

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208144Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.3 Debarment Certification

1.3.3 Debarment Certification

Bausch & Lomb, Incorporated (B&L), a wholly-owned subsidiary of Valeant Pharmaceuticals International Inc.(VPII), and an affiliate of Valeant Pharmaceuticals North America LLC (VPNA), 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.

Shaun A. Mbithi

Shaun A. Mbithi
Sr. Manager, Regulatory Affairs

Feb 27, 2017

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208144 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Lumify Established/Proper Name: brimonidine tartrate Dosage Form: ophthalmic solution		Applicant: Bausch + Lomb Agent for Applicant (if applicable):
RPM: Jung Lee		Division: Division of Nonprescription Drug Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 11/6/17 <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>December 27, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None (Refuse-To-File issued on May 29, 2015)
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5 (new formulation or new manufacturer)
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☒ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s): Approval Letter - 12/22/17
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
Most-recent draft labeling	☒ Included
❖ Proprietary Name - Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> - Review(s) <i>(indicate date(s))</i>	<u>Luminesse:</u> PNR Review: 5/4/17 Acceptance Letter: 5/16/17 PNR Withdrawn: 11/14/17 (b) (4) PNR Withdrawn: 12/19/17 <u>Lumify:</u> PNR Review: 12/21/17 Acceptance Letter: 12/21/17
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☒ None DMEPA: 11/8/17 DMPP/PLT (DRISK): ☒ None OPDP: ☒ None SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None DNDP: 11/28/17; 12/19/17; 12/21/17
Administrative / Regulatory Documents	

❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	RPM Filing Review: 5/4/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	12/13/17
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)	
○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
• Date reviewed by PeRC <u>November 29, 2017</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	RTF Letter: 5/29/15 Information Requests: 4/13/17; 4/25/17; 6/26/17; 7/14/17; 12/5/17; 12/15/17 (2)
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	T-con Mtg Minutes: 12/18/17; 12/21/17
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	IND 108524 on 10/24/14
• EOP2 meeting (<i>indicate date of mtg</i>)	IND 108524 on 6/10/13
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	12/22/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	11/29/17
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	DNDP: 10/31/17 DTOP: 11/2/17 DTOP Addendum Review: 11/27/17
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	11/2/17
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	11/2/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	OSI Letter: 8/10/17 OSI Review: 8/15/17
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	11/1/17

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	10/31/17
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	9/28/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	☒ None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	11/6/17 Addendum Review: 12/1/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	11/1/17 (Part of OPQ's Quality Assessment Executive Summary review dated 11/6/17)
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) <i>(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	10/18/17 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

JUNG E LEE
12/22/2017



NDA 208144

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE
ACKNOWLEDGEMENT/WITHDRAWAL**

Bausch & Lomb Incorporated
c/o Valeant Pharmaceuticals North America LLC
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

ATTENTION: Shaun A. Mbithi
Sr. Manager Regulatory Affairs

Dear Mr. Mbithi:

Please refer to your New Drug Application (NDA) dated and received February 27, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate Ophthalmic Solution, 0.025%.

We also refer to your correspondence, dated and received December 19, 2017, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4). Therefore, (b) (4) is considered withdrawn as of December 19, 2017.

Finally, we refer to your correspondence, dated and received December 19, 2017, requesting review of your proposed proprietary name, Lumify.

We have completed our review of the proposed proprietary name, Lumify and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022,
(<https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola M. Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Jung Lee, PharmD, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3559.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
12/21/2017

TELECONFERENCE MEETING MINUTES

Meeting Date Tuesday, November 7, 2017
Time: 3:30 PM – 4:00 PM
Meeting Location: White Oak Building 22, Room 5440

Application Number: NDA 208144
Product Name and Strength: Brimonidine Tartrate Ophthalmic Solution, 0.025%
Sponsor Name: Bausch & Lomb Inc.

Call-In Information: (b) (4); Attendee access code: (b) (4)

Meeting Chair: Danielle Harris, PharmD, Deputy Director (Acting)

FDA Participants:

Division of Nonprescription Drug Products (DNDP)
Karen Mahoney, MD, Deputy Director
Steven Osborne, MD, Lead Medical Officer
Jenny Kelty, MD, Medical Officer
Dan Brum, PharmD, MBA, BCPS, RAC, Chief, Project Management Staff

Division of Transplant and Ophthalmology Products (DTOP)
Wiley Chambers, MD, Deputy Director
William Boyd, MD, Medical Officer Team Leader

Office of Surveillance and Epidemiology (OSE) Project Management Staff
Abiola Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager
Sarah Harris, PharmD, SRPM Team Leader

Division of Medication Error Prevention and Analysis (DMEPA)
Danielle Harris, PharmD, Deputy Director (Acting)
Chi-Ming Tu, PharmD, Safety Evaluator Team leader
Grace Jones, PharmD, Safety Evaluator

Sponsor Participants:

Bausch & Lomb

Sharon A. Tonetta, PhD, Head Regulatory Affairs, R&D

Isabelle B. Lefebvre, VP, Regulatory Affairs

David Silberstein, Executive Director, Regulatory Affairs

Shaun Mbithi, Sr. Manager, Regulatory Affairs

BACKGROUND:

The sponsor submitted a Proprietary Name Request for Luminesse under NDA 208144, on February 28, 2017. The name was conditionally approved and the sponsor was notified of the decision via letter on May 16, 2017. Since that time the DNDP and DTOP review teams have identified concerns with the proprietary name.

MEETING OBJECTIVES:

The objective of this teleconference is to notify the applicant of the Agency's concerns with the proprietary name, Luminesse.

DISCUSSION:

DMEPA notified the applicant that our clinical colleagues had identified a safety concern with the proprietary name, Luminesse, submitted under NDA 208144.

DNDP acknowledged that Luminesse was found CONDITIONALLY ACCEPTABLE in a letter dated May 16th, 2017. However, since that time, both the ophthalmology clinical and DNDP clinical teams had identified safety concerns with the proprietary name, Luminesse, during the NDA review. The clinical team expressed concerns for confusion between the name Luminess Air (a line of airbrush makeup, moisturizer, and chemical cleaning fluid) and the proprietary name, Luminesse (the proposed eye product). Except for the 1 additional letter "e" at the end, the similarity in the names, and the similarity in the bottles of Luminess Air and Luminesse may cause confusion between the two products. DNDP communicated their concerns where consumers could end up putting the Luminess Air moisturizer, or the Luminess chemical cleaning fluid in the eye.

In the interest of transparency, DNDP informed the applicant that if the application moves towards approval, then DNDP will likely express this safety concern in the approval letter and request expedited reporting of adverse events. This courtesy teleconference was to inform the applicant of this safety concern and to inform the applicant that these concerns are likely to appear in the approval letter and clinical reviews should the application obtain approval.

The applicant indicated that they had considered an alternate name and would discuss internally and would likely propose an alternate name.

DMEPA recommended that the applicant notify the agency of their decision and if an alternate name will be proposed, DMEPA requested that the applicant submit the alternate name within the next week to 10 days. DMEPA committed to review this name before the goal date, however, could not guarantee that the name would be found acceptable. The applicant indicated that they would submit the mock up labeling with the alternate name a few days after the name submission.

