

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206276Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 2, 2015

TO: Lois Almoza, Regulatory Project Manager
Wiley Chambers, M.D., Deputy Division Director
William Boyd, M.D., Medical Team Leader
Division of Topical 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.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206276

APPLICANT: Alcon Research, Ltd.

DRUG: Olopatadine ophthalmic solution, 0.7%

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of ocular itching

CONSULTATION REQUEST DATE: September 9, 2014
 CLINICAL INSPECTION SUMMARY DATE: January 9, 2015
 DIVISION ACTION GOAL DATE: January 30, 2015
 PDUFA DATE: January 30, 2015

I. BACKGROUND:

The Applicant submitted this NDA to support the use of olopatadine ophthalmic solution, 0.7%, for the treatment of ocular itching.

The pivotal studies, C-10-126 entitled, “A Multicenter, Randomized, Double-Masked, Vehicle and Active Controlled, Parallel-Group Efficacy and Safety Study of AL-4943A Ophthalmic Solution, 0.77% in Patients with Allergic Conjunctivitis Using the Conjunctival Allergen Challenge (CAC) Model”, and C-12-028 entitled “A Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of AL-4943A Ophthalmic Solution 0.77% Administered Once Daily”, were inspected in support of this application.

Drs. Torkildsen’s and Rand’s clinical sites were selected for inspection because of high subject enrollments and previous inspection histories.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Gail Torkildsen, M.D. Andover Eye Associates 138 Haverhill Street Andover, MA 01810	C-10-126/ 3505/ 97	21-24 Oct 2014	NAI
Allison Rand, M.D. Rand Eye Institute 5 Sample Road Deerfield, FL 33064	C-12-028/ 6448/ 40	Nov 2014	Pending, preliminary classification 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. Gail Torkildsen, M.D.
Andover Eye Associates
138 Haverhill Street
Andover, MA 01810

- a. **What was inspected:** At this site for Protocol C-10-126, 163 subjects were screened, 97 subjects were enrolled, and 94 subjects completed the study.

The records for all subjects were reviewed which included but were not limited to informed consent forms for all screened subjects, financial disclosure forms, protocol adherence, subject eligibility, randomization, IRB communications, concomitant medications, adverse event reporting, and test article accountability and storage. Source data was compared with electronic case report forms (eCRFs) and verified against line listings.

- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- 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. Allison Rand, M.D.
Rand Eye Institute
5 Sample Road
Deerfield, FL 33064

- a. **What was inspected:** At this site for Protocol C-12-028, 41 subjects were screened, 40 subjects were enrolled in the study, and all 40 subjects completed the study.

Informed consent forms were reviewed for all 41 screened subjects. Study data were validated for all 41 sets of records and the records of 20 subjects were reviewed for protocol compliance.

- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- 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

The clinical sites of Drs. Torkildsen and Rand were inspected in support of this NDA. Neither Dr. Torkildsen nor Dr. Rand was issued a Form FDA 483, and these inspections were classified No Action Indicated (NAI). The data generated by these clinical sites appear adequate in support of the respective indication.

NOTE: The final Establishment Inspection Report (EIR) for Dr. Rand's site has not been received by OSI. Should the classification of this inspection change upon review of the EIR, an inspection summary addendum will be issued to DTOP.

{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.
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/s/

ROY A BLAY
01/07/2015

JANICE K POHLMAN
01/07/2015

KASSA AYALEW
01/07/2015

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

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

Memorandum

Date: January 6, 2015

To: Lois Almoza, Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Olopatadine hydrochloride ophthalmic solution 0.7%
NDA #2062^(b)₍₄₎**76**

As requested in DTOP's consult dated October 6, 2014, OPDP has reviewed the draft PI and proposed carton and container labeling for Pazeo.

OPDP reviewed the proposed substantially complete version of the PI titled, "Wiley's Edited Labeling.doc" received via the DTOP SharePoint website on January 5, 2015. OPDP's comments are provided in the attached clean version of the substantially complete labeling.

OPDP has also reviewed the following proposed carton and container labeling:

- "draft-carton-container-labels-0pt5carton.pdf"
- "draft-carton-container-labels-0pt5label.pdf"
- "draft-carton-container-labels-0pt5pouch.pdf"
- "draft-carton-container-labels-2pt5carton.pdf"
- "draft-carton-container-labels-2pt5label.pdf"

These were accessed on the DTOP SharePoint website on January 5, 2015. OPDP notes that the proposed carton and container labeling present a 0.77% percent, while the substantially complete PI refers to the product containing 0.7% of olopatadine. OPDP reminds DTOP to revise the carton and container labeling to be consistent with the PI. OPDP has no further comments on the proposed carton and container labeling.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Christine Corser at 6-2653 or Christine.Corser@fda.hhs.gov.

