This Associate Director for Labeling (ADL) memorandum provides recommendations for consideration by the management of the Division of Transplant and Ophthalmology Products (DTOP), on the content and format of the prescribing information (PI) to help ensure that the PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLL) requirements\(^1\)
- Is consistent with labeling guidance recommendations\(^2\) and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

This is a class 2 resubmission after the applicant received a Complete Response Letter (July 21, 2016), due to deficiencies at the manufacturing site. No labeling was agreed upon in the initial cycle.

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Labeling Related Consults

I. Medication Error and Proprietary Name Assessments, Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed container label, carton labeling, and PI for Vyzulta ophthalmic solution to determine whether there are safety concerns with respect to preventable medication errors. The primary reviewer Madhuri R. Patel, Pharm.D. and secondary reviewer, Sarah K. Vee, Pharm.D. reviewed the proposed container label, carton labeling concluded that the PI is acceptable from the medication error perspective (see review dated 05/25/2017). Only one recommendation was made to reduce the size of a graphic (the letter “V” on the principal display panel, to improve readability. This will be addressed in the review by the clinical team leader, W. Boyd, M.D.

DMEPA also evaluated the proposed proprietary name “Vyzulta” in the previous cycle, which was resubmitted in this cycle by the applicant. The primary reviewer, Teresa McMillan, Pharm.D. and secondary reviewer Sarah K. Vee, Pharm.D., concluded that the proposed name is acceptable since it will not misbrand the product and does not raise safety concerns (see DMEPA review dated 6/13/17 and review by Meena Ramachandra, Pharm.D., Office of Prescription Drug Promotion dated 04/21/16). The proprietary name “Vyzulta” was granted on 06/14/17.

II. Pregnancy and Lactation Labeling Rule, Division of Pediatric and Maternal Health

The Division of Pediatric and Maternal Health (DPMH) provided assistance with formatting of the label (see review by Melissa Tassinari, Ph.D., Sr. Clinical Advisor dated 07/21/17). The clinical team accepted their suggestion regarding the language for 8.2 Lactation (see attached label). Other suggestions regarding the nonclinical content of sections 8 and 13 are deferred to the nonclinical team and are addressed in the review by Andrew McDougal, Ph.D.

III. Risk Evaluation and Mitigation Strategy (REMS), Division of Risk Management, Office of Surveillance and Epidemiology

The Division of Risk Management evaluated the need for REMS for latanoprostene bunod ophthalmic solution 0.024%. DRISK and DTOP concurred that this product does not require a REMS based on the following:

- The risks of pigmentation of the iris, periorbital tissue (eyelid), and eyelashes, gradual eyelash changes including increased length, thickness, and number of lashes, intraocular inflammation and macular edema can be communicated through labeling.
- Ophthalmology providers, who treat patients for the reduction of intraocular pressure in the setting of open angle glaucoma or ocular hypertension, are familiar...
with the risks associated with this proposed formulation and understand the importance of frequent patient monitoring for the reported risks associated with the use of latanoprostene bunod 0.024%.

Labeling Formatting and Content

Formatting and content recommendations were made with the aim of improving clarity and readability of labeling. The edits and recommendations are shown throughout the proposed labeling in track changes and comments. In the attached PI, the ADL recommendations are presented in track changes (maroon) throughout the working version of the applicant’s draft PI and comments (in balloons) begin with the bolded acronym “ADL”. This version of the PI includes changes proposed by the applicant (green), nonclinical reviewer, Andrew McDougal, Ph.D. (gray), the clinical pharmacology team leader Phillip Colangelo, Ph.D. (blue), statistical reviewer Abel Eshete, Ph.D. (purple), and chemistry team leader Chunchun Zhang, Ph.D. (pink).

This review does not include final edits by the clinical team. The labeling review by the clinical team has not been finalized at the time of this review. The team does not concur with proposed by the applicant in section 14 CLINICAL STUDIES. In order to preserve the comments and track changes, the attached labeling may not reflect the final format of the labeling. A clean copy of the HIGHLIGHTS OF PRESCRIBING INFORMATION and FULL PRESCRIBING INFORMATION: CONTENTS is included in the APPENDIX.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/  
JANE FILIE  
08/02/2017

RENATA ALBRECHT  
08/03/2017

Reference ID: 4134084
### 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***

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<thead>
<tr>
<th>Date of This Review:</th>
<th>May 25, 2017</th>
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<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Transplant and Ophthalmology Products (DTOP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>NDA 207795</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td>Vyzulta (latanoprostene bunod) Ophthalmic Solution, 0.024%</td>
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<td>Product Type:</td>
<td>Single Ingredient</td>
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<tr>
<td>Rx or OTC:</td>
<td>Rx</td>
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<tr>
<td>Applicant/Sponsor Name:</td>
<td>Bausch &amp; Lomb, Inc.</td>
</tr>
<tr>
<td>Submission Date:</td>
<td>February 24, 2017</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2017-535</td>
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<tr>
<td>DMEPA Primary Reviewer:</td>
<td>Madhuri R. Patel, PharmD</td>
</tr>
<tr>
<td>DMEPA Team Leader (Acting):</td>
<td>Sarah K. Vee, PharmD</td>
</tr>
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1 REASON FOR REVIEW
The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed container label, carton labeling, and Prescribing Information (PI) for Vyzulta (latanoprostene bunod) Ophthalmic Solution (NDA 207795), submitted by Bausch & Lomb, Inc. on February 24, 2017, to determine if it is acceptable from a medication error perspective.

2 REGULATORY HISTORY
DMEPA previously reviewed the label and labeling for the proposed product, Vyzulta, in RCM 2015-1755 dated June 1, 2016. However, NDA 207795 received a Complete Response (CR) on July 21, 2016, due to facilities deficiencies. Thus, the applicant submitted a complete response to the CR along with revised label and labeling on February 24, 2017.