ACTION ITEMS/POST MEETING

- **POST TELECONFERENCE MEETING**

- The Applicant withdrew the proposed proprietary name Luminesse on November 14, 2017; and submitted a Request for Proprietary Name Review for the proposed proprietary name, (b) (4), on November 16, 2017.

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/s/

SARAH J HARRIS
12/21/2017

TELECONFERENCE MEETING MINUTES

Meeting Date Monday, December 18, 2017

Time: 3:00PM – 3:30PM

Meeting Location: TCON

Application Number: NDA 208144

Product Name and Strength: Brimonidine Tartrate Ophthalmic Solution, 0.025%

Applicant/Sponsor Name: Bausch & Lomb Inc.

Call-In Information: (b) (4)

Passcode (b) (4)

Meeting Chair: Chi-Ming (Alice) Tu, PharmD, BCPS, Team Leader

FDA Participants: Division of Medication Error Prevention and Analysis (DMEPA)

Danielle Harris, PharmD, BCPS, Deputy Director (acting)

Chi-Ming (Alice) Tu, PharmD, BCPS, Team Leader

Grace Jones, PharmD, BCPS, Safety Evaluator

Office of Surveillance and Epidemiology (OSE)

Sarah Harris, PharmD, Safety Regulatory Project Manager, Team Leader

Ameet Joshi, PharmD, Safety Regulatory Project Manager

Oyinlola Fashina, PharmD, Safety Regulatory Project Manager

Division of Nonprescription Drug Products (DNDP)

Jung Lee, RPh, Regulatory Project Manager

Sponsor Participants:

There will be four people from their Regulatory team participating in the meeting:

Sharon Tonetta

Isabelle Lefebvre

David Silberstein

Shaun Mbithi

MEETING OBJECTIVES

The purpose of this teleconference is to notify Bausch & Lomb of our preliminary findings for the proposed proprietary name, (b) (4) and to provide regulatory options to the Applicant to address our concerns.

BACKGROUND

Bausch & Lomb submitted a Request for Proprietary Name Review on Thursday, November 16, 2017, to review the proposed proprietary name, (b) (4).

DMEPA CONCERNS WITH THE PROPOSED PROPRIETARY NAME

DMEPA notified the applicant of our preliminary safety concerns with your proposed proprietary name, (b) (4), submitted under NDA 208144.

During our review of (b) (4), we identified that the proposed name (b) (4) is similar in spelling and pronunciation, and has orthographic and phonetic similarities to the proprietary name, (b) (4). This similarity is supported by FDA's Phonetic and Orthographic Computer Analysis (POCA), which calculates a combined score of 87%, indicating the names are highly similar.

In the interest of transparency and in light of the application action date of December 27, 2017, we informed Bausch & Lomb of our findings and provided regulatory options for Bausch & Lomb's consideration. We have also prescreened the alternate name Lumify. Our prescreening did not identify any safety concerns or conflicts with other names.

REGULATORY OPTIONS FOR THE PROPOSED PROPRIETARY NAME

DMEPA presented the applicant with the following options:

1. Request that DMEPA finalize the current name review by the proprietary name PDUFA date of February 14, 2018.
2. Withdraw the proposed proprietary name, (b) (4) and submit Lumify, or a different alternate name, as the primary name for our review. Although a 90 day PDUFA proprietary name review goal would be invoked, DMEPA will expedite the review to the extent possible with the goal of having an acceptable proprietary name prior to the application goal date.

DISCUSSION (IF ANY)

The applicant stated they intend to withdraw the proposed name, (b) (4) and submit their alternate name, Lumify, for proprietary name review.

NEXT STEPS/ACTION ITEMS

The applicant will withdraw the proposed name, (b) (4) and submit an alternate name for proprietary name review. The applicant will also submit revised labels and labeling to reflect the new primary proprietary name choice.

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/s/

SARAH J HARRIS
12/18/2017

From: [Mbithi, Shaun A](#)
To: [Lee, Jung E \(OND\)](#)
Subject: RE: NDA 208144 (brimonidine tartrate)-Information Request
Date: Friday, December 15, 2017 3:08:58 PM

So noted! The statement will also be removed from the bottle label.

Shaun A. Mbithi

Sr. Manager, Regulatory Affairs, OTCs

Phone: (908) 541-2166

Cell: (b) (6)

Shaun.Mbithi@bausch.com



400 Somerset Corporate Boulevard , Bridgewater, New Jersey 08807

From: Lee, Jung E (OND) [mailto:JungE.Lee@fda.hhs.gov]
Sent: Friday, December 15, 2017 3:02 PM
To: Mbithi, Shaun A
Subject: RE: NDA 208144 (brimonidine tartrate)-Information Request

Thank you Shaun for the quick response! I also wanted to note anywhere on the immediate container there are similar statements, these should be removed as well.

Thank you,
Jung

From: Mbithi, Shaun A [mailto:Shaun.Mbithi@bausch.com]
Sent: Friday, December 15, 2017 2:57 PM
To: Lee, Jung E (OND) <JungE.Lee@fda.hhs.gov>
Subject: RE: NDA 208144 (brimonidine tartrate)-Information Request

Dear Jung,

Thank you for bringing this to our attention.

We were able to meet and agree to remove the following claims from the labeling:

- on the PDP (b) (4) and
- on the right side of the outer carton (b) (4)

We look forward to meeting with you on Monday to discuss additional feedback on the proprietary name (b) (4)

Enjoy your weekend!

Thank you,

Shaun A. Mbithi

Sr. Manager, Regulatory Affairs, OTCs

Phone: (908) 541-2166

Cell: (b) (6)

Shaun.Mbithi@bausch.com



400 Somerset Corporate Boulevard , Bridgewater, New Jersey 08807

From: Lee, Jung E (OND) [<mailto:JungE.Lee@fda.hhs.gov>]

Sent: Friday, December 15, 2017 12:42 PM

To: Mbithi, Shaun A

Subject: NDA 208144 (brimonidine tartrate)-Information Request

Importance: High

Hi Shaun,

We have the following Information Request. Please note, we expect to provide additional feedback regarding the proprietary name next week so we ask that you hold off on submitting revised labeling until we have a decision on the proprietary name. However, we ask that you provide us with your response or your agreement to this IR as soon as possible.

The claims on the PDP (b) (4) and on the right side of the outer carton (b) (4) are not supported by adequate data.

The efficacy data submitted from study 11-100-0015 are subjective as the definition of (b) (4) is not established. The scoring was performed by the individual test subject and therefore, the study term (b) (4) would have different meanings to different individuals. Eye (b) (4) is not a medical condition and may mislead consumers to believe that the product is cosmetic in nature, which could lead to dosing more frequently or in larger quantities than is labeled. Misuse of this nature could constitute a safety issue.

Your labeling is based on previously approved class labeling for similar products treating eye discomfort and redness due to minor eye irritations. This new claim raises questions regarding how consumers may perceive the other instructions for use, which would require support from label comprehension and actual use to assure that the product is not misused.

FDA requests that you provide sufficient data to support the above claims or these claims should be removed from the labeling.

Please let me know if you have any questions.

