

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204822Orig1s000

OTHER REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 204-822

Submission Date(s): 07/15/2013

Applicant: Alcon Laboratories, Inc.

Product: travoprost ophthalmic solution 0.003%

Reviewer: Jennifer D. Harris, M.D.

Date of Review: 03/25/2014

Covered Clinical Study (Name and/or Number): C-11-034, A Multicenter, Double-Masked Study of the Safety and Efficacy of Travoprost Ophthalmic Solution, 0.003% Compared to Travatan in Patients with Open-Angle Glaucoma or Ocular Hypertension

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>60</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>none</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>4</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>none</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for travoprost 0.003%. There were 5 out of 60 investigators who disclosed financial ties to the sponsor. The financial interests disclosed do not raise questions about the integrity of the data.

Investigator	Amount	Source	Patients Randomized
(b) (6)	\$107k	Equity Grant and Expenses	(b) (6)
	\$152k	Grant	
	\$61k	Grant and Expenses	
	\$85	Grant and Consulting	

*subinvestigator

¹ See [web address].

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/s/

JENNIFER D HARRIS
05/19/2014

WILLIAM M BOYD
05/19/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 31, 2014

To: Judit Milstein, Chief Project Management Staff
Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA #204822
IZBA™ (travoprost ophthalmic solution) 0.003%

As requested in your consult dated August 30, 2013, OPDP has reviewed the draft labeling for IZBA™ (travoprost ophthalmic solution) 0.003%.

OPDP has reviewed the proposed PI. Our comments on the PI are based on the substantially complete version of the labeling titled, "NDA 204822 FDA V1 to Alcon 27Mar14.docx" which was sent via email from DTOP on March 28, 2014. OPDP's comments are provided in the attached, clean version of the labeling.

OPDP has also reviewed the proposed carton/container labeling received via email on March 28, 2014 (document titled, "2013-1990_Izba_(Travoprost)_Label_Labeling_Packaging_Review1.doc"). OPDP has no comments on the proposed carton/container labeling.

If you have any questions about our comments, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

Thank you for the opportunity to provide comments on the proposed PI and carton/container labeling.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CHRISTINE G CORSER
03/31/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 11, 2014

TO: Judit Milstein, Regulatory Project Manager
Jennifer Harris, M.D., Medical Officer
William Boyd, M.D., Medical Team Leader
Division of Transplantation and Ophthalmic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 204822

APPLICANT: Alcon Laboratories, Inc.

DRUG: Travoprost Ophthalmic Solution 0.003%

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

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

CONSULTATION REQUEST DATE: September 5, 2013
CLINICAL INSPECTION SUMMARY DATE: March 17, 2014
DIVISION ACTION GOAL DATE: April 10, 2014

PDUFA DATE:

May 15, 2014

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Travoprost for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The pivotal study (C-11-034, entitled “A Multicenter, Double-Masked Study of the Safety and Efficacy of Travoprost Ophthalmic Solution, 0.003% Compared to TRAVATAN in Patients with Open-Angle Glaucoma or Ocular Hypertension”) was inspected in support of the indication. The clinical sites of Drs. Branch and Peace were selected for inspection because of their relatively high enrollments.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
James D. Branch, M.D. 224 Town Run Lane Winston-Salem, NC 27101	C-11-034/ 3631/ 48	7-9 Jan 2014	NAI
James H. Peace, M.D. United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301	C-11-034/ 3627/ 33	3-6 Dec 2013	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. James D. Branch, M.D.

