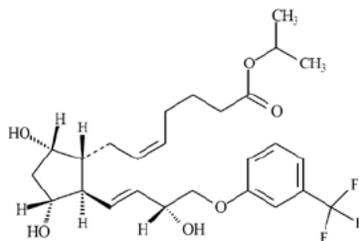
Not a SPOTS product

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

Chemical Name: [1R-[1 α (Z),2 β (1E,3R*),3 α ,5 α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester

Chemistry Review Data Sheet

Structural Formula:

Molecular Formula: C₂₆H₃₅F₃O₆

Molecular Mass: 500.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate		Reviewed by A. Fenselau for NDA- (b) (4) in Chemistry Review #2
	II			3	Adequate		Reviewed by Z. J. Tang for NDA (b) (4)
	III			4	Adequate		
	III			4	Adequate		
	III			3	Adequate		Reviewed by L. Rodriguez for NDA (b) (4)
	V			7	Adequate		See Quality Micro review by V. Pawar

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

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

Chemistry Review Data Sheet

B. Other Documents: (for internal use only)

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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NDA	(b) (4)	(b) (4)
NDA	21764	The use of POLYQUAD as preservative
NDA	20809	The use of POLYQUAD as preservative

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Pending		
Biopharm			
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Not required		
Microbiology	Approval	28-Oct-2013	VINAYAK B PAWAR

The Chemistry Review for NDA 204822

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 204822 has provided adequate CMC information to assure the identity, strength, purity and quality of the drug product. The Drug Master Files (DMF (b)(4) and DMF (b)(4)) for the Travoprost drug substance supporting this NDA are adequate. Revisions to the CMC sections of the labels and labeling are marked up and will be finalized during OND team review of the labeling. The overall recommendation from the Office of Compliance is PENDING as of Mar. 14, 2014 for the establishment evaluation. Therefore, from the CMC perspective, approval of this NDA is contingent upon an overall evaluation of "acceptable" in EES and the acceptability of the final labeling; a recommendation for approval is not made at this time.

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

None

II. Summary of Chemistry Assessments

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

Drug Substance

All drug substance information is referenced to (b)(4) Drug Master File (DMF) (b)(4) and (b)(4) DMF (b)(4). Letters of Authorization (LOA) to refer to these DMFs are provided. Both DMF (b)(4) and DMF (b)(4) are currently being used for NDA (b)(4) and NDA (b)(4) and they were found to be adequate. Since the last reviews of these DMFs, they have been updated in several annual reports and administrative changes. The changes made to the DMFs are minor and mostly editorial. Therefore, both DMF (b)(4) and DMF (b)(4) are adequate to support NDA 204822.

Drug Product

Travoprost Ophthalmic solution, 0.003% is a sterile, isotonic, buffered, preserved aqueous solution formulated for topical application. The inactive components include boric acid, hydrochloric acid, mannitol, polyoxyethylene hydrogenated castor oil 40 (HCO-40), Polyquaternium-1 (POLYQUAD), propylene glycol, sodium hydroxide,

Executive Summary Section

sodium chloride and purified water. HCO-40 excipient follows the JPE monograph which is of better quality than the HCO-40 USP Monograph. The applicant's NDA 21257 and NDA 21994 also use JPE quality HCO-40, (b) (4). POLYQUAD at the same concentration of 0.001% is used in some of Alcon's other commercial drug products including Brimonidine Tartrate Ophthalmic Solution, 0.15% (NDA 21764). The preservative, POLYQUAD, is tested according to the same specifications that have been approved for Travoprost 0.004% PQ in Europe which are (b) (4) those approved for NDA 21764.

The drug concentration (0.003%) is slightly lower than that approved for NDA 21257 and NDA 21994 (each at 0.004%). The product is packaged in a natural (b) (4) polypropylene (b) (4) oval bottle with a polypropylene (PP) natural plug and a turquoise polypropylene (PP) closure. The pH of the solution is (b) (4); the solution is sterile and isotonic. The major manufacturing steps are: (b) (4)

(b) (4) Sufficient information was provided to assess safety and controls for leachables from the container closure. Drug product specifications include identification, assay and impurities for travoprost, leachates, assay for boric acid and POLYQUAD, and physical measurements, e.g., particulates, color, clarity, etc. The microbiological attributes include sterility and Bacterial Endotoxins. Travoprost 0.003% Solution are acceptable and the Product Quality Microbiology review has recommended approval of the NDA. All stability results at the long term storage conditions through 52 weeks, accelerated condition through 26 weeks, and stressed conditions through 6 weeks are acceptable for 2.5 mL/4mL and 5 mL/7.5 mL bottle configurations. Therefore, a shelf-life of 18 months (78 weeks) is granted for both container closure sizes (2.5 mL/4 mL and 5 mL/7.5 mL bottles) when stored at 2°C to 25°C.