9 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
01/06/2015

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: November 19, 2014
Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number: NDA 206276
Product Name and Strength: Olopatadine Hydrochloride Ophthalmic Solution, 0.77%
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Alcon
Submission Date: July 30, 2014
OSE RCM #: 2014-1737
DMEPA Primary Reviewer: Rachna Kapoor, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container closure system, container label, carton labeling, pouch labeling, and prescriber information labeling for Olopatadine Hydrochloride Ophthalmic Solution, NDA 206276, for areas of vulnerability that could lead to medication errors.

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
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA identified that the container labels, carton labeling, and pouch labeling can be improved from a safety perspective by increasing the prominence of the route of administration on the container labels and deleting the line under Tradename to follow the Code of Federal Regulations for intervening graphic matter. We provide recommendations below in Section 4.1.

FAERS and ISMP search did not identify any relevant information to inform this review.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the prescriber information labeling is acceptable. We have no additional comments for the prescriber information labeling at this time.

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

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

4.1 RECOMMENDATIONS FOR ALCON

- A. Container Label (trade size and professional sample)
 - i. Delete (b) (4) Tradename as this is considered intervening graphic matter with the proprietary name. As per 21 CFR 201.10 (a), the proprietary name shall appear without any intervening graphic matter
 - ii. We recommend adding the statement “For Topical Ophthalmic Use Only” to highlight the correct route of administration. We recommend this revision to help prevent wrong route of administration errors. This can be achieved by decreasing the prominence of the manufacturer name by decreasing the font size or moving to the side panel.
- B. Carton Labeling (trade size and professional sample)
 - i. See A. i. and revise carton labeling accordingly.
 - ii. Increase the color contrast between the established name and the background of the label as it is hard to read the white text of established name on the (b) (4) background. As per the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors¹, the color contrast between the text and the container label background color should be chosen to afford adequate legibility of the text.
 - iii. Decrease the prominence of the manufacturer name by decreasing the font size and deleting the green box around it as per the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors¹. The company name appears prominent since it is bolded and surrounded by the green box and thus, takes attention away from more important information on the labeling such as product’s established name and strength.

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>

- iv. Ensure that all the panels on the carton labeling contain the proprietary name, established name, dosage form, and strength for ease of identification of the product.
- C. Carton Labeling (trade size)
- i. Add the statement “Shake well before use” to the principal display panel as this statement provides important information regarding the correct use of the product.
- D. Carton Labeling (professional sample)
- i. Relocate the statement “(b) (4)” to the principal display panel as this statement provides important information regarding the correct use of the product.
- E. Pouch Labeling
- i. See A. i., A. ii., B. iii., and C. i. and revise pouch labeling accordingly.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Olopatadine Hydrochloride that Alcon submitted on July 30, 2014.

Table 2. Relevant Product Information for Olopatadine Hydrochloride	
Initial Approval Date	N/A
Active Ingredient	Olopatadine hydrochloride
Indication	The treatment of ocular itching associated with allergic conjunctivitis
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic solution
Strength	0.77%
Dose and Frequency	Instill one drop in each affected eye once daily
How Supplied	2.5 mL fill in a 4 mL oval bottle
Storage	Store at 2° – 25°C (36° – 77°F)

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 10, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Date Range	No date range
Product	Olopatadine [active ingredient] Olopatadine hydrochloride [active ingredient]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search from Table 3 identified 9 cases. After individual review, 9 cases were excluded from the final analysis for the following reasons:

- Foreign case (n=1)
- Product quality issue (n=1)
- Concomitant medication (n=3)
- Adverse event not related to a medication error (n=1)
- Cases involving Patanase Nasal Spray (not relevant to this review) (n=2)
- Medication error (not relevant to this review) (n=1)
 - A prescription for Patanol drops written for a patient was filled in the name of the patient's spouse

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on November 13, 2014 using the term, olopatadine to identify reviews previously performed by DMEPA.

C.2 Results

A proprietary name review was completed on May 19, 2014² and August 20, 2013³ for olopatadine hydrochloride under IND 060991.

² Kapoor R and Maslov Y. Proprietary Name Review for PAZEO (IND 060991). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 05 19. 21 p. OSE RCM No.: 2013-16781.

³ Lee J and Wilkins-Parker J. Proprietary Name Review for SABERO (IND 060991). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 08 20. 40 p. OSE RCM No.: 2013-597.