224 Town Run Lane
Winston-Salem, NC 27101

- a. **What was inspected:** At this site for Protocol C-11-034, 50 subjects were screened, 48 subjects were enrolled, and 47 subjects completed the study. The records of all 50 subjects screened were reviewed, including the informed consent forms for all 48 enrolled subjects. Records reviewed included, but were not limited to, enrollment logs, IRB and monitor communications, training documentation, randomization, protocol deviations, adverse events, and test article accountability
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Minor issues including out-of-window visits for two subjects and record keeping errors were discussed with the clinical investigator.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. James H. Peace, M.D.
United Medical Research Institute
431-433 North Prairie Avenue
Inglewood, CA 90301

- a. **What was inspected:** At this site for Protocol C-11-034, 42 subjects were screened, 33 subjects were enrolled, and 31 subjects completed the study. The records of the 33 enrolled subjects were reviewed. Records reviewed included, but were not limited to, financial disclosure statements, inclusion/exclusion criteria, medical histories, patient screening and enrollment logs, IRB and monitor correspondence, test article accountability, the primary efficacy endpoint, concomitant medications, adverse events, source documents, and case report forms (CRFs).
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Dr. Branch's and Peace's conduct of Protocol C-11-034 were inspected in support of this NDA. The final classification of these two inspections is NAI (No Action Indicated). Data generated by these clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ROY A BLAY
03/14/2014

JANICE K POHLMAN
03/14/2014

KASSA AYALEW
03/14/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 3, 2014
Requesting Office or Division: Division of Transplant and Ophthalmology Products
Application Type and Number: NDA 204822
Product Name and Strength: Izba (Travoprost) Ophthalmic Solution, 0.003%
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Alcon Laboratories, Inc.
Submission Date: July 12, 2013
OSE RCM #: 2013-1990
DMEPA Primary Reviewer: Rachna Kapoor, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and package insert for Izba (Travoprost) Ophthalmic Solution NDA 204822 for areas of vulnerability that could lead to medication errors.

Alcon Laboratories submitted this original New Drug Application seeking approval to market a new formulation of travoprost ophthalmic solution. The proposed indication is reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Labels and Labeling	B

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA did not identify any major issues with container, carton labeling, or prescriber information labeling. As a result, we will be providing routine recommendations regarding the route of administration, ancillary statements placement, font size for the company name, and text style for the proprietary name in our conclusion and recommendation section.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container label and carton labeling can be improved to increase the prominence of important information on the label to promote the safe use of the product.

Additionally, DMEPA concludes that the package insert is acceptable. We have no additional comments for the package insert as this time.

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

4.1 RECOMMENDATIONS FOR THE APPLICANT

A. Container Label (2.5 mL and 5 mL)

- i. Reduce the font size and use regular font (no bold font) for the ‘Alcon’ statement. We recommend this because the proprietary name and established names should be the most prominent information on the labels to promote easy identification of the product as recommended in the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.¹
- ii. Capitalize only the first letter in the proprietary name to increase the legibility of the proprietary name. We recommend this because words written in all-capital letter are less legible than words written in mixed case letter. This is consistent with the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. (b) (4)
- iii. Place the route of administration “For Ophthalmic Use Only” on the principal display panel of the container label to highlight the correct route of administration. We recommend this revision to help prevent wrong route of administration errors. This can be achieved by making the statement (b) (4) less prominent by moving it to a side panel or using smaller font size and regular font (no bold font).

B. Carton Labeling (All Strengths)

- i. See both A.i and A.ii and revise carton labeling accordingly.
- ii. Place the route of administration “For Ophthalmic Use Only” on the principal display panel of the container label to highlight the correct route of administration. We recommend this revision to help prevent wrong route of administration errors.

¹ 2013 Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Izba that Alcon Laboratories submitted on November 22, 2013.

Table 2. Relevant Product Information for Izba	
Active Ingredient	Travoprost
Indication	For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic solution
Strength	0.003%
Dose and Frequency	One drop instilled in each eye once daily in the evening
How Supplied	Alcon's Drop Tainer packaging system in 2.5 mL solution in a 4 mL bottle and 5 mL solution in a 7.5 mL bottle
Storage	store at 2° – 25°C (36° – 77°F)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Izba labels and labeling submitted by Alcon Laboratories on July 12, 2013.