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

Travoprost is a synthetic prostaglandin analog and a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure. The recommended dosage is one drop in the affected eye(s) once daily in the evening. The drug product (travoprost ophthalmic solution, 0.003%) is a sterile, isotonic, buffered, preserved aqueous solution of travoprost (0.03 mg/mL). The drug product is supplied as a 2.5 mL solution in a 4 mL bottle and a 5 mL solution in a 7.5 mL bottle. The dispenser bottles are made of natural (b) (4) polypropylene and fitted with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package. The storage recommendation is "Store at 2° - 25°C (36° - 77°F)" and the expiration dating period granted is 18 months.

C. Basis for Approvability or Not-Approval Recommendation

Information provided for NDA 204822 regarding drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is

Executive Summary Section

adequate to support the quality of the drug product through a shelf-life of 18 months. The DMFs for the Travoprost drug substance are adequate.

Labels and labeling are pending final OND team review. Revisions to the CMC sections of the labels and labeling are marked up and will be finalized during team review.

As of Mar. 14, 2014, the overall recommendation for the manufacturing and testing facilities is PENDING.

Approval of this NDA is contingent upon an overall evaluation of “acceptable” in EES and the acceptability of the final labeling. Therefore, at this time, this NDA is not recommended for approval.

III. Administrative

A. Reviewer’s Signature

Fuqiang Liu, Ph.D.
On file

B. Endorsement Block

Rapti Madurawe, Ph.D., Branch chief

C. CC Block

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/s/

FUQIANG P LIU
03/18/2014

RAPTI D MADURawe
03/18/2014

Initial Quality Assessment Branch V Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products
NDA: 204-822

Applicant: Alcon

Stamp Date : 15 July, 2013

Proposed Trademark: Izba*

Established Name: Travoprost

Dosage Form: Ophthalmic solution

Route of Administration: Topical

Strength: 0.003%

Indication: Reduction of elevated IOP

Reviewer : Fuqiang Liu

Biopharm Reviewer: Houda Mahayni

Prdt. Qual. Micro Reviewer: Vinayak Pawar

CMC Lead : Bala Shanmugam

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

Summary and Critical Issues

Summary

Travoprost belongs to the prostaglandin class of compounds and is an isopropyl ester prodrug, hydrolyzed by esterases in the cornea to its biologically active free acid. The product is similar to Alcon's U.S. approved Travoprost 0.004% BAK (NDA 21-994) and Travoprost 0.004% sofZia (NDA 21-257) except for minor changes in the formulation (discussed below).

The NDA is filed as a 505 (b) (1). The submission, including methods validation is all electronic and located in the EDR. The drug product is formulated as a sterile, preserved, multi-dose ophthalmic solution. The drug product will be packaged in the same system for other travoprost products in two sizes, 4 mL and 7.5 mL with fill volume of 2.5 mL and 5 mL, respectively. While no specific shelf-life has been requested, the company claims the product to be stable for at least 78 weeks when stored at 2°C-25°C.

All manufacturing and testing facilities have been entered in EES. Please note that at a teleconference on October 3, 2011, the Phase 3 clinical development plan for a multi-dose, preservative-free presentation was discussed (please see meeting minutes in DARRTS under IND 51000). (b) (4)

* Under review

Alcon has applied QbD principles in the manufacturing process, specifically to determine the potential critical variables, including material attributes and process parameters. Based on a quick perusal of the report, Alcon does not appear to have established design space nor are there claims for regulatory flexibility. This should be verified during review. The limited application of QbD principles does not warrant a PQM. The Office of Compliance has been duly notified.

This NDA will be reviewed on a Standard time line. The PDUFA goal date is May 15, 2014.

Drug Substance

The drug substance will be manufactured by (b) (4). Both sources have been used (b) (4).