Thank You,

LCDR Jung E. Lee, RPh

Regulatory Project Manager

Center for Drug Evaluation and Research

Office of Drug Evaluation IV

Division of Nonprescription Drug Products

U.S. Food and Drug Administration

Tel: 301-796-3599

JungE.Lee@fda.hhs.gov



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/s/

JUNG E LEE
12/15/2017

From: [Lee, Jung E \(OND\)](#)
To: [Mbithi, Shaun A](#)
Subject: NDA 208144 (brimonidine tartrate)-Information Request
Date: Friday, December 15, 2017 12:42:03 PM
Importance: High

Hi Shaun,

We have the following Information Request. Please note, we expect to provide additional feedback regarding the proprietary name next week so we ask that you hold off on submitting revised labeling until we have a decision on the proprietary name. However, we ask that you provide us with your response or your agreement to this IR as soon as possible.

The claims on the PDP ((b) (4)) and on the right side of the outer carton (b) (4) are not supported by adequate data.

The efficacy data submitted from study 11-100-0015 are subjective as the definition of (b) (4) is not established. The scoring was performed by the individual test subject and therefore, the study term (b) (4) would have different meanings to different individuals. Eye (b) (4) is not a medical condition and may mislead consumers to believe that the product is cosmetic in nature, which could lead to dosing more frequently or in larger quantities than is labeled. Misuse of this nature could constitute a safety issue.

Your labeling is based on previously approved class labeling for similar products treating eye discomfort and redness due to minor eye irritations. This new claim raises questions regarding how consumers may perceive the other instructions for use, which would require support from label comprehension and actual use to assure that the product is not misused.

FDA requests that you provide sufficient data to support the above claims or these claims should be removed from the labeling.

Please let me know if you have any questions.

Thank You,

LCDR Jung E. Lee, RPh

Regulatory Project Manager

Center for Drug Evaluation and Research

Office of Drug Evaluation IV

Division of Nonprescription Drug Products
U.S. Food and Drug Administration
Tel: 301-796-3599
JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
12/15/2017

Lee, Jung E (OND)

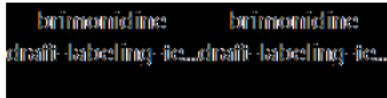
From: Lee, Jung E (OND)
Sent: Tuesday, December 05, 2017 2:40 PM
To: Mbithi, Shaun A
Subject: NDA 208144 (brimonidine tartrate)-Labeling Comments

Importance: High

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Shaun,

Please find attached a PDF and WORD versions of the draft labeling which includes our recommendations/revisions in track changes. These recommendations apply to all carton sizes (2.5 mL and 7.5 mL). We ask that you provide your response/revisions by **Monday, December 11, 2017**.



Thank you,
LCDR Jung E. Lee, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Nonprescription Drug Products
U.S. Food and Drug Administration
Tel: 301-796-3599
JungE.Lee@fda.hhs.gov



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

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/s/

JUNG E LEE
12/05/2017



NDA 208144

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

Bausch & Lomb Incorporated
c/o Valeant Pharmaceuticals North America LLC
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

ATTENTION: Shaun A. Mbithi
Sr. Manager Regulatory Affairs

Dear Mr. Mbithi:

Please refer to your New Drug Application (NDA) dated and received February 27, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate Ophthalmic Solution, 0.025%.

We also refer to your correspondence, dated and received on November 14, 2017, notifying us that you are withdrawing your request for a review of the proposed proprietary name, Luminesse. Therefore, Luminesse is considered withdrawn as of November 14, 2017.

Finally, we refer to your correspondence, dated and received November 16, 2017, requesting review of your proposed proprietary name, (b) (4). Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Therefore, the user fee goal date to review your request for proprietary name is February 14, 2018.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola M. Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Jung Lee, PharmD, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3559.

Sincerely,

{See appended electronic signature page}

Abiola M. Olagundoye-Alawode, PharmD, MS
LCDR, USPHS Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
11/29/2017

From: [Lee, Jung E \(OND\)](#)
To: [Mbithi, Shaun A](#)
Cc: david.silberstein@valeant.com
Subject: NDA 208144 (Luminesse)-Information Request Re: 120-day Safety Update
Date: Friday, July 14, 2017 4:08:36 PM

Hi Shaun,

We have the following information request regarding the 120-day Safety Update submitted on June 26, 2017:

- Provide narratives of the deaths and SAEs generated from the FAERS database or if already submitted, the location of the narratives in your submission.

Please provide this information by July 20, 2017.

Thank you,

LCDR Jung E. Lee, RPh

Regulatory Project Manager

Center for Drug Evaluation and Research

Office of Drug Evaluation IV

Division of Nonprescription Drug Products

U.S. Food and Drug Administration

Tel: 301-796-3599

JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
07/14/2017

From: [Lee, Jung E \(OND\)](#)
To: [Mbithi, Shaun A](#)
Cc: david.silberstein@valeant.com
Subject: NDA 208144 (Luminesse)-Information Request Re: SAS Programs
Date: Monday, June 26, 2017 5:55:41 PM

Hi Shaun,

We have the following information request.

1. The SAS programs for the efficacy analyses of studies 11-100-0015 and 13-100-0005 (eCTD sequence number 0006) on 05/21/2015 was submitted. According to the SAS program a-addiry.sas, the diary analysis dataset (addiry.xpt in ADaM) was derived from the DIRY dataset. The define.xml in ADaM also indicates that some variables in addiry.xpt were originated from the DIRY dataset. However, we cannot find the DIRY dataset in the folders for ADaM and SDTM datasets. To help us better understand the derivation of addiry.xpt, please submit the DIRY dataset and associated SAS programs if it was derived from the SDTM datasets.
2. In the a-addiry.sas for Study 11-100-0015, we noticed that multiple time points on the date of 2012-09-22 were assigned to different analysis visits for the subject with ID- (b) (6) (See the part of the a-addiry.sas below that you submitted). Please provide an explanation for this.

(b) (4)

Please provide your response by **Monday, July 3, 2017**.

Thank you,

LCDR Jung E. Lee, RPh

Regulatory Project Manager

Center for Drug Evaluation and Research

Office of Drug Evaluation IV

Division of Nonprescription Drug Products

U.S. Food and Drug Administration

Tel: 301-796-3599

JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
06/26/2017



NDA 208144

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bausch & Lomb
Subsidiary of Valeant Pharmaceuticals International Inc.
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

ATTENTION: Shaun A. Mbithi
Sr. Manager Regulatory Affairs

Dear Ms. Mbithi:

Please refer to your New Drug Application (NDA) dated and received February 27, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Brimonidine Tartrate Ophthalmic Solution, 0.025%.

We also refer to your correspondence, dated and received February 28, 2017 requesting review of your proposed proprietary name, Luminesse.

We have completed our review of the proposed proprietary name, Luminesse and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola M. Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3982. For any other information regarding this application, contact Jung Lee, Regulatory Project Manager in the Office of New Drugs, at 301-796-3599.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
05/16/2017



NDA 208144

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Bausch + Lomb
Attention: Shaun A. Mbithi
Senior Manager, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Mbithi:

Please refer to your New Drug Application (NDA) dated and received February 27, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Luminesse (brimonidine tartrate ophthalmic solution, 0.025%).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 27, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 29, 2017. If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug and contains a paragraph IV certification, this filing communication is the "paragraph IV acknowledgment letter" described in 21 CFR 314.52(b) and the "postmark" is 4 calendar days after the date on which this letter is signed. Notice of the paragraph IV certification must be sent to the persons described in 21 CFR 314.52(a) no later than 20 days after the date of the postmark on this paragraph IV acknowledgment letter and must contain the information described in 21 CFR 314.52(c).