APPENDIX D. NOT APPLICABLE

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on November 13, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	(b) (4)
Search Strategy and Terms	Match Exact Word or Phrase: olopatadine

E.2 Results

Our search identified two articles in ISMP Medication Safety Alert^{4,5} that were specific to the currently marketed product Patanol which is olopatadine hydrochloride 0.1% ophthalmic solution. One article⁴ specifically discussed name confusion with Patanol and another product and the other article⁵ was associated with the advertisement of Patanol. Therefore, neither article is relevant to this review.

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⁴ Institute for Safe Medication Practices. Safety Briefs. ISMP Med Saf Alert. 1997;2(1):1-2.

⁵ Institute for Safe Medication Practices. Drug ad promotes sharing eye drops. ISMP Med Saf Alert Acute Care. 2004;9(20):1-3.

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/s/

RACHNA KAPOOR
11/19/2014

YELENA L MASLOV
11/19/2014

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 # 206276 BLA# N/A	NDA Supplement #:S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Per e-mail sent to Lois Almoza of Division of Transplant and Ophthalmology Products (DTOP) on October 8, 2014, Applicant plans to submit request for proprietary name review on or before October 15, 2014. A letter issued to the Applicant on May 21, 2014 by Office of Surveillance and Epidemiology (OSE) under IND 060991 noting the proposed proprietary name, Pazeo was conditionally acceptable and would need to be submitted for review again once the NDA was submitted. Established/Proper Name: olopatadine hydrochloride Dosage Form: ophthalmic solution Strengths: 0.7%		
Applicant: Alcon Research, Ltd. Agent for Applicant (if applicable): N/A		
Date of Application: July 30, 2014 Date of Receipt: July 30, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: January 30, 2015		Action Goal Date (if different):
Filing Date: September 28, 2014		Date of Filing Meeting: September 26, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication/Proposed change(s): treatment of ocular itching associated with allergic conjunctivitis		
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.</i>		
Type of BLA		<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal?	<input checked="" type="checkbox"/> N/A	Resubmission after refuse to file? <input checked="" type="checkbox"/> N/A
Part 3 Combination Product? N/A	<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	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

	<input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <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: N/A	<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)
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Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): 060991

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"/>	Review Priority:P
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.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	X	

	YES	NO	NA	Comment
User Fees				
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <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>	Payment for this application: <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 Note: Receipt date for user fee is May 15, 2014			
<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>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)	YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)				
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)].	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<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>				
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, please list below:				
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>				
Exclusivity	YES	NO	NA	Comment
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Requested 3-year Exclusivity in submission received July 30, 2014.
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>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)?</p> <p><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i></p> <p><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<input type="checkbox"/>	All paper (except for COL)
<input checked="" type="checkbox"/>	All electronic

Do not check mixed submission if the only electronic component is the content of labeling (COL).	<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"/> 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.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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)? If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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"/>	Additional facility information was submitted on

1

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

Information requests regarding establishments, based on information provided in the July 30, 2014, submission, was sent to the applicant on August 7, 2014 and August 25, 2014.				September 4, 2014 by the Applicant per FDA requests made on August 7, 2014 and August 25, 2014.
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542as per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Desk copy provided September 23, 2014, and Applicant plans to submit to the application on file by October 15, 2014 due to internal publishing issues per 10/8/2014 e-mail sent to Lois Almoza of DTOP.
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)? <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Submitted in original submission on July 30, 2014. Updated desk copy submitted via e-mail on September 26, 2014. Applicant plans to submit to the application on file by October 15, 2014 due to internal publishing issues per 10/8/2014 e-mail sent to Lois Almoza of DTOP.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Submitted in original submission on July 30, 2014.
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, <u>both</u> 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"/>	Submitted in original submission on July 30, 2014.
Field Copy Certification	YES	NO	NA	Comment

(NDAs/NDA efficacy supplements only)				
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"/>	
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 reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		In the original submission, the Applicant noted, "In response to the letter from the Agency's Edward M Cox dated October 3, 2013 related to the subject matter, we are pleased to advise that pediatric patients were included in the clinical studies reported in this NDA. The pertinent data obtained from the pediatric patients will be reported separately collated and submitted subsequently to the NDA submission. Additionally, per the Applicant's, October 6, 2014 submission, they plan to submit, "...a follow-up report to the Agency that provides a complete clinical study report just for the pediatric patients within the next two months."
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" 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?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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

<i>If no, request in 74-day letter</i>				
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Partial waiver and pediatric assessment received 08/28/2014.
<i>If no, request in 74-day letter</i>				
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 checked="" type="checkbox"/>	<input type="checkbox"/>		Pediatric Exclusivity Board notified, awaiting date determination to meet with Exclusivity Board.
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"/>	Per e-mail sent to Lois Almoza of DTOF on October 8, 2014, Applicant plans to submit request for proprietary name review on or before October 15, 2014. A letter issued to the Applicant on May 21, 2014 by Office of Surveillance and Epidemiology (OSE) under IND 060991 noting the proposed proprietary name, Pazeo was conditionally acceptable and would need to be submitted for review again once the NDA was submitted.
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 checked="" type="checkbox"/>	<input 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 checked="" type="checkbox"/> Carton labels <input checked="" 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 format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Submitted in original submission on July 30, 2014.

