



NDA 216442

COMPLETE RESPONSE

Aldeyra Therapeutics, Inc.
Attention: David Noskowitz
Regulatory Affairs Consultant
131 Hartwell Ave., Suite 320
Lexington, MA 02421

Dear David Noskowitz:

Please refer to your new drug application (b) (4)
for Reproxalap Ophthalmic Solution, (b) (4).

We acknowledge receipt of your amendment dated (b) (4), which constituted a complete response to our (b) (4), 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. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

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. The application has failed to demonstrate efficacy in adequate and well controlled studies in treating ocular symptoms associated with dry eyes.

After reviewing Study 030, we have identified concerns with the data that make it difficult to interpret the study results. Some of this may be related to methodological issues. These include:

1. Using the Visit 2 data as a comparison to Visit 4 because of accustomization on the part of the subject adds variability to the results. We have no data to understand whether accustomization influences patients consistently.
2. The mean change in the VAS score is influenced directly by the difference in baseline at visit 2 between groups. Because of this, it is unclear the difference in the 80 – 100 mean VAS scores is related to a drug treatment effect.
3. The reproxalap Visit 4 data shows a difference between 80 – 100 minute mean VAS score and baseline of 1.8. This is unexpected when compared to the results of Study 024 and Study 027.

4. It is not clear that the models proposed by you adequately account for the difference in baseline.
5. The difference in the Visit 4 baseline of greater than 7 between raises concerns of whether these reflect similar populations. Ideally, baseline scores between groups should be similar.

You used Visit 2 and Visit 4 DEC results as the dependent variable and performed linear contrasts to obtain treatment differences between Visit 4 and Visit 2 results. The Agency finds the Study 030 primary efficacy endpoint analysis problematic, and we do not find the study results to be robust.

Study 030 was similar in design to Study 024 from the original submission. When Study 030 is analyzed in a similar method to Study 024 from the initial submission (Visit 4 DEC score at each timepoint as the dependent variable), the study does not achieve statistical significance.

You should conduct at least one additional adequate and well controlled study to demonstrate a positive effect on the treatment of ocular symptoms of dry eye. In the conduct of this study, you should not make changes to the protocol or the statistical analysis plan after the first subject is enrolled in the study without expressed agreement by the FDA.

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 Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² 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.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

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 product 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 guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact (b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (4)

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