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug, we recommend that the cover letter for amendments to your unapproved 505(b)(2) application either: 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 5 to 17 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Jung Lee, Regulatory Project Manager, at (301) 796-3599.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD, FACE
Deputy Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

KAREN M MAHONEY
05/04/2017

From: [Lee, Jung E \(OND\)](#)
To: [Mbithi, Shaun A](#)
Cc: [Lefebvre, Isabelle \(Isabelle.Lefebvre@Valeant.com\)](#); [david.silberstein@valeant.com](#)
Subject: NDA 208144 (Luminesse)-Information Request (BIMO Data)
Date: Tuesday, April 25, 2017 1:38:10 PM
Attachments: [Combined Pre-NDA Request Document 7 25 2011 \(2\).doc](#)

Hi Shaun,

While going through the NDA resubmission, it does not appear the Bioresearch Monitoring (BIMO) clinical data was submitted. Attached are the instructions for providing this information. Please provide the information listed under sections I and II of the attached for **study IDs 10-100-008, 11-100-0015, and 13-100-0005.**

We request that you provide this information by **Wednesday, May 10, 2017.**

Thank You,

LCDR Jung E. Lee, RPh

Regulatory Project Manager

Center for Drug Evaluation and Research

Office of Drug Evaluation IV

Division of Nonprescription Drug Products

U.S. Food and Drug Administration

Tel: 301-796-3599

JungE.Lee@fda.hhs.gov

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/s/

JUNG E LEE
04/25/2017

From: [Lee, Jung E \(OND\)](#)
To: [Mbithi, Shaun A](#)
Cc: [Lefebvre, Isabelle](#)
Subject: NDA 208144-Luminesse (brimonidine tartrate): Information Requests
Date: Thursday, April 13, 2017 1:13:36 PM
Importance: High

Hi Shaun,

We have the following information requests for NDA 208144:

1. In the analysis dataset “adored.xpt” of Study 861/13-100-0005, the labels for the variables ANL01FL and ANL02FL provided in define.xml were ‘Analysis Flag for Unscheduled Visits’ and ‘Analysis Flag for Scheduled Visits’, respectively. On the other hand, in your SAS codes for the analyses of the primary variable, ANL01FL and ANL02FL were used to flag the ‘ITT with LOCF data’ and the ‘observed data only’, respectively. Please provide clarification on this inconsistency.

Drug Product and Facility:

2. Per your submitted Form 356h and NDA Section 3.2.P.3.1 (Table 3.2.P.3.1–1), the drug product is packaged at the manufacturing site Bausch & Lomb, Inc 8500 Hidden River Parkway Tampa, FL 33637 (FEI: 1000113778, DUNS: 079587625). From the General Manufacturing Process Description (Section 3.2.P.3.3), some secondary packaging is performed at this manufacturing site.

Another manufacturing site, (b) (4)

(b) (4)

(b) (4)) is listed as “Alternate secondary packaging facility.”

However, on review, the (b) (4) site appeared to have no contract or quality agreement for processing/packaging the product. This information was corroborated by our field office.

Describe in detail the manufacturing process (b) (4)

(b) (4)

Describe the role and responsibility for each site involved in the process. Also, describe the role and responsibility of any other process performed under contract and quality agreement at the (b) (4) site. Please submit an updated Form 356h, if necessary, listing changes and updates.

Microbiology:

Table 3.2.P.3.3.3-1 in Section 3.2.P.3.3.3.2 of the submission dated February 27, 2017,

lists equipment for commercial manufacture of the subject drug product. Please address the following:

(b) (4)



Please provide your responses to the above information requests by **Friday, May 5, 2017.**

Thank You,

LCDR Jung E. Lee, RPh

Regulatory Project Manager

Center for Drug Evaluation and Research

Office of Drug Evaluation IV

Division of Nonprescription Drug Products

U.S. Food and Drug Administration

Tel: 301-796-3599

JungE.Lee@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

JUNG E LEE
04/13/2017



NDA 208144

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

Bausch + Lomb
Attention: Shaun A. Mbithi
Senior Manager, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Mbithi:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in response to our May 29, 2015, refusal to file letter for the following:

Name of Drug Product:	LUMINESSE (BRIMONIDINE TARTRATE OPHTHALMIC SOLUTION, 0.025%)
Date of Application:	FEBRUARY 27, 2017
Date of Receipt:	FEBRUARY 27, 2017
Our Reference Number:	NDA 208144

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 28, 2017 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was

amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3599.

Sincerely,

{See appended electronic signature page}

Jung Lee, RPh
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

JUNG E LEE
03/01/2017



NDA 208144

REFUSAL TO FILE

Bausch + Lomb
A division of Valeant Pharmaceuticals North America, LLC
Attention: Shaun A. Mbithi
Senior Manager, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Mbithi:

Please refer to your New Drug Application (NDA) received March 31, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Luminesse (brimonidine tartrate ophthalmic solution, 0.025%).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

The following is required by regulation and is missing in your application [21 CFR 314.50(d)(5)(iv)]:

The application fails to provide post-marketing data critical for an adequate safety review of this product for its proposed use in an over-the-counter (OTC) consumer population.

FDA's prior requests for these data are documented in minutes for the pre-NDA meeting held on October 24, 2014. Pages 6 and 7 of those meeting minutes state:

"In addition to safety data generated from clinical efficacy and safety trials, also include summaries and analyses of post-marketing safety surveillance information of currently marketed products (including all adverse events) beginning from 2001 from the following databases:

- Your own pharmacovigilance database (U.S. and worldwide)*
- FDA's Adverse Events Reporting System (FAERS) Database*
- World Health Organization's (WHO) International Drug Monitoring Program (analyze U.S. and ex-U.S. reports separately)*
- Published medical literature review*

Given brimonidine tartrate's highly selective alpha-2 agonist properties and known central nervous system and respiratory depressant effects, particularly in young children and the

elderly, provide summaries and analyses of drug abuse and overdose data from the following sources:

- *National Poison Data System (NPDS) from American Association of Poison Control Centers (AAPCC)*
- *Drug Abuse Warning Network (DAWN)*
- *Emergency department reports*

Tabulate, summarize, and analyze post-marketing adverse event data by the following:

- *Seriousness and outcome for each case*
- *Relationship to the drug exposure*
- *Concomitant drugs*
- *Underlying medical conditions*
- *Product specific attributes (dose, dosage strength and duration of use)*
- *Event year*
- *Subject demographics (age sub-groups, sex, race)*

Begin the time period for the review of the post-marketing safety databases in 2001. Provide narrative summaries of deaths.”

Page 7 of the pre-NDA meeting minutes also states:

“FDA expressed concern that the proposed product might be accidentally ingested by children or misused with intent to harm. FDA stated that there have been case reports involving misuse of similar products as date rape drugs.”