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

Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OPDP consulted 10/6/2014.
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-DMEPA consulted 10/6/2014.
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? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment

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

End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 30, 2012 and August 26, 2013 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		2 Pre-NDA meetings
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 26, 2014

BLA/NDA/Supp #: 206276

PROPRIETARY NAME: Not submitted yet

ESTABLISHED/PROPER NAME: olopatadine hydrochloride

DOSAGE FORM/STRENGTH: ophthalmic solution/0.7%

APPLICANT: Alcon Research, Ltd.

PROPOSED INDICATION/PROPOSED CHANGE(S): treatment of ocular itching associated with allergic conjunctivitis

BACKGROUND: Alcon Research, Ltd. (Alcon) submitted this NDA on July 30, 2014, and it was received electronically on July 30, 2014. We note that under Item 1 of the Form 356h submitted with this NDA, July 31, 2014, was listed as the “Date of Submission.” However, this NDA was received in our Document Room on July 30, 2014. In follow-up to my conversations with Alcon regarding this discrepancy, your submission of September 4, 2014, stated that “... Alcon would like to confirm the submission date of the NDA was July 30, 2014, not July 31, 2014 as Form 356h stated.”

Alcon submitted to the application on file revisions to the facility information contained in the FDA Form 356h on August 5, 2014 and August 25, 2014. Alcon submitted to the application on file a partial waiver for children 2 years old and under and a pediatric assessment on August 28, 2014 after requests were made verbally by Dr. Wiley A. Chambers, Clinical Reviewer for this application on August 12, 2014 and August 13, 2014, as documented in the cover letter included in Alcon’s formal submission to the file. On September 17, 2014, the Agency verbally requested further information from the Applicant regarding financial disclosure information. A follow-up request for this information was sent on September 22, 2014, via e-mail. On September 26, 2014, the Applicant forwarded their responses which included financial disclosure information to the Agency via e-mail which they plan to formally submit to the application on file on or before October 15, 2014 due to Alcon’s internal publishing issues per their October 8, 2014 e-mail sent to Lois Almoza of DTOP.

On September 22, 2014, the Agency requested further information from the Applicant via e-mail requesting a signed FDA Form 3542a. On September 23, 2014, the Applicant forwarded a signed FDA Form 3542a to the Agency via e-mail which they plan to formally submit to the application on or before October 15, 2014 due to Alcon’s internal publishing issues per their October 8, 2014 e-mail sent to Lois Almoza of DTOP.

On October 3, 2014, the Applicant submitted updated labeling in SPL format to the application on file with plans to submit a request for proprietary name review. Per e-mail sent to Lois Almoza of DTOP on October 8, 2014 from the Applicant, they plan to submit a request for proprietary name review on or before October 15, 2014. A letter issued to the Applicant on May 21, 2014 from the Office of Surveillance and Epidemiology (OSE) under IND 060991 noting the proposed proprietary name, Pazeo was conditionally acceptable and would need to be submitted for review again once the NDA was submitted.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lois Almoza	Y
	CPMS/TL:	Diana Willard	Y
Cross-Discipline Team Leader (CDTL)	William Boyd		Y
Clinical	Reviewer:	Wiley Chambers	Y
	TL:	William Boyd	Y
Clinical Pharmacology	Reviewer:	Gerlie Gieser	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Yunfan Deng	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Aaron Ruhland	Y
	TL:	Lori Kotch	Y
Product Quality (CMC)	Reviewer:	Libaniel Rodriguez	Y
	TL:	Balajee Shanmugam	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Stephen Langille	Y
	TL:	John Metcalfe	Y

FILING MEETING DISCUSSION:

GENERAL	
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Comments:	<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? Comments:	<input checked="" 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 <input type="checkbox"/> Review issues for 74-day letter
Comments:	
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<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 <input type="checkbox"/> Review issues for 74-day letter
Comments:	
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<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
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments:</p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <ul style="list-style-type: none"> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <ul style="list-style-type: none"> <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <ul style="list-style-type: none"> <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<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>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <ul style="list-style-type: none"> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <ul style="list-style-type: none"> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<input type="checkbox"/> Not Applicable
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <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
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)		<input checked="" type="checkbox"/> N/A
<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? 		<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> If so, were the late submission components all submitted within 30 days? 		<input type="checkbox"/> YES <input type="checkbox"/> NO
<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		
Signatory Authority: Renata Albrecht, M.D. Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:		
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.	

