CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208073Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208073

COMPLETE RESPONSE

Shire Development, LLC.
Attention: Kimberly McCormick, PharmD
Global Regulatory Affairs
725 Chesterbrook Blvd
Wayne, PA 19087-5637

Dear Dr. McCormick:

Please refer to your New Drug Application (NDA) dated and received February 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lifitegrast ophthalmic solution, 5%.

We acknowledge receipt of your amendments dated.

March 23, 2015	March 25, 2015	June 3, 2015
June 8, 2015	June 10, 2015	June 16, 2015
June 18, 2015	June 19, 2015	July 20, 2015
Sept. 9, 2015		

We also acknowledge receipt of your amendments dated October 1 and 5, 2015, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically:

    a. The Phase 2 Dry Eye study did not meet its primary efficacy endpoint, inferior corneal staining score at Day 84. None of the lifitegrast groups achieved a statistically significant difference in the inferior corneal staining score at Day 84 compared to vehicle although there were increasing numerical improvements in the inferior corneal staining score with higher lifitegrast doses.

b. The OPUS-1 study, did not meet its co-primary efficacy endpoints; change from baseline to Day 84 in inferior corneal staining score and visual related function Ocular Surface Disease Index subscale score. Statistical significance was only achieved for the objective efficacy endpoint (the change from baseline to Day 84 in inferior corneal staining score).

c. The OPUS-2 study, did not meet its co-primary efficacy endpoints: change from baseline to Day 84 in inferior corneal staining score and eye dryness score measured on the visual analogue scale. Statistical significance was only achieved for the subjective efficacy end point (the change from baseline to Day 84 in eye dryness score).

It is recommended that an additional clinical trial be conducted to provide substantial evidence of efficacy of the drug product in the intended patient population.

PRODUCT QUALITY

2. There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling. Specifically, information to support the safety (b) (4) (b) (4) in the drug substance has not been submitted. Since no detectable levels (b) (4) were present in the late-stage process batches tested to date (detection limit of (b) (4) ppm), the acceptance limit should be revised to "less than (b) (4) ppm."

3. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing or holding of the drug substance are inadequate to preserve its identity, strength, quality, purity, stability and bioavailability. Specifically,

   a. The (b) (4) are not acceptable. Removal of the test (b) (4) may be requested once adequate data is available.

   b. The USP specification for particulate matter in ophthalmic solutions has been revised. The proposed acceptance criterion for particulate matter is not consistent with the current USP specification. The acceptance criteria should be revised to be consistent with the USP monograph, USP<789>.

   c. Impurities have been identified which are not being tracked. While it is claimed that most of the impurities are degradents from the drug product evidence has not been provided that these impurities originate from the drug product. The remaining unknown impurities currently claimed as leachables should be identified and qualified (i.e., provide safety data).

   d. The current specification do not account for (b) (4) (b) (4) unexpected issues in manufacturing. Changing the specification to all unidentified impurities and lowering

the limit to the standard used for ophthalmic drug products (<0.1%) should minimize the chances that no harmful impurities (degradants, leachables or other) are included in the drug product.

e. The Comparability Protocol (b) (4) both manufacturer and manufacturing process changes for both the drug substance and the drug product is not acceptable. The comparability protocol is not acceptable for either the proposed post-approval changes to the drug substance or the drug product. Additional data will need to be provided for a number of the proposed changes and changes to the reporting categories will need to be made. It is recommended that the Comparability Protocol be revised or deleted from the new drug application.

ADDITIONAL COMMENTS

In addition, we have the following comments/recommendations that are not approvability issues:

4. In the Amendment dated 16-Jun-2015, you provided the method validation report for *Assay, Purity, Impurities, and Identification Test by HPLC (Test Method TM.2975)*. The (b) (4) does not appear to give (b) (4) (b) (4) (b) (4). Thus, the HPLC method is not stability-indicating for all potential drug substance degradation pathways. Optimize the method (b) (4) for all potential degradation pathways or develop a new method that is stability-indicating.

5. The reconciliation table submitted in your amendment dated 6/10/2015 (table 1 of question 10) is unclear, incomplete, and inaccurate. Consider the following recommendations when you revise the reconciliation table and/or submit any new tables.

   a. The table should contain acceptance criteria for actual yield (minimum and maximum of the corresponding theoretical yield) for each phase of production as per CFR 211.186(b)(7).

   b. Provide definitions of the items listed in the first left column of the table, and indicate how they are calculated.

   c. Waste/loss/rejects during manufacturing should be indicated for each step with proper explanation.

   d. The actual yield for formulation (b) (4) should be the amount of solution available for filling plus that used for sampling, excluding any (b) (4).

   e. Provide the actual and theoretical yield for packaging. The actual yield for this step should be (b) (4) (b) (4).

f. The reported [redacted] (b) (4) is incorrect. It should be [redacted] (b) (4) (b) (4)

PRESCRIBING INFORMATION

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* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 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, April 29, 2015, which addresses the proposed proprietary name, Xiidra. 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 deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, 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. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. 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 Christina Marshall, Regulatory Project Manager, at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

John J. Farley, MD, MPH
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
10/16/2015