Applications are expected to be complete at the time of submission. At the time of submission, your application fails to provide:

- 1) Data from the National Poison Data System (NPDS) from the American Association of Poison Control Centers. These data are necessary for adequate review of important safety concerns related to medicines of this type. Examples of these safety concerns include misuse related to the intent to harm others; drug abuse; drug overdose; and safety in special populations such as children and the elderly.
- 2) Post-marketing safety surveillance data from the World Health Organization’s International Drug Monitoring Program.
- 3) Comprehensive summaries and analyses (as requested in the pre-NDA meeting minutes) of post-marketing adverse event data. For example, narratives of deaths are missing.

In addition to the above filing issues, we have identified other review issues which will be communicated in a separate letter.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, call Jung Lee, Regulatory Project Manager, at (301) 796-3599.

Sincerely yours,

{See appended electronic signature page}

Karen Murry Mahoney, MD
Deputy Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

KAREN M MAHONEY
05/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: December 31, 2015

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

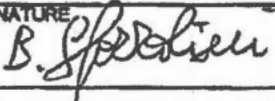
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

- ☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	see attached list	

- ☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- ☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Baldo Sforzolini, MD, PhD	TITLE Vice President, Development Eyecare
FIRM/ORGANIZATION Bausch & Lomb, a division of Valeant Pharmaceuticals North America, LLC	
SIGNATURE 	DATE (mm/dd/yyyy) 03/23/2015

This section applies only to the requirements of the Paperwork Reduction Act of 1995. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Do NOT send your completed form to the PRA Staff email address below.
Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
PRAStaff@fda.hhs.gov

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.



IND 108524

MEETING PRELIMINARY COMMENTS

Valeant Pharmaceuticals North America LLC
Attention: Shaun A. Mbithi
Senior Manager, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Mbithi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for brimonidine tartrate ophthalmic solution, 0.025%.

We also refer to your August 4, 2014, correspondence, received August 5, 2014, requesting a meeting to discuss the nonclinical, clinical, and regulatory development for brimonidine tartrate ophthalmic solution, 0.025%, and to gain agreement that the proposed programs are sufficient for review of the New Drug Application (NDA) for the proposed indication.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-3599.

Sincerely,

{See appended electronic signature page}

Jung Lee, RPh
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV

Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Friday, October 24, 2014 at 11 a.m. EST
Meeting Location: White Oak Bldg 22 Room 1313

Application Number: IND 108524
Product Name: Brimonidine tartrate ophthalmic solution, 0.025%
Indication: For relief of ocular redness
Sponsor/Applicant Name: Valeant Pharmaceuticals North America, LLC

FDA ATTENDEES (tentative)

Division of Nonprescription Drug Products (DNBP)

Theresa Michele, MD, Director
Daniel Brum, PharmD, MBA, BCPS, RAC Chief, Project Management Staff
Jane Filie, MD, Acting Lead Medical Officer
Mona Khurana, MD, Medical Officer
Cindy Xinguang Li, PhD, Pharmacology-Toxicology Reviewer
Barbara Cohen, MPA, Social Science Analyst
Ruth E. Scroggs, PharmD, Associate Director of Labeling (acting)
Steven Adah, PhD, Interdisciplinary Scientist Team Leader
Elaine Abraham, RPh, Interdisciplinary Scientist
Jung Lee, RPh, Regulatory Project Manager

Office of Drug Evaluation IV, Immediate Office (ODEIV/IO)

Jagjit Grewal, MPH, Associate Director of Regulatory Affairs

Division of Transplant and Ophthalmology Products (DTOP)

Renata Albrecht, MD, Director
Wiley Chambers, MD, Deputy Director
William Boyd, MD, Medical Officer Team Leader
Martin P. Nevitt, MD, MPH, Medical Officer

Office of Clinical Pharmacology (OCP)

Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader
Yongheng Zhang, PhD, Clinical Pharmacology Reviewer

Office of Translational Sciences/Office of Biostatistics

Division of Biometrics IV (OTS/OB/DBIV)

Karen Higgins, ScD, Mathematical Statistician Team Leader (OTC)

Scott Komo, DrPH, Mathematical Statistician Reviewer (OTC)
Yan Wang, PhD, Statistician Team Leader (DTOP)
Dongliang Zhuang, PhD, Statistician Reviewer (DTOP)

Office of New Drug Quality Assessment (ONDQA)

Eric Duffy, PhD, Director, Chemistry, Manufacturing and Controls
Danae Christodoulou, PhD, Branch Chief
Swapan De, PhD, Chemistry, Manufacturing and Controls Team Leader
Bryan Riley, PhD, Microbiologist

SPONSOR ATTENDEES

Bausch & Lomb

Baldo Sforzolini, MD, PhD, Vice President, Development Eyecare
Sharon A. Tonetta, PhD, Vice President, Regulatory Affairs
David Silberstein, Executive Director, Regulatory Affairs
Shaun A. Mbithi, Sr. Manager, Regulatory Affairs
Linda Galbier, Sr. Manager, CMC
Quintus Ngumah, OD, PhD, Director, Clinical Affairs

Ora, Inc

Donna Welch, RN, BSN, Sr. VP & COO
Paul Gomes, MS, VP, Allergy
Matthew Chapin, VP, Corporate Development
Jeffrey Coderre, PhD, Director, Regulatory Writing

(b) (4)

(b) (4) MS, Director of Biostatistics

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Friday, October 24, 2014 at 11 a.m. at White Oak Building 22, Room 1313 between Valeant Pharmaceuticals North America, LLC and the Division of Nonprescription Drug Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On August 4, 2014, Bausch & Lomb, a division of Valeant Pharmaceuticals North America LLC, submitted a request to the Food and Drug Administration (FDA) for a Type B pre-new drug application (pre-NDA) meeting to obtain agreement that the proposed programs are sufficient for an NDA review.

Brimonidine tartrate is a topical imidazoline vasoconstrictor agent which binds to the α_2 -adrenergic receptor and causes vasoconstriction by acting post-synaptically on sympathetic nerves. Brimonidine tartrate ophthalmic solutions are approved in the prescription setting in concentrations of 0.1%, 0.15%, and 0.2% for the chronic treatment of increased intraocular pressure (IOP) in glaucoma patients and 0.5% for the prevention of post-operative IOP elevations in patients undergoing argon laser trabeculoplasty (ALT).

The proposed brimonidine tartrate ophthalmic solution will be for a new strength (0.025%) and for a new indication (relief of ocular redness) in the over the counter (OTC) rather than prescription setting. The Sponsor states that other similar OTC products are commonly associated with tachyphylaxis (tolerance or loss of effectiveness) or rebound congestion. The Sponsor suggests their product will help minimize this effect.

Results from six clinical studies have been provided in the briefing package for the proposed OTC product. The Sponsor states it will rely on the nonclinical safety data for the approved Rx product, brimonidine 0.2% and no new nonclinical studies will be conducted. At an End-of-Phase 2 meeting held with the Agency on May 15, 2013, FDA agreed that no new nonclinical studies would be required for the proposed dose and indication; however, the adequacy of the nonclinical data would be a review issue.

The Sponsor's questions are in **bold** font; FDA's introductory comments and preliminary responses are in *italics*.

2.0 DISCUSSION

Introductory Comments

Because brimonidine tartrate would be a novel active ingredient to the OTC market, consumer studies may be needed if the proposed Drug Facts Label provides for directions for use or a safety profile that substantially differs from existing OTC products labeled for the same indication.

