

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207795Orig1s000

OTHER ACTION LETTERS



NDA 207795

COMPLETE RESPONSE

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC
Director, Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) dated July 21, 2015, received July 21, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyhzulta (latanoprostene bunod ophthalmic solution), 0.024%.

We acknowledge receipt of your amendment dated February 24, 2017, which constituted a complete response to our July 21, 2016, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product must comply with the current good manufacturing practice regulations in 21 CFR 210 and 211. During a recent inspection of the Bausch & Lomb Inc. (FEI 1000113778) manufacturing facility for this application, our field investigator conveyed findings to the representative of the facility. Satisfactory resolution of this deficiency is required before this application may be approved.

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated 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>

PROPRIETARY NAME

Please refer to correspondence dated, June 14, 2017 which addresses the proposed proprietary name, Vyhzulta. This name was found acceptable pending approval of the application in the

current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiency.

SAFETY UPDATE

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address the deficiency listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiency outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lois Almoza, M.S., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

John Farley, M.D., M.P.H.
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

JOHN J FARLEY
08/07/2017



NDA 207795

COMPLETE RESPONSE

Bausch & Lomb Inc.
Attention: Mary Harrell, BsBM, RAC (US)
Associate Director, US Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) dated July 21, 2015, received July 21, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product must comply with the current good manufacturing practice regulations in 21 CFR 210 and 211. During a recent inspection of the Bausch & Lomb Inc. (FEI 1000113778) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated 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>

PROPRIETARY NAME

Please refer to correspondence dated, January 15, 2016, which addresses the proposed proprietary name, Vyzulta. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiency.

SAFETY UPDATE

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

ADDITIONAL COMMENTS:

We have the following comments/recommendations that are not approvability issues:

1. The in-use stability data does not support the label storage statement (b) (4). A scientific justification was not provided to address the observed (u) (4). From the recent inspection of the Bausch and Lomb facility, we are aware of investigations into the (b) (4) issues. A definitive root cause for the (b) (4) (b) (4) failures had not been determined.

In your resubmission, we recommend that you include a copy of the protocol for the in-use stability of drug product and provide data from multiple batches analyzed for all quality attributes, including (b) (4), once every 2 weeks until the desired storage duration. Additionally, please update your submission to include any information presented in the NDA that is impacted by your actions to address the inspectional issues related to the NDA (e.g. 3.2.R Investigation Report for the (b) (4)).

2. The data you have provided concerning pregnancy risk are limited (b) (4). (b) (4) Currently proposed labeling provides exposure margins based on dose multiples (on a mg/m² basis, presuming 100% absorption). To further refine the exposure margin estimates, the following could be informative:
 - a. Conduct a rabbit embryofetal study by the topical ocular route to more directly address the assessment of risk for the human route of administration.
 - b. Provide adequate toxicokinetic data in embryofetal development studies. Measure parent (latanoprostene bunod) and its two active metabolites (latanoprost acid and butanediol mononitrate), as well as release of nitric oxide. Assays should be sufficiently sensitive, and LLOQ adequate to capture the lowest biologically active exposure.
 - c. Based on the results of item a. above, conduct a pre-/postnatal study (or peri-/post-natal study) if needed to complete the reproductive and developmental assessments.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address the deficiency listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiency outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,
{See appended electronic signature page}

John Farley, M.D., M.P.H.
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

JOHN J FARLEY
07/21/2016