- Container Label
- Carton Labeling
- Package Insert (no image included)

B.2 Label and Labeling Images



² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

RACHNA KAPOOR
03/03/2014

YELENA L MASLOV
03/04/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA #204822	NDA Supplement #: BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: Travoprost Dosage Form: ophthalmic solution Strengths: 0.003%		
Applicant: Alcon Research, Inc Agent for Applicant (if applicable):		
Date of Application: July 12, 2013 Date of Receipt: July 15, 2013 Date clock started after UN:		
PDUFA Goal Date: May 15, 2014		Action Goal Date (if different):
Filing Date: September 13, 2013		Date of Filing Meeting: August 27, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>): NO				
List referenced IND Number(s): 51000				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1488 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Electronic submission.
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		This NDA provides for a new formulation.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	YES			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSE was informed of this submission on 9/10/13 and no formal consult was deemed necessary
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

study report to QT Interdisciplinary Review Team)				
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 27, 2013

NDA: 204822

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: Travoprost

DOSAGE FORM/STRENGTH: ophthalmic solution, 0.003%

APPLICANT: Alcon Research, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

BACKGROUND:

NDA 21257, TRAVATAN (travoprost ophthalmic solution), 0.004%, preserved with benzalkonium chloride, was approved on March 16, 2001.

NDA 21994, TRAVATAN Z (travoprost ophthalmic solution), 0.004%, preserved with sofZia was approved on September 21, 2006. This formulation eliminates the use of benzalkonium chloride, which is associated with conjunctival inflammation, tear film disruption and symptoms of ocular surface health disease following chronic exposure.

NDA 204822, the subject of this review, provides for a new formulation for travoprost solution 0.003%, preserved with poliquaternium. The applicant claims that this formulation also allows for a reduction the drug exposure (0.003% vs 0.004%) while maintaining efficacy and improving safety profile.

REVIEW TEAM:

Clinical: Jennifer Harris

Statistics: Solomon Chefo

Pharm/Tox: Andrew McDougal, Ilona Bebenek

Clinical Pharmacology: Yongheng (Eric) Zhang

Product Quality: Fuqiang Liu

Biopharmaceutics: Houda Mahayni

Micro Sterility: Vinayak Pawar

PM: Judit Milstein

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Judit Milstein	N
		Michael Puglisi	Y
	CPMS/TL:	Judit Milstein	N
Cross-Discipline Team Leader (CDTL)	William M. Boyd		Y

Clinical	Reviewer:	Jennifer Harris	Y
	TL:	William M. Boyd	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Yongheng Zhang	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Solomon Chefo	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrew McDougal Ilona Bebenek	Y Y
	TL:	Lori Kotch	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Fuqiang Liu Houda Mahayni (Biopharmaceutics)	Y Y
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Vinayak Pawar	N
	TL:	Brian Riley	N
CMC Labeling Review	Reviewer:		
	TL:		

Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Renata Albrecht		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

If no, explain:	
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: none</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter

PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter

<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
If no, was a complete EA submitted?	<input type="checkbox"/> YES <input type="checkbox"/> NO
If EA submitted, consulted to EA officer (OPS)?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Renata Albrecht, MD, Director</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter <i>PLR format review was conducted and comments sent to the sponsor via e-mail (August 30, 2013).</i>
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

JUDIT R MILSTEIN

09/16/2013

NDA 204822-CSO Filing Review

DSI CONSULT: Request for Clinical Inspections

Date: September 5, 2013

To: Kassa Ayalew, M.D., M.P.H, GCPAB Acting Branch Chief
Janice Pohlman, M.D., M.P.H., GCPAB Team Leader
Roy Blay, Ph.D., GCPAB Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Jennifer Harris, MD, Medical Officer
Division of Transplant and Ophthalmology Products

From: Judit Milstein, Regulatory Health Project Manager, 301-796-0763
Division of Transplant and Ophthalmology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#:	NDA 204822
Applicant/ Applicant contact information:	Alcon Laboratories, Inc 6201 South Freeway Fort Worth, TX 76134-2099 Contact: Naj Sharif, PhD Global Regulatory Project Manager Tel 817-568-6494
Drug:	Travoprost Ophthalmic Solution 0.003%
NME:	No
Review Priority:	No
Study Population includes < 17 years of age:	No
Is this for Pediatric Exclusivity:	No
Proposed Indication:	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
PDUFA:	May 15, 2014
Action Goal Date:	April 10, 2014

Inspection Summary Goal Date:

March 10, 2014

II. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Randomized	Indication
DSI Choice	C-11-034	864	treatment of elevated intraocular pressure (IOP)

III. Site Selection/Rationale

The clinical portion of the application has been preliminarily reviewed, and no issues have been identified to date to suggest a problem with data integrity.