Given brimonidine tartrate's potential for causing serious central nervous system (CNS) depression, particularly in young children, you will need to address what steps you plan to take to mitigate the risk of accidental pediatric ingestions or other misuse of your proposed product if it were to become available OTC. We strongly recommend you consider the use of a child-protective cap and encourage you to discuss with us the design of packaging configurations which could further help mitigate the risk of product misuse.

2.1. Nonclinical

Question 1: Does the Agency agree that the nonclinical information described in the meeting package is adequate to support the NDA submission and review for 0.025% brimonidine tartrate ophthalmic solution as a 505(b)(2) application?

FDA Response to Question 1:

Yes, it appears acceptable.

2.2. Clinical

Question 2: Does the Agency agree that the data for study 13-100-0005 summarized in Attachment 2 Section 1.4 of the meeting package is adequate to support PDP claims for 1 minute onset of action and up to 8 hour duration of action?

FDA Response to Question 2:

Study 13-100-0005 does not appear adequate to support the claims for 1 minute onset and up to 8 hour duration of action, although a final determination can only be made at the time of NDA review. Figure 6 (page 66 of Clinical Summary) shows the beginning of a loss of effect on redness after only 120 minutes (Hour 2). While there is still an effect at Hour 8, it is not clear that it is a clinically significant effect. Propose a dosing regimen commensurate with the efficacy data of your product. Adequacy of the dosing recommendations will be a review issue. Also propose and justify the duration of use of your product.

Question 3: Does the Agency agree that the duration of action (i.e. up to 8 hours) along with the safety data provided in Attachment 2 Sections 1.4 and 1.5 will support the proposed dosing regimen in the drug facts labeling of up to 4 times a day (dosed 6-8 hours apart)?

FDA Response to Question 3:

See response to Question 2. Final labeling is a review issue and can only be determined at the time of NDA submission and review.

Question 4: The clinical program includes a study with a pediatric cohort consistent with the Pediatric Study Protocol presented to the Agency (refer to Attachment 2). Does the Agency agree that no additional clinical studies beyond those described are required prior to submitting the NDA?

FDA Response to Question 4:

No additional pediatric studies would likely be required given the planned enrollment of 50 subjects greater than or equal to 5 years of age and less than or equal to 17 years of age, although a final determination can only be made at the time of NDA submission and review.

Question 5: Does the agency have any comments on our plan for ISS/ISE study integration and analyses (including specified subgroups)?

FDA Response to Question 5:

In general, relevant safety information in the ISS must be provided from all sources including pertinent animal data, clinical pharmacology studies, controlled and uncontrolled clinical trials (including controlled clinical trials for indications not claimed in your application and for any listed drug for which you are relying upon safety data), and foreign marketing experience or epidemiologic studies related to any use of the drug.

In addition to safety data generated from clinical efficacy and safety trials, also include summaries and analyses of post-marketing safety surveillance information of currently marketed products (including all adverse events) beginning from 2001 from the following databases:

- *Your own pharmacovigilance database (U.S. and worldwide)*
- *FDA's Adverse Events Reporting System (FAERS) Database*
- *World Health Organization's (WHO) International Drug Monitoring Program (analyze U.S. and ex-U.S. reports separately)*
- *Published medical literature review*

Given brimonidine tartrate's highly selective alpha-2 agonist properties and known CNS and respiratory depressant effects, particularly in young children and the elderly, provide summaries and analyses of drug abuse and overdose data from the following sources:

- *National Poison Data System (NPDS) from American Association of Poison Control Centers (AAPCC)*
- *Drug Abuse Warning Network (DAWN)*
- *Emergency department reports*

Tabulate, summarize, and analyze post-marketing adverse event data by the following:

- *Seriousness and outcome for each case*
- *Relationship to the drug exposure*
- *Concomitant drugs*
- *Underlying medical conditions*
- *Product specific attributes (dose, dosage strength and duration of use)*
- *Event year*
- *Subject demographics (age sub-groups, sex, race)*

Begin the time period for the review of the post-marketing safety databases in 2001. Provide narrative summaries of deaths.. Include a table listing the references with the type of study, objectives, population and principal results. If you rely in part on the published literature to support safety, you will need to explain the relevance of each publication to the safety of your proposed product, summarize and analyze information relevant to the safety of brimonidine tartrate, include a list of retrieved references, and be able to provide articles in full-text in the English language if requested by the Agency.

a) Are these pooling and analysis strategies acceptable?

FDA Response to Question 5(a):

Your pooling strategy for the ISS is acceptable. Study 10-100-0008 (CAC model study with less frequent dosing) may be excluded from the ISS pooled summary data provided that the complete study report is provided in Module 5. Explore the time dependency of any reported adverse reactions to identify adverse reactions which occurred later in treatment. Also identify any dose-response and blood-level relationships as well as any drug-drug or drug-disease interactions.

b) Are these planned subgroup analyses sufficient and acceptable?

FDA Response to Question 5(b):

In addition to your proposed subgroups of age, sex, race, and ethnicity, also include subgroup analyses based on iris color. For subgroup analysis by age, include the following pediatric age strata: greater than 5 years to less than 12 years and greater than 12 years to less than 18 years. Within the pediatric age subgroup, further analyze by weight (> 20 kilograms).

c) Is this data submission strategy acceptable?

FDA Response to Question 5(c):

Address all deaths, serious AEs, and discontinuations across all studies in the ISS. Include separate AE tables for deaths, SAEs, and non-serious AEs.

In addition to providing the case report forms (CRFs) for the categories of patients defined by ICH E3 (i.e., Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events) within the individual study reports, provide CRFs for all patients who withdrew for any reason.

2.3 Chemistry, Manufacturing and Controls Questions

Question 6: Does the Agency agree that the specifications proposed are appropriate to support the filing requirements for the New Drug Application?

FDA Response to Question 6:

Your drug product proposed specifications (testing attributes) appear appropriate. Acceptance limits will be assessed during review of the NDA.

Question 7: Does the Agency agree that the stability program described adequately meets the filing requirements for the New Drug Application?

FDA Response to Question 7:

Your proposed stability program appears acceptable. Review of the stability data will be performed during NDA review and expiration dating will be assessed based on ICH Q1E guidelines.

Question 8: The company may submit a type V DMF to support the non-product-specific environmental monitoring and sterilization activities at the Tampa, FL facility (e.g. sterilization of packaging components and equipment). The company would then cross-reference this DMF in the NDA.

a) Does the Agency have any concerns or recommendations regarding this proposal?

FDA Response to Question 8(a):

Your proposal to submit a Type V DMF is acceptable.

b) Is a letter of intent required to be submitted to FDA?

FDA Response to Question 8(b):

A Letter of Authorization for any cross-referenced Drug Master File supporting your application should be submitted in the NDA and the DMF.

c) Are there fees associated with the submission, similar to Type II DMFs for drug substance?

FDA Response to Question 8(c):

No fees are associated with the submission of DMFs supporting drug substances for new drugs.

We note that on [REDACTED] (b) (4), a Deficiency Letter was sent to DMF [REDACTED] (b) (4) supporting the drug substance. You should communicate with your drug substance supplier and ensure that at the time of NDA submission, the DMF holder have provided to the Agency a complete response to the drug substance deficiencies.