3 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>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
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<td>Human Factors Study</td>
<td>C – N/A</td>
</tr>
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<td>ISMP Newsletters</td>
<td>D – N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E – N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F – N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
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</table>

N/A = not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
We reviewed proposed container label, carton labeling, and Prescribing Information (PI) to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We find the PI and container label acceptable from a medication error perspective. However, we note that the carton labeling can be improved to enhance the readability and prominence of important information (e.g. proprietary name, established name, strength, route of administration).

5 CONCLUSION & RECOMMENDATIONS
DMEPA finds the Prescribing Information and container label acceptable from a medication error perspective. However, we note that the proposed carton labeling can be improved to

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a Rutledge M. Label and Labeling Review for Vyzulta (latanoprostene bunod) NDA 207795. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 1. RCM No.: 2015-1755.

Reference ID: 4102919
enhance the readability and prominence of important information (e.g. proprietary name, established name, strength, route of administration).

5.1 RECOMMENDATIONS FOR BAUSCH & LOMB, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Reduce the size of the graphic image with the letter “V” on the principal display panel as it competes in size and prominence with the most important information on the carton labeling such as proprietary name, established name, and strength, as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
Table 2 presents relevant product information for Vyzulta that Bausch & Lomb, Inc. submitted on February 24, 2017.

<table>
<thead>
<tr>
<th><strong>Initial Approval Date</strong></th>
<th>N/A</th>
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</thead>
<tbody>
<tr>
<td><strong>Active Ingredient</strong></td>
<td>latanoprostene bunod</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Ophthalmic</td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
<td>Ophthalmic Solution</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>0.024%</td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
<td>One drop in the affected eye(s) once daily in the evening</td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
<td>natural low density polyethylene, 7.5 mL bottle with dropper tip and a turquoise cap filled with a 5 mL fill volume</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Unopened bottle should be stored refrigerated at 2° to 8°C (36° to 46°F). Once a bottle is opened it may be stored at 2° to 25°C (36° to 77°F) for 8 weeks</td>
</tr>
<tr>
<td><strong>Container Closure</strong></td>
<td>n/a</td>
</tr>
</tbody>
</table>
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 17, 2017, we searched the L:drive and AIMS using the terms, Vyzulta and latanoprostene bunod, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous label and labeling review\(^b\) and we confirmed that the previous recommendation was not implemented.

\(^b\) Rutledge M. Label and Labeling Review for Vyzulta (latanoprostene bunod) NDA 207795. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 1. RCM No.: 2015-1755.
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/s/

MADHURI R PATEL
05/25/2017

SARAH K VEE
05/25/2017
**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:** June 1, 2016  
**Requesting Office or Division:** Division of Transplant and Ophthalmology Products (DTOP)  
**Application Type and Number:** NDA 207795  
**Product Name and Strength:** Vyzulta (Latanoprostene bunod) Ophthalmic Solution, 0.024%  
**Product Type:** Single Ingredient  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Valeant Pharmaceuticals North America LLC  
**Submission Date:** July 21, 2015  
**OSE RCM #:** 2015-1755  
**DMEPA Primary Reviewer:** Michelle Rutledge, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD
1 REASON FOR REVIEW
This review evaluates the proposed container label, carton labeling, and prescribing information for Vyzulta (Latanoprostene bunod) Ophthalmic Solution, 0.024%, NDA 207795, for areas of vulnerability and could lead to medication errors. This is a New Drug Application.

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.

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<th>Material Reviewed</th>
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<td>ISMP Newsletters</td>
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<td>E – N/A</td>
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<td>Other</td>
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<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
Valeant Pharmaceuticals North America LLC is seeking approval of Vyzulta Ophthalmic Solution, for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The proposed product will provide an alternative option in the ophthalmological setting for this indication.

We reviewed the proposed label and labeling and identified the following areas of vulnerability to errors.

- Readability and prominence of important information on the carton labeling

4 CONCLUSION & RECOMMENDATIONS
DMEPA concludes that the proposed carton labeling can be improved to increase the readability and prominence of important information.
A. CARTON LABELING
   1. Consider reducing the size of the graphic image with letter “V” on the principal display panel as it takes away attention from the most important information on the carton labeling such as proprietary name, established name, and strength statements.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table 2 presents relevant product information for Vyzulta that Valeant Pharmaceuticals North American LLC submitted on July 21, 2015.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Vyzulta</th>
</tr>
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<tbody>
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<td>Initial Approval Date</td>
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<tr>
<td>Active Ingredient</td>
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<td>Indication</td>
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<tr>
<td>Route of Administration</td>
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<tr>
<td>Dosage Form</td>
</tr>
<tr>
<td>Strength</td>
</tr>
<tr>
<td>Dose and Frequency</td>
</tr>
<tr>
<td>How Supplied</td>
</tr>
<tr>
<td>Storage</td>
</tr>
</tbody>
</table>
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods
On May 26, 2016, we searched the L: drive using the terms, Vyzulta to identify reviews previously performed by DMEPA.

B.2 Results
Our search identified no previous label and labeling reviews.
APPENDIX D. ISMP NEWSLETTERS

D.1 Methods
On May 27, we searched the Institute for Safe Medication Practices (ISMP) newsletters 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.

<table>
<thead>
<tr>
<th>ISMP Newsletters Search Strategy</th>
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<tbody>
<tr>
<td>ISMP Newsletter(s)</td>
</tr>
<tr>
<td>Search Strategy and Terms</td>
</tr>
</tbody>
</table>

D.2 Results
No articles were located.
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/s/

MICHELLE K RUTLEDGE
06/01/2016

YELENA L MASLOV
06/02/2016
Clinical Inspection Summary

Date: April 21, 2015
From: Roy Blay, Ph.D., Reviewer, GCPAB\OSI
       Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI
       Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To: Lois Almoza, Regulatory Project Manager
    Lucious Lim, M.D., Medical Officer
    William Boyd, M.D., Medical Team Leader
    Division of Transplant and Ophthalmology Products

NDA/BLA #: NDA 207795
Applicant: Bausch & Lomb Inc.
Drug: Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%
NME (Yes/No): Yes
Therapeutic Classification: Standard Review
Proposed Indication(s): Reduction of intraocular pressure for patients with open-angle glaucoma or ocular hypertension
Consultation Request Date: August 28, 2015
Summary Goal Date: May 1, 2016
Action Goal Date: July 1, 2016
PDUFA Date: July 21, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Christie and Wirta were inspected in support of this NDA. The final classification of the inspection of Dr. Christie was Voluntary Action Indicated (VAI) due to deviations from protocol in the protocol-specified storage temperature of the test article. Discussion with the chemistry reviewer indicated that the noted temperature excursions would not have affected the stability of the test article. The final classification of the inspection of Dr. Wirta was No Action Indicated (NAI).