	<p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input 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 type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<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/

LOIS A ALMOZA
10/09/2014

DIANA M WILLARD
10/09/2014

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 206276

Application Type: New NDA

Name of Drug/Dosage Form: olopatadine hydrochloride ophthalmic solution, 0.7%

Applicant: Alcon Research, Ltd.

Receipt Date: July 30, 2014

Goal Date: January 30, 2015

1. Regulatory History and Applicant's Main Proposals

The applicant has submitted a New Drug Application (NDA) for olopatadine hydrochloride ophthalmic solution, 0.7% for the treatment of ocular itching associated with allergic conjunctivitis.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (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).

3. Conclusions/Recommendations

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

In addition, the following labeling issues were identified:

1. In the Patient Counseling Information Statement in Highlights, please add a hyphen in between the words **FDA** and **approved** and add a period at the end of the statement so it reads, "**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**"
2. The section and subsection headings in the Table of contents (TOC) must match the section and subsection headings in the FPI.

Subsections under section 17 are not included in the TOC. Subsections 17.1 Topical Ophthalmic Use Only, 17.2 Sterility of Dropper Tip, 17.3 Concomitant Use of Contact Lenses need to be added in the TOC.
3. In section 16 of the TOC, SUPPLIED is misspelled as SUPPIED and needs to be corrected.

Selected Requirements of Prescribing Information

All SRPI format deficiencies of the PI and other labeling issues identified above will be incorporated into the substantially complete FDA draft working label. The Medical Officer's review was completed on 9/15/14 and placed into DARRTS; it contains substantive edits to Sections 3, 5, 6, 8, 13, 14, and 17. Because the labeling issues described in this review are relatively minor and because substantive changes are anticipated to the package insert based on the clinical review, these issues will not be included in the 74-day letter. The Division plans to communicate proposed labeling, and, if necessary, any postmarketing requirement/commitment requests by the week of January 14, 2014, approximately.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
Comment: None.
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
Comment: None.
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: None.
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
Comment: None.
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Selected Requirements of Prescribing Information

Comment: None.

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: None.

- YES** 7. Section headings must be 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
• 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: None.

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment: None.

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: None.

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment: None.

Initial U.S. Approval in Highlights

Selected Requirements of Prescribing Information

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

Comment: *None.*

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment: *None.*

- N/A** 13. The BW 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 and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment: *None.*

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment: *None.*

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment: *None.*

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *None.*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment: *None.*

- N/A** 18. The RMC 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: *None.*

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *None.*

Selected Requirements of Prescribing Information

Dosage Forms and Strengths in Highlights

- N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *None.*

Contraindications in Highlights

- YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *None.*

Adverse Reactions in Highlights

- YES 22. 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: *None.*

Patient Counseling Information Statement in Highlights

- NO 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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: *A hyphen needs to be added to this statement, in between FDA and approved and the period needs to be taken off the end of the statement.*

Revision Date in Highlights

- YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *None.*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES 25. The TOC should be in a two-column format.

Comment: *None.*

Selected Requirements of Prescribing Information

- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment: None.
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: None.
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment: None.
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment: None.
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: Subsections under section 17 are not included in the TOC. Subsections 17.1 Topical Ophthalmic Use Only, 17.2 Sterility of Dropper Tip, 17.3 Concomitant Use of Contact Lenses needs to be added in the TOC.
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. 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: None.

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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

Selected Requirements of Prescribing Information

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
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: In section 16 of the TOC, **SUPPLIED** is misspelled as **SUPIED** and needs to be corrected.

- N/A 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

Comment: None.

- N/A 34. 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: None.

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment: None.

BOXED WARNING Section in the FPI

- N/A 36. In the BW, all text should be **bolded**.

Comment: None.

- N/A 37. The BW 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 and ACUTE HEPATIC FAILURE**”).

Selected Requirements of Prescribing Information

Comment: *None.*

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state “None.”

Comment: *None.*

ADVERSE REACTIONS Section in the FPI

N/A 39. When clinical trials adverse reactions data are 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 practice.”

Comment: *None.*

N/A 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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: *None.*

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *None.*

YES 42. 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 FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *None.*

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/s/

LOIS A ALMOZA
10/08/2014