2.4 Regulatory

Question 9: B&L plans on including the phrase [REDACTED] (b) (4) on the PDP of our labeling. A Label Interpretation study will be conducted to provide support that consumers understand that [REDACTED] (b) (4) is interpreted to mean 'redness relief'. Attachment 4 provides a high level summary of how we plan to conduct the Label Interpretation study. Does the Agency agree with the purpose and design of the study?

FDA Response to Question 9:

See our introductory comments. In light of the fact that the proposed Drug Facts Label has not been submitted, it is not possible at this time for FDA to respond to this question. However, we note that promotional claims (e.g., claims beyond what is stated in the Drug Facts) are not allowed on the PDP.

2.5 Administrative

Question 10: B&L will follow the current eCTD guidance for this application. Attachment 5 provides the eCTD backbone structure of the documents that we intend to provide in the NDA. We welcome any comments regarding the submission outline that would facilitate the Agency review of the application.

FDA Response to Question 10:

As you develop your label and labeling, we call your attention to the following pertinent labeling regulations and guidances:

LABELING REGULATIONS AND GUIDANCES

Regulations under the Code of Federal Regulations (CFR)

When you prepare your NDA for submission to FDA include the following:

1. All of the proposed labels and labeling (i.e., all count sizes with immediate container and carton labeling, including samples, and consumer information leaflet if proposed) as required under 21 CFR 314.50.
 - a. “clean” labeling and marked up labeling (i.e., annotated) defining the information in the summary and technical sections of the application that support the inclusion of each statement in the proposed labeling.
 - b. font and format specified under 21 CFR 201.66 as part of the annotated labeling or detailed in a separate document.
2. In addition to the format and content requirements for over-the-counter (OTC) drug product labeling (21 CFR 201.66), we refer you to the following:
 - a. 21 CFR, Part 201 Subpart A-General Labeling Provisions and
 - b. Subpart C-Labeling Requirements for Over-the-Counter Drugs, which provides the labeling required for packaging (Principal Display Panel (PDP)-21 CFR 201.60 and statement of identity- 21CFR 201.61 etc.).

Guidances

1. See “Guidance for Industry– Labeling OTC Human Drug Products –Questions and Answers” (December 2008) for assistance with OTC labeling development.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078792.pdf>
2. We recommend that you formally submit your proposed labeling in portable document format (PDF) electronically to your NDA. See “Guidance for Industry – Providing Regulatory Submissions in Electronic Format – General Considerations” (January 1999).
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072390.pdf>
 - a. To ensure electronic storage, retrieval, and viewability of the submitted labeling, which are often oversized and complex documents (i.e., OTC labeling usually has

complex graphics and large file size), follow FDA's portable document format (PDF) specifications detailed in the document found at the following URL:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionsRequirements/ElectronicSubmissions/UCM163565.pdf>

- b. Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER at esub@fda.hhs.gov.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

5.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should

include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>

3. <i>Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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

/s/

JUNG E LEE
10/23/2014



PIND 108524

MEETING MINUTES

Ora, Inc.
Attention: Donna Welch, RN, BSN
Sr. VP/COO
(Agent for Eye Therapies, LLC)
300 Brickstone Square, 3rd Floor
Andover, MA 01810

Dear Ms. Welch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for brimonidine tartrate ophthalmic solution, 0.025%.

We also refer to the meeting between representatives of your firm and the FDA on May 15, 2013. The purpose of the meeting was to discuss your completed Phase 2 study data and planned Phase 3 studies.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have questions, contact Jeff Buchanan, Regulatory Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Division Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: End-of-Phase 2

Meeting Date and Time: May 15, 2013, at 12:00 P.M.

Meeting Location: FDA/White Oak
10903 New Hampshire Avenue
Building 22/Room 1415
Silver Spring, MD 20993

Application Number: IND 108524

Product Name: brimonidine tartrate ophthalmic solution, 0.025%.

Indication: Relief of ocular redness

Sponsor/Applicant Name: Ora, Inc. (Agent for Eye Therapies, LLC)

Meeting Chair: Joel Schiffenbauer, M.D.
Deputy Division Director
Division of Nonprescription Clinical Evaluation

Meeting Recorder: Jeffrey Buchanan
Regulatory Health Project Manager
Division of Nonprescription Clinical Evaluation

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation

Joel Schiffenbauer, M.D., Deputy Division Director
Lesley-Anne Furlong, M.D., Medical Team Leader
Linda Hu, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacology/Toxicology Reviewer
Dan Brum, Pharm.D., M.B.A., B.C.P.S., R.A.C., Chief, Project Management Staff
Jeffrey Buchanan, Regulatory Health Project Manager

Division of Transplant and Ophthalmology Products

Wiley Chambers, M.D., Deputy Director
William Boyd, M.D., Medical Team Leader
Martin Nevitt, M.D., Medical Officer

Division of Biometrics IV

Yan Wang, Ph.D., Statistician Team Leader

SPONSOR ATTENDEES

Eye Therapies, LLC

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1.0 BACKGROUND

Ora, Inc. (Ora) requested a type B, End-of-Phase 2 meeting on December 28, 2012, in order to discuss their completed Phase 2 study data and planned Phase 3 studies for brimonidine tartrate ophthalmic solution, 0.025%.

The FDA's preliminary responses to the questions contained in Ora's April 16, 2013 meeting background package were provided to Ora on May 14, 2013, via electronic mail. These preliminary responses appear in italics below. The discussion centered on questions 4, 10, and the additional comments. For questions where no additional discussion is indicated, neither Ora nor FDA raised additional issues pertaining to these questions.

2.0 DISCUSSION

Questions:

1. As the Sponsor plans to rely on the Agency's prior findings of safety for other brimonidine products used at higher doses, no further preclinical studies are planned. Assuming no unexpected adverse events arise during the proposed clinical program, please confirm no further preclinical testing will be required.

FDA Preliminary Response:

No new nonclinical studies are required at this time for your proposed dose and indication (refer to our comments at the previous meeting held September 1, 2010). If the levels of inactive ingredients, impurities or degradants in your drug product are not acceptable or there are safety signals identified during clinical studies, additional nonclinical studies may be necessary. The adequacy of the nonclinical data to support your submission will be a review issue.

2. We propose the completed Phase 2 efficacy/safety Clinical Study 11-100-0015 can be used as one of the two well-controlled clinical trials to support approval for Brimonidine Tartrate Ophthalmic Solution 0.025% (see **Section 10.2.1** for the Clinical Study Summary). Does the Agency agree?

FDA Preliminary Response:

We agree. Assuming the Clinical Study Summary reflects the pre-specified study design and statistical analysis plan, the study can be considered a well-controlled study. However, the acceptability of the results and conclusion will depend on the review of the full Clinical Study Report.

3. Is the proposed Phase 3 single-center efficacy study presented in **Appendix 2**, in concert with an adequate safety study with subjects down to 6 years of age, sufficient to obtain NDA approval for the proposed OTC product and indication with dosing up to four times daily?

FDA Preliminary Response:

The Proposed Phase 3 study would support your NDA submission; final labeling is a review issue and can only be determined at the time of the NDA review.

4. Is the proposed safety study presented in **Appendix 3**, in concert with and to be run in parallel with the proposed Phase 3 single-center efficacy study presented in **Appendix 2**, sufficient to obtain NDA approval for the proposed OTC product and indication with dosing up to four times daily?