Based on the results of the clinical investigator inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

The Applicant submitted this NDA to support the use of Vyzulta for the reduction of intraocular pressure (IOP) for patients with open-angle glaucoma or ocular hypertension.

Protocols 769 and 770 entitled, “A Randomized, Multicenter, Double-Masked, Parallel-Group Study Comparing the Safety and Efficacy of BOL-303259-X 0.024% (Latanoprostene Bunod)
Ophthalmic Solution With Timolol Maleate Ophthalmic Solution 0.5% in Subjects With Open-Angle Glaucoma or Ocular Hypertension – APOLLO Study” and “A Randomized, Multicenter, Double-Blind, Parallel-Group Study Comparing the Safety and Efficacy of BOL-303259-X 0.024% (Latanoprostene Bunod) Ophthalmic Solution With Timolol Maleate Ophthalmic Solution 0.5% in Subjects With Open-Angle Glaucoma or Ocular Hypertension – LUNAR Study” respectively, were inspected in support of this application.

The sites of Drs. Christie and Wirta were chosen for inspection based on relatively large study enrollments and a lack of recent inspections.

Protocol 769 was conducted at 47 clinical sites in the United States (US), Bulgaria, and the Czech Republic with first enrollment on January 31, 2013 and an interim data cutoff date of December 19, 2014. The study analyzed a total of 417 subjects. The three-month efficacy phase of this study involved subjects being randomized to either latanoprostene or timolol maleate for 3 months from Visit 3 (Day 0) through Visit 6 (Month 3). The primary objective was to demonstrate that the mean intraocular pressure (IOP) reduction after 3 months (90 days) of treatment with latanoprostene was noninferior to timolol maleate. The sponsor’s conclusion with regard to efficacy was that the mean IOP reduction after 3 months (90 days) of treatment with latanoprostene was non-inferior, and, in fact, superior to treatment with timolol maleate.

Protocol 770 was conducted at 46 domestic and foreign sites comprising 420 randomized subjects with first subject enrollment on January 28, 2013, and the last subject completed on November 26, 2014. The primary objective was to demonstrate that the mean intraocular pressure (IOP) reduction after 3 months (90 days) of treatment with latanoprostene was non-inferior to timolol maleate. The sponsor’s conclusion with regard to efficacy was that the mean IOP reduction after 3 months (90 days) of treatment with latanoprostene was non-inferior to timolol maleate.

3. RESULTS (by site):

<table>
<thead>
<tr>
<th>Site #/ Name of CI/ Address</th>
<th>Protocol #/ # of Subjects (enrolled)</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
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<tbody>
<tr>
<td>130785/ William C. Christie, M.D. Scott &amp; Christie and Associates, PC 1101 Freeport Road Pittsburgh, PA 15238 and 105 Brandt Drive Cranberry Township, PA 16066</td>
<td>769/ 35</td>
<td>6-14 Jan 2016</td>
<td>VAI</td>
</tr>
<tr>
<td>330042/ David L. Wirta, M.D. Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA 92663</td>
<td>770/ 49</td>
<td>17-20 Nov 2015</td>
<td>NAI</td>
</tr>
</tbody>
</table>
Compliance 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 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. William C. Christie, M.D.

At this site for Protocol 769, 45 subjects were screened, nine subjects failed screening and one subject withdrew consent, 35 subjects were enrolled in the study, one subject discontinued due to an adverse event, and 34 subjects completed the study. Source data was compared to line listings. The study records of the enrolled subjects were reviewed in detail with respect to randomization, early terminations, adverse events, and intraocular pressures (IOPs). The records of 18 subjects were reviewed for general protocol adherence and reporting of concomitant medications and illnesses. Other records reviewed included, but were not limited to, financial disclosure, delegation of authority, sponsor, monitor, and IRB communications, and test article accountability and storage.

Signed informed consent was obtained from all enrolled subjects prior to study entry. A Form FDA 483 was issued at the conclusion of the inspection noting that the study deviated from protocol in that the refrigerator containing the study drug was at a temperature (0°C) below the specified storage temperature of 2-8°C for at least 31 days at varying intervals, and that there were 19 days where the temperature was not recorded. Follow up with the review chemist indicated there were no stability concerns with the temperature excursions to 0°C. Dr. Christie acknowledged his responsibility for the overall conduct of the study in his written response dated January 26, 2016. For those periods when refrigerator temperatures were not recorded, Dr. Christie said that review of temperature logs prior to and after these periods provided no basis for concluding that temperature excursions occurred in those periods. Dr. Christie appears to have implemented corrective actions to his study practices that should prevent similar findings in future studies.

This finding of improper drug storage conditions would not appear to adversely affect subject safety or data quality. The data generated by this site appear acceptable in support of the respective indication.
2. **David L. Wirta, M.D.**

At this site for Protocol 770, 72 subjects were screened, 50 subjects were randomized, and 40 subjects completed the study. Per the study report, three subjects were discontinued for noncompliance with the protocol, four subjects experienced adverse events, and three subjects withdrew from the study. Records reviewed included, but were not limited to, informed consent, financial disclosure, medical histories, inclusion/exclusion criteria, concomitant medications, sponsor and IRB communications, and test article storage and accountability. The site was responsible for transferring the source data to electronic Case Report Forms (eCRFs). For primary endpoints and adverse events, source records for all subjects completing the study were compared against data listings.

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.