An inspection is requested for at least two sites for this clinical trial only as your resources permit.

Note that the highest DOMESTIC enrollers are: James Branch, MD (44) and David Wirta, MD (40).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Routine Inspections

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Goal Date for Completion:

We request that the inspections be performed and that the Inspection Summary Results be provided by March 10, 2014. We intend to issue an action letter on this application by April 10, 2014. The PDUFA due date for this application is **May 15, 2013**.

Should you require any additional information, please contact Judit Milstein at 301-796-0763.

Additional Information:

This is an electronic NDA. The List and Description of Investigators for the previously identified study are provided below.

List of Investigators and Subinvestigators Study C-11-034

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
<i>Austria</i>				
6175	Prof. Dr. Herbert A. Reitsamer SALK – Universitätsklinik für Augenheilkunde und Optometrie der PMU Müllner Hauptstrasse 48 5020 Salzburg AUSTRIA	(b) (4)	1	1
5356	Prof. Dr. Clemens Vass Medical University of Vienna, Department of Ophthalmology and Optometry Währinger Gürtel 18-20, 1090 Vienna AUSTRIA	(b) (4)	1	0
<i>Finland</i>				
6517	Prof. Hannu Uusitalo FinnMedi Oy Tutkimusvastaanotto Biokatu 10, rakennus Finn-Medi 3,2.krs 33520 Tampere FINLAND	(b) (4)	0	0

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
<i>Germany</i>				
6497	Dr. Klaus Rosbach Breite Straße 60 55124 Mainz Germany	(b) (4)	6	5
3713	Prof. Dr. Mathias Wagner Seestrasse 78 01983 Grossraeschen GERMANY	(b) (4)	4	4
<i>Spain</i>				
6496	Dr. Mercè Guarro Vallés Oftalmologia Recerca Capiro Hospital General de Catalunya Pero i Pons 1 08195 Sat Cugat del Vallés – Barcelona SPAIN Hospital General de Catalunya Farmacia Josep Trueta, 1 08195 Sant Cugat del Valles – Barcelona - SPAIN	(b) (4)	5	7

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
<i>Sweden</i>				
5920	Dr. Peter Ahlberg Dept. of Ophthalmology Falun Hospital SE-791 82 Falun SWEDEN	(b) (4)	2	2
5380	Dr. Lena Viklund Backman Eye Clinic Vrinnevi Hospital SE-601 82 Norrkoping SWEDEN	(b) (4)	1	1
<i>United States</i>				
6100	Guy Angella, MD Eye Surgery Associates 603 N. Flamingo Road, Suite #250 Pembroke Pines, FL 33028	(b) (4)	5	6
2434	Jason Bacharach, MD North Bay Eye Associates, Inc. 104 Lynch Creek Way, Suite 12 Petaluma, CA 94954	(b) (4)	4	5
Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
2195	Howard Barnebey, MD Specialty Eyecare Centre 1920 116 th Avenue NE Bellevue, WA 98004	(b) (4)	7	8
6439	Nicholas P. Bell, MD Robert Cizik Eye Clinic 6400 Fannin St., Suite 1800 Houston, TX 77030	(b) (4)	1	0
5443	Ettaleah C. Bluestein, MD Bluestein Custom Vision 2145 Henry Tecklenburg Drive, Suite 100 Charleston, SC 29414	(b) (4)	6	7
6405	Carla Bourne, MD University of South Florida Eye Institute 12901 Bruce B Downs Blvd, MDC 21 Tampa, FL 33612	(b) (4)	4	2