FDA Preliminary Response:

The proposed safety study appears adequate for the safety trial and would support the proposed indication, though final labeling is a review issue and can only be determined at the time of the NDA review.

If there is disparity between the proposed dosing interval and the duration of effect, then consumers may dose too frequently; the safety study should capture possible overuse concerns and should capture the safety consequences, if any.

Diaries should be provided to collect additional information related to alertness.

Discussion:

Ora's previous experience indicated that weekly investigator evaluations of alertness are more accurate than diaries maintained in-home by study subjects. FDA suggested that diaries maintained by subjects could supplement the investigators' evaluations and could provide more daily detail about alertness rather than the subject trying to remember how they felt for the previous week. Ora agreed to utilize daily subject diaries in order to complement the weekly investigator evaluations. FDA suggested that the diary be designed to gather data on alertness (by, for example, including a targeted question).

5. In the Phase 2 efficacy/safety Clinical Study 11-100-0015 the primary efficacy parameter was ocular redness as assessed by the investigator at Visit 1 (post-instillation assessments at 5, 15, 30, 60, 90, 120, 180, and 240 minutes) using an analysis of covariance (ANCOVA) model accounting for repeated measures and adjusting for baseline (pre-instillation). The brimonidine tartrate (0.025%) group showed statistically significantly lower ($P < 0.0001$) ocular redness scores at Visit 1 for at least 240 minutes (4 hours) when all time points were accounted for with an ANCOVA model. The Sponsor believes that these data demonstrate duration of action of at least 4 hours in an adequately powered and well-controlled study. Does the Agency agree?

FDA Preliminary Response:

Based on our preliminary review, the data appear to support the duration of action, though the establishment of efficacy for this indication is a review issue and can only be determined at the time of the NDA review.

6. Based on the demonstrated duration of action in the Phase 2 efficacy/safety Clinical Study 11-100-0015 and the proposed Phase 3 efficacy and safety study (cf. **Appendix 2**), we believe we are able to support dosing terminology for the label to be “up to four times daily dosing”. Does the Agency agree?

FDA Preliminary Response:

Based on the information provided and our preliminary review, we agree. See Response to Question 5.

7. In the proposed Phase 3 efficacy and safety study (cf. **Appendix 2**), the in-office ocular redness assessments by the investigator will be extended to 6 hours and 8 hours. If the 6-hour data are statistically significant relative to the vehicle group, would the Agency allow labeling of “(b) (4)?”

FDA Preliminary Response:

Yes; however, the final dosing directions will be determined at the time of the NDA review.

8. In the 12 December 2011 FDA Official Meeting Minutes, page 8 (cf. **Appendix 1**), FDA stated that if the duration of effect of our product turns out to be substantially shorter than the proposed dosing interval, a label comprehension study should be conducted. If we demonstrate duration of action of at least 4 hours in the proposed Phase 3 efficacy and safety study (cf. **Appendix 2**), we propose that a label comprehension study will not be required. Does the Agency agree?

FDA Preliminary Response:

We generally recommend a label comprehension study if an important concept appears for the first time on an OTC label. If your label contains an uncomplicated dosing interval that reflects the efficacy and safety of your clinical trials, we do not anticipate the need for a label comprehension study. If you feel that a label comprehension study is not needed, you would need to provide a clinical rationale for why this is the case.

9. We have included results of a completed study (Study 12-150-0001) investigating IOP reduction in patients with ocular hypertension and glaucoma. We believe the IOP reduction in this crossover study is minimal and not clinically significant. We also believe the potential IOP effect can be adequately addressed with inclusion of language in the product label for consumers to notify their eye care professional if they have been using the product and whether they used the product on the day of an eye exam.

Are the IOP data collected in studies 11-100-0015 and 12-150-0001 adequate to demonstrate minimal IOP reduction in the proposed OTC product and is the plan outlined in this question acceptable to the Agency to address the potential IOP effect with labeling?

FDA Preliminary Response:

Based on our preliminary review, the IOP data collected in studies 11-100-0015 and 12-150-0001 appear adequate to demonstrate IOP reduction, but it is minimal; final labeling is a review issue and can only be determined at the time of the NDA review.

10. We intend to collect efficacy and safety data in a proposed Phase 3 study (cf. **Appendix 2**) for an adult subject population 18 years of age and older. If we demonstrate safety for brimonidine 0.025% dosed 4 times daily with subjects down to 6 years of age in a separate large Phase 3 safety study (cf. **Appendix 3**), is it acceptable to the Agency to label the proposed OTC drug product for use by individuals 6 years of age and older?

FDA Preliminary Response:

Yes. The adult findings of efficacy could be extrapolated to pediatric patients down to age 6 years provided safety has been demonstrated; final labeling is a review issue and can only be determined at the time of the NDA review.

There will be approx 60 pediatric patients –approx 25 subjects in 6-12 yr age group and 13-17 yr age group. We recommend that subjects be stratified by age group, when assigned to investigational product.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach), any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

Discussion:

Ora commented that the 60-day time period given to complete a PSP (Pediatric Study Plan) appeared short. FDA informed Ora that only a PSP *outline* of the studies was required within 60 days of the End-of-Phase 2 meeting. Ora agreed to submit a PSP within 60 days.

Ora inquired as to what minimum study subject age should be included in their PSP study. FDA stated that all ages should be addressed, including any waiver and deferral requests with rationale.

Ora stated their modified Phase 3 safety study would collect data down to 5 years of age.

Additional Comments:

For the safety and efficacy trial described in Appendix 2, the subject must be on a medically acceptable form of birth control throughout the study duration, for at least 14 days prior to the pregnancy test, and for one month after the last dose of investigational product.

In addition to the safety data collected from the trials in your development program, when you submit your NDA, you need to:

- summarize and analyze the literature for safety of your product,*
- provide a narrative summary and analysis of any postmarketing safety information data available for currently marketed brimonidine tartrate ophthalmic solution products including the FDA Adverse Event Reporting System (FAERS) database (stratified by dose),*
- provide a summary of clinical trial safety data from the prescription NDAs.*

Discussion:

Ora's *safety* study included the requirement that female study subjects should be on an acceptable form of birth control for at least 14 days prior to the screening urine pregnancy test through 30 days after the final dose of the investigational drug product. However, Ora's *efficacy* study proposed only a negative pregnancy test upon screening and an agreement by study subjects to use birth control throughout the study. FDA commented that since there is a lag period between conception and a positive pregnancy test such that a subject could be pregnant but have a negative pregnancy test, the Sponsor should implement the safety study criteria for both trials. The Sponsor agreed.

Administrative Comments:

For applications submitted after February 2, 1999, applicants are required either to certify the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21 CFR 314.50(k).

3.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS

1. Ora agreed to require subjects to use birth control for 14 days prior to trial screening and 30 days following the final administration of the investigational drug product in the safety and efficacy studies.
2. Ora agreed to provide a PSP within 60 days of this End-of-Phase 2 meeting.
3. Ora agreed to utilize daily subject diaries, which will include a question or questions targeting alertness, to supplement weekly investigator evaluations in the proposed safety study.

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

/s/

JOEL SCHIFFENBAUER
06/10/2013