The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

*{See appended electronic signature page}*

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

CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
CC:
Central Doc. Rm.
DTOP/Division Director/Albrecht
DTOP/Medical Team Leader/Boyd
DTOP/MO/Lim
DTOP/Project Manager/Almoza
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
OSI/DCCE/Team Leader/Pohlman
OSI/DCCE/GCP Reviewer/Blay
OSI/ GCP Program Analysts/ Patague/Peacock
OSI/Database PM/Walters
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/s/

ROY A BLAY
04/22/2016

KASSA AYALEW
04/22/2016
Memorandum

Date: April 21, 2016

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

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Vyzulta (latanoprostene bunod ophthalmic solution), 0.024% For Topical Ophthalmic Use
NDA 207795

As requested in DTOP’s consult dated September 3, 2015, OPDP has reviewed the draft PI and proposed carton and container labeling for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

OPDP reviewed the proposed substantially complete version of the PI titled, “draft-labeling-text.doc” accessed via the DTOP SharePoint website on April 14, 2016. OPDP’s comments are provided in the attached clean version of the substantially complete labeling.

OPDP has no comments on the version of the proposed carton and container labeling titled “1-14-1-1 Draft Carton Label.pdf” and “1-14-1-1 Draft Container Label.pdf” accessed on the DTOP SharePoint website on April 14, 2016.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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

MEENA RAMACHANDRA
04/21/2016
# 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

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<td>Comparative Efficacy Claim (SE4)</td>
</tr>
<tr>
<td>New Patient Population (SE5)</td>
</tr>
<tr>
<td>RX To OTC Switch (SE6)</td>
</tr>
<tr>
<td>Accelerated Approval Confirmatory Study (SE7)</td>
</tr>
<tr>
<td>Labeling Change With Clinical Data (SE8)</td>
</tr>
<tr>
<td>Manufacturing Change With Clinical Data (SE9)</td>
</tr>
<tr>
<td>Animal Rule Confirmatory Study (SE10)</td>
</tr>
<tr>
<td>N/A</td>
</tr>
</tbody>
</table>

Proprietary Name: **Vesneo (under review by OSE)**
Established/Proper Name: **latanoprostene bunod**
Dosage Form: **ophthalmic solution**
Strengths: **0.024%**

Applicant: **Bausch & Lomb Inc.**
Agent for Applicant (if applicable): **N/A**

Date of Application: **July 21, 2015**
Date of Receipt: **July 21, 2015**
Date clock started after UN: **N/A**

PDUFA Goal Date: **July 21, 2016**
Action Goal Date (if different): **N/A**

Filing Date: **September 19, 2015**
Date of Filing Meeting: **August 31, 2015**

Chemical Classification (original NDAs only):

- X Type 1- New Molecular Entity (NME); NME and New Combination
- Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
- Type 3- New Dosage Form; New Dosage Form and New Combination
- Type 4- New Combination
- Type 5- New Formulation or New Manufacturer
- Type 7- Drug Already Marketed without Approved NDA
- Type 8- Partial Rx to OTC Switch

Proposed indication(s)/Proposed change(s): **reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension**

Type of Original NDA: **AND (if applicable)**
Type of NDA Supplement: **X 505(b)(1)**

If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: [http://wusdonlinelibrary.fda.gov/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499](http://wusdonlinelibrary.fda.gov/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499)
Type of BLA

If 351(h), notify the OND Therapeutic Biologics and Biosimilars Team

Review Classification:

- The application will be a priority review if:
  - A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMI)
  - The product is a Qualified Infectious Disease Product (QIDP)
  - A Tropical Disease Priority Review Voucher was submitted
  - A Pediatric Rare Disease Priority Review Voucher was submitted

Resubmission after withdrawal? NO
Resubmission after refuse to file? NO

Part 3 Combination Product? NO
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults

- Convenience kit/Co-package
- Pre-filled drug delivery device/system (syringe, patch, etc.)
- Pre-filled biologic delivery device/system (syringe, patch, etc.)
- Device coated/impregnated/combined with drug
- Device coated/impregnated/combined with biologic
- Separate products requiring cross-labeling
- Drug/Biologic
- Possible combination based on cross-labeling of separate products
- Other (drug/device/biological product)

Other:

Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): IND 73435

<table>
<thead>
<tr>
<th>Goal Dates/Product Names/Classification Properties</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDUFA and Action Goal dates correct in tracking system?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</td>
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<tr>
<td>Are the established/proper and applicant names correct in tracking system?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>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</td>
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<tr>
<td>Application Integrity Policy</td>
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<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
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<td>-----------------------------</td>
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</tr>
<tr>
<td>Is the application affected by the Application Integrity Policy (AIP)?</td>
<td></td>
<td>☐</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Check the AIP list at:</td>
<td></td>
<td></td>
<td></td>
<td><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
</tr>
<tr>
<td>If yes, explain in comment column.</td>
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<tr>
<td>If affected by AIP, has OC been notified of the submission?</td>
<td></td>
<td>☐</td>
<td>☐</td>
<td>X</td>
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<tr>
<td>If yes, date notified:</td>
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<table>
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<tr>
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<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?</td>
<td>X</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Payment for this application (check daily email from UserFeeAR@fda.hhs.gov):**

- ☐ Paid
- ☐ Exempt (orphan, government)
- ☐ Waived (e.g., small business, public health)
- ☐ Not required

**Note:** Receipt date for user fee is June 17, 2015

**User Fee Bundling Policy**


- ☐ Yes
- ☐ No

**505(b)(2) (NDAs/NDA Efficacy Supplements only)**

Is the application a 505(b)(2) NDA? *(Check the 356h form.)*

- ☐ Yes
- X No
cover letter, and annotated labeling). If yes, answer the bulleted questions below:

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?  
  - [ ] Yes  
  - [x] No  
  - [x] NA

- 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)].  
  - [ ] Yes  
  - [ ] No  
  - [x] NA

- 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)]?  
  - [ ] Yes  
  - [ ] No  
  - [x] NA

If you answered yes to any of the above bulleted 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 for advice.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?  
  - [ ] Yes  
  - [ ] No  
  - [x] NA

Check the Electronic Orange Book at:  
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Drug Name</th>
<th>Exclusivity Code</th>
<th>Exclusivity Expiration</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td></td>
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</tbody>
</table>

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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.