A letter of authorization from the DMF holders has been provided.

Drug Substance	DMF #	LOA provided (Yes/No)	Status	Comments
Travoprost	(b) (4)	Y	There are no reviews in DARRTS	The DMF will need to be reviewed.
Travoprost	(b) (4)	Y	Per last review by Zhe J. Tang, dated April 23, 2010, the DMF is adequate.	Several Annual Reports have been submitted since the last review. These submissions will require review.

- The NDA also provides substantial amount of information on the drug substance and during review it should be verified that the specifications between the two vendors are same and include adequate tests and acceptance criteria.

Drug Product

The product is formulated as a sterile, preserved, multi-dose topical ophthalmic formulation containing 30 µg/mL travoprost.

- The drug product will be manufactured by Alcon in Fort Worth, TX or by S.A. Alcon-Couvreur N.V., Belgium.
- All excipients other than polyquatrenium are of compendial quality. A previous formulation had BAK as a preservative. *Polyquatrenium, a non-compendial excipient has not been previously used in any approved ophthalmic formulation and therefore its acceptability from a tox perspective should be consulted with the pharm/tox group. Alcon formulated this compound for use as a preservative for contact lens storage solution. COA and specification for polyquatrenium is provided. It appears to comply with (b) (4).*

- *Whether any of the impurities (b) (4), from polyquatrenium affect the drug product quality should be evaluated.*
- (b) (4)
- The drug product composition is attached to this review.
- Manufacturing process is (b) (4)
- *The travoprost stock solution is stored. How long is the stock stored and under what storage container/conditions? What quality tests are conducted before further processing? If stored longer, has Alcon provided stability data?*
- Executed batch record for batch 203002F (b) (4) has been provided.
- *As noted above, Alcon has applied QbD principles primarily to determine key process variables/material attributes (Technical Report TDOC - 0016966) and also in the UHPLC for assay of travoprost assay and degradation products (Technical Report TDOC-0007046, this is located in 3.2.P.2 and not in 3.2.P.5.2). The risk assessment and scoring studies is documented in TDOC 0016964. The approach appears to be very similar to what Alcon has presented in the past (NDAs 203491 and 204251).*
- *The DP specification is attached to serve as a quick reference. The acceptance criteria proposed for the impurity (b) (4) appears to be (b) (4) than what was approved for other travoprost products. Is the proposed (b) (4) level qualified? Additionally, the proposed level of (b) (4) % for total impurities is (b) (4) than what was approved (b) (4) % under NDA 204,822. The (b) (4) levels proposed should be evaluated and (b) (4) if needed based on batch and stability data. Similarly the acceptance criteria for boric acid assay and pH is slightly different to other formulations. The specification does not include a preservative effectiveness test. Has Alcon justified not including this test and if so, is the justification acceptable? Perhaps the need for PET test should also be consulted with Quality Micro. Also, the acceptability of the proposed (some what wide range) criteria for polyquatrenium assay of (b) (4) % should be evaluated and (b) (4) if need be, based on batch analysis and stability data.*
- *Any individual unspecified impurity is reported as ppm. Any reason/justification provided by Alcon?*
- *Please verify if a one-time drop volume and freeze-thaw study was conducted.*
- *The container closure is sterilized using (b) (4). Reviewer should check if (b) (4) levels of (b) (4) are controlled.*
- *The container and carton label does not list all the inactive ingredients. Space on the container label could be an issue. Check with DMEPA and Clinical on this issue.*

Early action needed:

- 1) Reviewer should evaluate items identified (*in italics*) in this IQA.

Comments for 74-day letter

None at this time.

Comments and Recommendation:

Based on the perusal of this NDA, it is determined to be complete and therefore filable from CMC perspective. Dr. Fuqiang Liu is assigned to review this NDA.

Balajee Shanmugam
CMC Lead

See DARRTS
Date

Rapti Madurawe, Ph.D.
Branch Chief

See DARRTS
Date

Drug Product Composition

Component	% w/v	mg/ml	Function	Quality Reference
Travoprost (AL-6221)	0.003 ^a	0.03 ^a	Active	In-House ^b
Polyoxyethylene Hydrogenated Castor Oil 40 (HCO-40)	(b) (4)			JPE ^c
Propylene Glycol				USP
Boric Acid				NF
Mannitol				USP
Sodium Chloride				USP
Polyquaternium-1 Solution ^d (eq. to Polyquaternium-1)				0.001
Hydrochloric Acid and /or Sodium Hydroxide	Adjust pH to 6.8	Adjust pH to 6.8	pH Adjustment	NF
			pH Adjustment	NF
Purified Water	(b) (4)			USP

^a (b) (4)

^b Travoprost will be tested to the approved specifications for TRAVATAN.