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
3631	James David Branch, MD James D. Branch 224 Town run Lane Winston-Salem, NC 27101	(b) (4)	24	24
6548	Ronald Caronia, MD (Previous PI – Stanley Berke, MD) Ophthalmic Consultants of Long Island 360 Merrick Road, 3 rd Floor Lynbrook, NY 11563		0	0
3349	Andrew J. Cottingham, Jr., MD Texas Quest Medical Research, LLC 15900 La Cantera Parkway, Suite 19205 San Antonio, TX 78256		6	6
4189	Charles J. Crane, MD Northern New Jersey Eye Institute, PA 71 Second Street South Orange, NJ 07079		7	6
1931	Monte S. Dirks, MD Black Hills Regional Eye Institute 2800 3 rd Street Rapid City, SD 57701		5	4
Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
5303	El-Roy Dixon, MD Dixon Eye Care 806 N. Jefferson Street Albany, GA 31701	(b) (4)	9	9
1927	Harvey B. DuBiner, MD Eye Care Centers Management Clayton Eye Center 1000 Corporate Center Drive, Suites 100, 120 Morrow, GA 30260		14	13
5010	Eran Duzman, MD (Previous PI – Efaim Duzman, MD) Lakeside Vision Center 4605 Barranca Pkwy, Suite 100 Irvine, CA 92604		9	9

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
553	Richard Evans, MD Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240	(b) (4)	13	12
5465	Asra S. Firozi, MD North Carolina Eye, Ear, Nose & Throat 4102 N. Roxboro Road Durham, NC 27704	(b) (4)	9	8
5145	William J. Flynn, MD, OD R and R Eye Research, LLC 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	(b) (4)	1	2
1930	Robert S. Friedman, MD The Eye Associates of Manatee, LLP 2111 Bee Ridge Road Sarasota, FL 34239	(b) (4)	3	3

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
4567	Robert F. Haverly, MD Laser Eye Surgery of Erie 311 West 24 th Street, Suite 401 Erie, PA 16502	(b) (4)	8	6
5480	William L. Haynes, MD Asheville Eye Associates 8 Medical Park Drive Asheville, NC 28803	(b) (4)	4	3

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
3731	Gregory J. Katz, MD Huron Ophthalmology, PC 5477 W. Clark Road Ypsilanti, MI 48197	(b)(4)	5	4
2449	Barry Katzman, MD West Coast Eye Care Associates 6945 El Cajon Blvd San Diego, CA 92115	(b)(4)	10	9
Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
3112	Bradley R. Kwapiszeski, MD Heart of America Eye Care, PA 8901 West 74 th Street, Suite 281 Shawnee Mission, KS 66204	(b)(4)	7	6
5515	John M. Lim, MD Houston Eye Associates 2855 Gramercy St. Houston, TX 77025	(b)(4)	19	19
3678	Jeffery Lozier, MD Arch Health Partners 15611 Pomerado Road, Suite 400 Poway, CA 92064	(b)(4)	9	11

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
4780	Jodi Ian Luchs, MD South Shore Eye Care, LLP 2185 Wantagh Avenue Wantagh, NY 11520	(b) (4)	9	8
2029	Jonathan I. Macy, MD Macy Eye Center 8635 W. Third St #360 W Los Angeles, CA 90048	(b) (4)	4	6
5387	Donald McCormack, MD Boulder Medical Center 2750 Broadway Boulder, CO 80304	(b) (4)	9	8
6099	John L. Michaelos, MD St. Michael's Eye & Laser Institute 1018 West Bay Drive Largo, FL 33770	(b) (4)	5	6
3397	Marlene Moster, MD Ophthalmic Partners of Pennsylvania Pc 100 Presidential Blvd, Ste 200 Bala Cynwyd, PA 19004	(b) (4)	3	3
Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
1473	Thomas Mundorf, MD Mundorf Eye Center 1718 East 4 th Street, Suite #703 Charlotte, NC 28204	(b) (4)	4	3
1011	Katherine Isabel Ochsner, MD Eye Associates of Wilmington 1729 New Hanover Medical Park Dr. Wilmington, NC 28403	(b) (4)	1	2
750	Kenneth W. Olander, MD, PhD University Eye Surgeons 622 Smithview Drive Maryville, TN 37803	(b) (4)	4	2
3627	James H. Peace, MD United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301	(b) (4)	17	16
2448	Ned M Reinstein, MD Reinstein Eye Associates, PC 7171 South Yale, Suite 101 Tulsa, OK 74136	(b) (4)	4	3