<table>
<thead>
<tr>
<th>Exclusivity</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>
| 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  
  - [ ] Yes  
  - [x] No  
  - NA
| 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)]?  
  - [ ] Yes  
  - [ ] No  
  - [x] NA
| If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy  
  - [ ] Yes  
  - [ ] No  
  - [ ] NA
| NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  
  - [x] Yes  
  - [ ] No  
  - [ ] NA
| If yes, # years requested: 5 years  
  - [ ] Yes  
  - [ ] No  
  - [x] NA

Note: An applicant can receive exclusivity without requesting it;

Applicant requested 5-year exclusivity in original submission dated and received July 21, 2015.
therefore, requesting exclusivity is not required.

| NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use? | □ | X | □ |
| 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)? | □ | □ | X |
| If yes, contact the Orange Book Staff (CDER-Orange Book Staff). | |

| BLaS only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? | □ | □ | X |
| If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager | |

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.

### Format and Content

**Do not check mixed submission if the only electronic component is the content of labeling (COL).**

<table>
<thead>
<tr>
<th></th>
<th>All paper (except for COL)</th>
<th>All electronic</th>
<th>Mixed (paper/electronic)</th>
<th>CTD</th>
<th>Non-CTD</th>
<th>Mixed (CTD/non-CTD)</th>
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</thead>
</table>

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

<table>
<thead>
<tr>
<th>Overall Format/Content</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>If electronic submission, does it follow the eCTD guidance?¹</td>
<td>X</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>If not, explain (e.g., waiver granted).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index: Does the submission contain an accurate comprehensive index?</td>
<td>X</td>
<td>□</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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:</td>
<td>X</td>
<td>□</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **X** legible  
| **X** English (or translated into English)  
| **X** pagination  
| **X** navigable hyperlinks (electronic submissions only)  

*If no, explain.*

**BLAs only**: Companion application received if a shared or divided manufacturing arrangement? ☐ ☐ X

**If yes, BLA #**

---

**Forms and Certifications**

*Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., .pdf) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), 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.*

<table>
<thead>
<tr>
<th><strong>Application Form</strong></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</td>
<td>X</td>
<td>☐</td>
<td></td>
<td>Submitted in original submission received July 21, 2015.</td>
</tr>
</tbody>
</table>

*If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].*

| **Patent Information**  
<table>
<thead>
<tr>
<th><strong>(NDAs/NDA efficacy supplements only)</strong></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
<td>X</td>
<td>☐</td>
<td></td>
<td>Submitted in original submission received July 21, 2015.</td>
</tr>
</tbody>
</table>

**Financial Disclosure**

Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?

*Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*

*Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

<table>
<thead>
<tr>
<th><strong>Clinical Trials Database</strong></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Is form FDA 3674 included with authorized signature?</td>
<td>X</td>
<td>☐</td>
<td></td>
<td>Submitted in original submission received July 21, 2015.</td>
</tr>
<tr>
<td>Debarment Certification</td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
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<td>-------------------------</td>
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<tr>
<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
<td>X</td>
<td></td>
<td></td>
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</tbody>
</table>

*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].*

*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…”*

<table>
<thead>
<tr>
<th>Field Copy Certification (NDAs/NDA efficacy supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
<td></td>
<td></td>
<td>X</td>
<td>Electronic Submission Only</td>
</tr>
</tbody>
</table>

*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)*

*If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.*

<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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</tbody>
</table>

*If yes, date consult sent to the Controlled Substance Staff:*

*For non-NMEs: Date of consult sent to Controlled Substance Staff:*

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
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<tbody>
<tr>
<td>PREA</td>
<td>X</td>
<td></td>
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</tbody>
</table>

*Does the application trigger PREA?*

*If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting*²

*Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*

² [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm)
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.

| If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? | X | ☐ | ☐ | Agreement to iPSP issued 1/9/2015 to IND 73435 |
| If no, may be an RTF issue - contact DPMH for advice. | ☐ | ☐ | ☐ |
| If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? | ☐ | ☐ | X | Pediatric studies were not required by the agreed iPSP |
| If no, may be an RTF issue - contact DPMH for advice. | ☐ | ☐ | ☐ |
| BPCA: | ☐ | ☐ | ☐ |
| Is this submission a complete response to a pediatric Written Request? | ☐ | ☐ | X |
| If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³ | YES | NO | NA | Comment |
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? | ☐ | ☐ | X | ☐ |
| If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox | ☐ | ☐ | ☐ | ☐ |
| Prescription Labeling | ☐ | Not applicable | ☐ | ☐ |
| Check all types of labeling submitted. | X | Package Insert (PI) | ☐ | ☐ |
| ☐ | Patient Package Insert (PPI) | ☐ | ☐ |
| ☐ | Instructions for Use (IFU) | ☐ | ☐ |
| ☐ | Medication Guide (MedGuide) | ☐ | ☐ |
| X | Carton labels | ☐ | ☐ |
| X | Immediate container labels | ☐ | ☐ |
| ☐ | Diluent | ☐ | ☐ |
| ☐ | Other (specify) | ☐ | ☐ |
| YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? | X | ☐ | ☐ | ☐ |
| If no, request applicant to submit SPL before the filing date. | ☐ | ☐ | ☐ | ☐ |