^c JPE = Japanese Pharmaceutical Excipients. The Ph. Eur. (Macrogolglycerol Hydroxystearate) tests for heavy metal, alkalinity and appearance of solution will be substituted for the corresponding JPE tests. In addition, the following (supplemental) tests from the Ph. Eur. Monograph will be applied: free ethylene oxide, dioxan and iodine value. This is the same compendial designation and specification as approved for TRAVATAN).

^d Polyquaternium-1 = POLYQUAD = polvquat = polidronium chloride. (b) (4)

(b) (4) (b) (4) (b) (4)

Drug Product Specification

Test	Specification
Travoprost Identity (UHPLC) ^a	Positive
Travoprost Identity (TLC) ^a	Positive
Travoprost Assay (UHPLC)	(b) (4) % Label
Travoprost Degradation Products (UHPLC) (b) (4) Total Travoprost Degradation Products	NMT (b) (4) % of active NMT (b) (4) % of active NMT (b) (4) % of active NMT (b) (4) % of active
Unrelated Impurities (UHPLC) (b) (4)	NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm
Unspecified Impurities (UHPLC) Any Single Unspecified Impurity Total Unspecified Impurities	NMT (b) (4) ppm NMT (b) (4) ppm
Boric Acid Identity (HPIC) ^a	Positive
Boric Acid Assay (HPIC)	(b) (4) % Label
Polyquaternium-1 (Polyquad) Identity (Spectrophotometric) ^a	Positive
Polyquaternium-1 (Polyquad) Assay (Spectrophotometric)	(b) (4) % Label
pH (Potentiometric)	(b) (4)
Osmolality (Freezing Point Depression)	(b) (4) mOsm/kg
Appearance (Visual): Color Clarity Particles/Particulates Precipitate	Colorless to Light Yellow (b) (4) NMT Ph. Eur. II (b) (4) None
Particulate Matter (Microscopy or HIAC)	NMT (b) (4) particles/mL ≥ (b) (4) μm NMT (b) (4) particles/mL ≥ (b) (4) μm NMT (b) (4) particles/mL ≥ (b) (4) μm
Sterility ^b	Meets USP requirements
Bacterial Endotoxins ^a	< (b) (4) EU/mL

^a Release test only.

^b Sterility testing will not be routinely conducted on production lots except at release. However, if tested, samples will comply with USP Requirements.

NMT = Not more than

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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>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:</p> <ul style="list-style-type: none"> • 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) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

* 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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	LOAs for DMFs (b) (4) and (b) (4) (drug substance) and (b) (4) and (b) (4) (container closure) have been provided.

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
13.	Does the section contain a description of the DS manufacturing process?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The (b) (4) drug substance is referenced to DMF (b) (4) and (b) (4).
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	See above
15.	Does the section contain information on impurities?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	See above
16.	Does the section contain information regarding the characterization of the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	See above
17.	Does the section contain controls for the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	See above
18.	Has stability data and analysis been provided for the drug substance?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
21.	Does the section contain container and closure information?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	LOA has been provided in the NDA for DMF (b) (4) and (b) (4).

F. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
22.	Does the section contain quality controls of excipients?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
26.	Is there a batch production record and a proposed master batch record?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
28.	Have any biowaivers been requested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
30.	Does the section contain controls of the final drug product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
31.	Has stability data and analysis been provided to support the requested expiration date?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	This review highlights the reports submitted in the NDA.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

G. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
34.	Is there a methods validation package?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

H. MICROBIOLOGY				
	Parameter	Yes	No	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

I. LABELING				
	Parameter	Yes	No	Comment
36.	Has the draft package insert been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain tradename and established name?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
39.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓		
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
41.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		✓	

{See appended electronic signature page}

Balajee Shanmugam
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
Branch Chief
Branch V
Division of Pre-Marketing Assessment
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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
09/05/2013

RAPTI D MADURawe
09/05/2013