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
1393	Michael H. Rotberg, MD Charlotte Eye Ear Nose & Throat Associates, PA 6035 Fairview Rd Charlotte, NC 28210	(b) (4)	11	9
1806	Kenneth Sall, MD Sall Research Medical Center 11423 187 th Street, Suite 200 Artesia, CA 90701	(b) (4)	18	18
4347	John R. Samples, MD Glaucoma Consultants of Colorado dba Specialty Eye Care 11960 Lioness Way, Suite 190 Parker, CO 80134	(b) (4)	5	5

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
731	Elizabeth D. Sharpe, MD Glaucoma Consultants & Center for Eye Research, PA 721 Long Point Rd., Suite 407 Mount Pleasant, SC 29464	(b) (4)	8	8
3346	Philip Lee Shettle, DO Lee Shettle D.O.P.A 13113 66 th Street North Largo, FL 33773	(b) (4)	11	9
1892	Shannon L. Smith, MD Cataract, Glaucoma & Retina Consultants of East Texas 3302 N.E. Stallings Dr. Nacogdoches, TX 75965	(b) (4)	9	9
6160	Stacy R. Smith, MD Stacy R. Smith, MD, PC 4568 South Highland Drive, Suite 160 Salt Lake City, UT 84117	(b) (4)	8	7
3988	Stephen E. Smith, MD Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901	(b) (4)	9	7

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
4341	Sriram Sonty Midwest Eye Center SC 1700 East West Road Calumet City, IL 60409	(b) (4)	6	5
3851	Emil Stein, MD Nevada Eye Care Professionals 2090 E. Flamingo Road, Suite 100 Las Vegas, NV 89119		7	7
3626	Michael E. Tepedino, MD Cornerstone Eye Care 307 N. Lindsay Street High Point, NC 27262		7	8

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
2353	George C. Thome, MD Eye Physicians of Austin 5011 Burnet Road Austin, TX 78756	(b) (4)	11	10
4424	Robert Trefl, MD Mountain View Eye Center 1580 West Antelope Drive, Suite 175 Layton, UT 84041		5	5
5468	Farrell C. Tyson II, MD Argus Research Dba Cape Coral Eye Center 4120 Del Prado Blvd Cape Coral, FL 33904		4	4

Principal Investigator No.	Contact Information	Subinvestigator(s)	Trav 0.003%	Travatan
1007	Thomas R. Walters, MD Texan Eye, PA 5717 Balcones Drive Austin, TX 78731	(b) (4)	11	9
394	Mark J. Weiss, MD Mark J. Weiss, MD, Inc. 1717 South Utica, Suite 107 Tulsa, OK 74104		13	13
2600	David Wirta, MD Eye Research Foundation 520 Superior Ave, Suite #235 Newport Beach, CA 92663		20	20

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/s/

JENNIFER D HARRIS
09/09/2013

WILLIAM M BOYD
09/09/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204822

Application Type: New NDA

Name of Drug: Travoprost ophthalmic solution, 0.003%

Applicant: Alcon Research, Inc.

Submission Date: July 12, 2013

Receipt Date: July 15, 2013

Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by either December 13, 2013 (wrap up meeting) or at the time of the submission of the first draft labeling during negotiations, whichever comes first.

Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- NO** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional

Selected Requirements of Prescribing Information (SRPI)

• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: Missing ^{(b) (4)}Heading

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: Addition of IZBA (travoprost ophthalmic solution)0.003% needs to be added as a separate sentence, as a new paragraph

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

YES

22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

NO

23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment: CONTRAINDICATIONS: none subtitle

N/A

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information (SRPI)

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- N/A** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES

Selected Requirements of Prescribing Information (SRPI)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *Cross references are in CAPITAL Format where they should be in italics.*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information (SRPI)

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JUDIT R MILSTEIN

08/30/2013

NDA 204288-Initial SRPI CSO review