³ [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm)
<table>
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<tr>
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<th>Comment</th>
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<tbody>
<tr>
<td>Is the PI submitted in PLR format?</td>
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<tr>
<td>If PI not submitted in PLR format, was a waiver or deferral requested</td>
<td></td>
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<tr>
<td>IF requested before application was submitted, what is the status of the</td>
<td></td>
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<tr>
<td>request?</td>
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<td>If no waiver or deferral, request applicant to submit labeling in PLR</td>
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<td>format before the filing date.</td>
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<tr>
<td>For applications submitted on or after June 30, 2015: Is the PI</td>
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<tr>
<td>Has a review of the available pregnancy and lactation data been</td>
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<td>included?</td>
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<tr>
<td>requested before application was submitted, what is the status of the</td>
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<tr>
<td>request?</td>
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<tr>
<td>If no waiver or deferral, request applicant to submit labeling in PLR</td>
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<td></td>
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<tr>
<td>format before the filing date.</td>
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<td></td>
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</tr>
<tr>
<td>All labeling (PI, PPI, MedGuide, IFU, carton and immediate</td>
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<td></td>
<td>Consult Request dated 9/4/2015</td>
</tr>
<tr>
<td>container labels) consulted to OPDP?</td>
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<tr>
<td>MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>if available)</td>
<td></td>
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<td>Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and</td>
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<tr>
<td>appropriate CMC review office in OPQ (OBP or ONDP)?</td>
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<td>OTC Labeling</td>
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<td>Not Applicable</td>
</tr>
<tr>
<td>Check all types of labeling submitted.</td>
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<td>Outer carton label</td>
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<td>Immediate container label</td>
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<td>Blister backing label</td>
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<td>Consumer Information Leaflet (CIL)</td>
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<td>Physician sample</td>
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<td>Consumer sample</td>
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<td>Other (specify)</td>
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<tr>
<td>Is electronic content of labeling (COL) submitted?</td>
<td></td>
<td></td>
<td>X</td>
</tr>
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<td>IF no, request in 74-day letter.</td>
<td></td>
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Reference ID: 3821449
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<th>No</th>
<th>NA</th>
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<tr>
<td>Are annotated specifications submitted for all stock keeping units (SKUs)?</td>
<td>☐</td>
<td>☐</td>
<td>✕</td>
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<tr>
<td><strong>If no, request in 74-day letter.</strong></td>
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<tr>
<td>If representative labeling is submitted, are all represented SKUs defined?</td>
<td>☐</td>
<td>☐</td>
<td>❑</td>
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<tr>
<td><strong>If no, request in 74-day letter.</strong></td>
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<tr>
<td>All labeling/packaging sent to OSE/DMEPA?</td>
<td>☐</td>
<td>☐</td>
<td>❑</td>
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<tr>
<td><strong>Other Consults</strong></td>
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</tr>
<tr>
<td>Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)</td>
<td>☐</td>
<td>☐</td>
<td>❑</td>
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<tr>
<td><strong>If yes, specify consult(s) and date(s) sent:</strong></td>
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<tr>
<td>Meeting Minutes/SPAs</td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
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<tr>
<td>End-of Phase 2 meeting(s)?</td>
<td>☒</td>
<td>☐</td>
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<tr>
<td><strong>Date(s):</strong> 9/26/2012, 6/11/2013</td>
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<td><strong>If yes, distribute minutes before filing meeting</strong></td>
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<tr>
<td>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</td>
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<td><strong>Date(s):</strong> 2/9/2015</td>
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<td><strong>If yes, distribute minutes before filing meeting</strong></td>
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<tr>
<td>Any Special Protocol Assessments (SPAs)?</td>
<td>☐</td>
<td>☐</td>
<td>❑</td>
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<tr>
<td><strong>Date(s):</strong></td>
<td></td>
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<tr>
<td><strong>If yes, distribute letter and/or relevant minutes before filing meeting</strong></td>
<td></td>
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</table>
MEMO OF FILING MEETING

DATE: August 31, 2015

BACKGROUND: NDA 207795 was submitted on July 21, 2015, for reduction of intraocular pressure for patients in with open-angle glaucoma or of ocular hypertension.

REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Lois Almoza, MS</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>CPMS/TL: Diana Willard</td>
<td>Y</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>William Boyd, MD</td>
<td>Y</td>
</tr>
<tr>
<td>Division Director</td>
<td>Renata Albrecht, MD</td>
<td>Y</td>
</tr>
<tr>
<td>Deputy Director</td>
<td>Wiley Chambers, MD</td>
<td>Y</td>
</tr>
<tr>
<td>Office Director/Deputy</td>
<td>John Farley</td>
<td>Y</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Lucious Lim, MD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: William Boyd, MD</td>
<td>Y</td>
</tr>
<tr>
<td>Clinical Microbiology (for antimicrobial products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Clinical Pharmacology</td>
<td>Reviewer: Yongheng Zhang, PhD</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Philip Colangelo, PhD</td>
<td>Y</td>
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<tr>
<td>Genomics</td>
<td>Reviewer:</td>
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<td>Pharmacometrics</td>
<td>Reviewer:</td>
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<tr>
<td>Biostatistics</td>
<td>Reviewer: Abel Eshete, PhD</td>
<td>Y</td>
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<tr>
<td></td>
<td>TL: Yan Wang, PhD</td>
<td>Y</td>
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<tr>
<td>Nonclinical (Pharmacology/Toxicology)</td>
<td>Reviewer: Andrew McDougal, PhD</td>
<td>Y</td>
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<tr>
<td>--------------------------------------</td>
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</tr>
<tr>
<td>TL: Lori Kotch, PhD</td>
<td>Y</td>
<td></td>
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<tr>
<td>Statistics (carcinogenicity)</td>
<td>Reviewer:</td>
<td></td>
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<tr>
<td>TL:</td>
<td></td>
<td></td>
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<tr>
<td>Product Quality (CMC) Review Team:</td>
<td>ATL: Anamitro Banerjee, PhD</td>
<td>Y</td>
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<tr>
<td>RBPM:</td>
<td></td>
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<tr>
<td>• Drug Substance</td>
<td>Reviewer: Gaetan Ladouceur, PhD</td>
<td>N</td>
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<tr>
<td>• Drug Product</td>
<td>Reviewer: Chunchun Zhang, PhD</td>
<td>N</td>
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<tr>
<td>• Process</td>
<td>Reviewer: Sung Kim, PhD</td>
<td>N</td>
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<tr>
<td>• Microbiology</td>
<td>Reviewer: Daniel Schu, PhD</td>
<td>Y</td>
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<tr>
<td>• Facility</td>
<td>Reviewer: Denise DiGiulio, PhD</td>
<td>N</td>
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<tr>
<td>• Biopharmaceutics</td>
<td>Reviewer: Om Anand, PhD</td>
<td>Y</td>
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<tr>
<td>• Immunogenicity</td>
<td>Reviewer:</td>
<td></td>
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<tr>
<td>• Labeling (BLAs only)</td>
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<tr>
<td>• Branch Chiefs</td>
<td>Balajee Shanmugam, PhD</td>
<td>N</td>
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<tr>
<td>OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)</td>
<td>Reviewer:</td>
<td></td>
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<tr>
<td>TL:</td>
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<td></td>
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<tr>
<td>OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)</td>
<td>Reviewer:</td>
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<td>TL:</td>
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<td>OSE/DMEPA (proprietary name, carton/container labels)</td>
<td>Reviewer: Michelle Rutledge, PhD</td>
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<td></td>
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<tr>
<td>OSE/DRISK (REMS)</td>
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<td>OC/OSI/DSC/PMSB (REMS)</td>
<td>Reviewer:</td>
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<td>TL:</td>
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### Filing Meeting Discussion

**General**

- **505(b)(2) filing issues:**
  
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?  
    - **X** Not Applicable  
      - **YES**  
      - **NO**
  
  - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?  
    - **X** Not Applicable  
      - **YES**  
      - **NO**
  
  Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):

- Per reviewers, are all parts in English or English translation?  
  - **X** YES  
  - **NO**

  If no, explain:

- **Electronic Submission comments**  
  - List comments:  
    - **X** No comments  
    - **Not Applicable**  
    - **YES**  
    - **NO**
<table>
<thead>
<tr>
<th>Clinical</th>
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<tbody>
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<tr>
<td></td>
<td>FILE</td>
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<tr>
<td></td>
<td>Review issues for 74-day letter</td>
</tr>
<tr>
<td></td>
<td>NONE</td>
</tr>
<tr>
<td><strong>Clinical study site(s) inspections(s) needed?</strong></td>
<td></td>
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<tr>
<td>If no, explain:</td>
<td>YES</td>
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<td><strong>Advisory Committee Meeting needed?</strong></td>
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<td>Comments:</td>
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<td>Date if known:</td>
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<td></td>
<td>NO</td>
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<tr>
<td>Reason: the application did not raise significant safety or efficacy issues</td>
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<tr>
<td><strong>If no, for an NME NDA or original BLA, include the reason. For example:</strong></td>
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<tr>
<td>o this drug/biologic is not the first in its class</td>
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<tr>
<td>o the clinical study design was acceptable</td>
<td></td>
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<tr>
<td>o the application did not raise significant safety or efficacy issues</td>
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<tr>
<td>o 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</td>
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<tr>
<td><strong>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?</strong></td>
<td>Not Applicable</td>
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<tr>
<td>Comments:</td>
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<td></td>
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<td>REFUSE TO FILE</td>
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<td>Review issues for 74-day letter</td>
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<tr>
<td>Section</td>
<td>Yes</td>
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<td><strong>CLINICAL PHARMACOLOGY</strong></td>
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<td>Comments:</td>
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<td>• Clinical pharmacology study site(s) inspection(s) needed?</td>
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<td><strong>BIOSTATISTICS</strong></td>
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<td><strong>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</strong></td>
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<tr>
<td>Comments:</td>
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</tr>
<tr>
<td><strong>PRODUCT QUALITY (CMC)</strong></td>
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<tr>
<td>Comments:</td>
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<tr>
<td><strong>New Molecular Entity (NDAs only)</strong></td>
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<tr>
<td>• Is the product an NME?</td>
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<td><strong>Environmental Assessment</strong></td>
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<td>• Categorical exclusion for environmental assessment (EA) requested?</td>
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<tr>
<td>If no, was a complete EA submitted?</td>
<td>☑ YES</td>
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<td>Comments:</td>
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<td>Facility Inspection</td>
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| Establishment(s) ready for inspection? | □ Not Applicable  
| ☒ YES |  
| ☐ NO |  

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<th>Facility/Microbiology Review (BLAs only)</th>
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<tr>
<td>☐ REFUSE TO FILE</td>
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<tr>
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<table>
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<td>☐ Review issues for 74-day letter</td>
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<table>
<thead>
<tr>
<th>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</th>
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</table>
| 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? | □ N/A  
| ☒ YES |  
| ☐ NO |  

<table>
<thead>
<tr>
<th>If so, were the late submission components all submitted within 30 days?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒ YES</td>
</tr>
<tr>
<td>☐ NO</td>
</tr>
</tbody>
</table>

| What late submission components, if any, arrived after 30 days? | N/A |  

| Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | □ YES |  
| ☒ NO |  

| Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | □ YES |  
| ☒ NO |  

Version: 7/10/2015  
Reference ID: 3821449
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</strong></td>
<td>X  YES</td>
</tr>
<tr>
<td></td>
<td>□  NO</td>
</tr>
</tbody>
</table>
REGULATORY PROJECT MANAGEMENT

Signatory Authority: John Farley, MD, MPH

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): December 8, 2015

21st Century Review Milestones (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>x</td>
<td>The application, on its face, appears to be suitable for filing.</td>
</tr>
</tbody>
</table>

Review Issues:

| x | No review issues have been identified for the 74-day letter. |
|   | Review issues have been identified for the 74-day letter. |

Review Classification:

| x | Standard Review |
|   | Priority Review |

ACTION ITEMS - NONE

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<table>
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<tbody>
<tr>
<td></td>
<td>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).</td>
</tr>
<tr>
<td></td>
<td>If RTF, notify everyone who already received a consult request, OSE PM, and RBPM</td>
</tr>
<tr>
<td></td>
<td>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.</td>
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<tr>
<td></td>
<td>If priority review, notify applicant in writing by day 60 (see CST for choices)</td>
</tr>
<tr>
<td></td>
<td>Send review issues/no review issues by day 74</td>
</tr>
<tr>
<td></td>
<td>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</td>
</tr>
<tr>
<td></td>
<td>Update the PDUFA V DARRTS page (for applications in the Program)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
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Annual review of template by OND ADRAs completed: September 2014

Version: 7/10/2015
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
09/17/2015

DIANA M WILLARD
09/17/2015

Reference ID: 3821449
REGULATORY PROJECT MANAGER
PHYSICIAN’S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: NDA 206911

Application Type: New NDA

Name of Drug/Dosage Form: Vesneo (latanoprostene bunod ophthalmic solution), 0.024%

Applicant: Bausch & Lomb Inc.

Receipt Date: July 21, 2015

Goal Date: July 21, 2016

1. Regulatory History and Applicant’s Main Proposals
This NDA was dated and received July 21, 2015. The proposed indication is for the reduction of intraocular pressure for patients with open-angle glaucoma of ocular hypertension.

2. Review of the Prescribing Information
This review is based on the applicant’s July 21, 2015, 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 identified deficiencies see below.

See item 22.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter or during scheduled labeling negotiations.

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

RPM PLR Format Review of the PI: May 2014

Reference ID: 3812004
Selected Requirements of Prescribing Information

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:

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:

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:

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:

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.

Comment:

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:

YES 7. Section headings must be presented in the following order in HL:

<table>
<thead>
<tr>
<th>Section</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>Highlights Limitation Statement</td>
<td>Required</td>
</tr>
<tr>
<td>Product Title</td>
<td>Required</td>
</tr>
<tr>
<td>Initial U.S. Approval</td>
<td>Required</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>Required if a BOXED WARNING is in the FPI</td>
</tr>
<tr>
<td>Recent Major Changes</td>
<td>Required for only certain changes to PI*</td>
</tr>
<tr>
<td>Indications and Usage</td>
<td>Required</td>
</tr>
<tr>
<td>Dosage and Administration</td>
<td>Required</td>
</tr>
<tr>
<td>Dosage Forms and Strengths</td>
<td>Required</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Required (if no contraindications must state “None.”)</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>Not required by regulation, but should be present</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>Required</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Optional</td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Requirement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in Specific Populations</td>
<td>Optional</td>
</tr>
<tr>
<td>Patient Counseling Information Statement</td>
<td>Required</td>
</tr>
<tr>
<td>Revision Date</td>
<td>Required</td>
</tr>
</tbody>
</table>

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

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:

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:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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:

Boxed Warning (BW) in Highlights

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

Comment:

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:

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:

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.**”).
Selected Requirements of Prescribing Information

Comment:

Recent Major Changes (RMC) in Highlights

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:

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:

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:

Indications and Usage in Highlights

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:

Dosage Forms and Strengths in Highlights

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:

Contraindications in Highlights

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:

Adverse Reactions in Highlights

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”.
Selected Requirements of Prescribing Information

Comment: www.fda.gov/medwatch is underlined

Patient Counseling Information Statement in Highlights

YES 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:

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:
Selected Requirements of Prescribing Information

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:*

**YES** 26. The following heading must appear at the beginning of the TOC: “FULL PRESCRIBING INFORMATION: CONTENTS”. This heading should be in all UPPERCASE letters and **bolded**.

*Comment:*

**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 UPPERCASE letters and **bolded**.

*Comment:*

**YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPERCASE.

*Comment:*

**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:*

**YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

*Comment:*

**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:*
Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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.

<table>
<thead>
<tr>
<th>BOXED WARNING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
</tr>
<tr>
<td>4 CONTRAINDICATIONS</td>
</tr>
<tr>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
<td>7 DRUG INTERACTIONS</td>
</tr>
<tr>
<td>8 USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
<td>8.1 Pregnancy</td>
</tr>
<tr>
<td>8.2 Labor and Delivery</td>
</tr>
<tr>
<td>8.3 Nursing Mothers</td>
</tr>
<tr>
<td>8.4 Pediatric Use</td>
</tr>
<tr>
<td>8.5 Geriatric Use</td>
</tr>
<tr>
<td>9 DRUG ABUSE AND DEPENDENCE</td>
</tr>
<tr>
<td>9.1 Controlled Substance</td>
</tr>
<tr>
<td>9.2 Abuse</td>
</tr>
<tr>
<td>9.3 Dependence</td>
</tr>
<tr>
<td>10 OVERDOSAGE</td>
</tr>
<tr>
<td>11 DESCRIPTION</td>
</tr>
<tr>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>12.1 Mechanism of Action</td>
</tr>
<tr>
<td>12.2 Pharmacodynamics</td>
</tr>
<tr>
<td>12.3 Pharmacokinetics</td>
</tr>
<tr>
<td>12.4 Microbiology (by guidance)</td>
</tr>
<tr>
<td>12.5 Pharmacogenomics (by guidance)</td>
</tr>
<tr>
<td>13 NONCLINICAL TOXICOLOGY</td>
</tr>
<tr>
<td>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
</tr>
<tr>
<td>13.2 Animal Toxicology and/or Pharmacology</td>
</tr>
<tr>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td>15 REFERENCES</td>
</tr>
<tr>
<td>16 HOW SUPPLIED/STORAGE AND HANDLING</td>
</tr>
<tr>
<td>17 PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>

**Comment:**

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:**
Selected Requirements of Prescribing Information

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:

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:

BOXED WARNING Section in the FPI

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

Comment:

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”).

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

YES 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:

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:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 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
Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

**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:**
Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

• [text]

• [text]

RECENT MAJOR CHANGES
[section (X.X.X)]
[im/year]

INDICATIONS AND USAGE
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION
• [text]

• [text]

DOSAGE FORMS AND STRENGTHS
[text]

CONTRAINDICATIONS
• [text]

• [text]

WARNING AND PRECAUTIONS
• [text]

• [text]

ADVERSE REACTIONS
Most common adverse reactions (incidence > x%) are [text]

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• [text]

• [text]

USE IN SPECIFIC POPULATIONS
• [text]

• [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
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
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12.4 Microbiology
12.5 Pharmacogenetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
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
08/27/2015

WILLIAM M BOYD
08/27/2015