CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215352Orig1s000

OTHER ACTION LETTERS

NDA 215352

COMPLETE RESPONSE

Eyenovia, Inc.
Attention: Ms. Ginger Clasby
Vice President, Clinical and Regulatory Affairs
295 Madison Avenue
Suite 2400
New York, NY 10017

Dear Ms. Clasby:

Please refer to your new drug application (NDA) dated and December 28, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for MYDCOMBI (tropicamide and phenylephrine hydrochloride ophthalmic spray), 1%/2.5%.

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.

1. 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 do not comply with the current good manufacturing practice regulations in parts 210 and 211, and 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 are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability. During a recent inspection of the (b) (4) drug product 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. Stability data collected from a facility that is not compliant with current Good Manufacturing Practices may not be sufficient to support the stability of your product.

2. The investigations required under section 505(b) of the Federal Food, Drug, and Cosmetic Act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

   a. The (b) (4) microbial ingress container closure integrity testing (CCIT) performed (b) (4) is acknowledged. However, your proposed system has yet to demonstrate the ability to withstand a worst-case

microbial challenge. Please consider the following options to demonstrate the integrity of the assembled device:

i. (b) (4)

ii.

iii.

b. It is acknowledged that the Alcami facility has performed (b) (4) Provide the results of this hold time study.

c. The validation information for (b) (4) is acknowledged. Please address the following:

i. (b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

iv. (b) (4) [redacted]

3. In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product. For each submission for this application, indicate that the product is a combination product in field #24 of the FDA Form 356h. Additionally, please refer to the Guidance for Industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, from Oct 2019. For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product should be included on Form 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.

4. Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

   If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For

further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

5. In your submission, you have stated that the (b) (4) Please clarify the electrical component of your device.

6. In your submission, you have stated that the device is (b) (4) Please clarify the reusability of the device in order to determine if additional testing is needed.

7. In your submission, you have provided a table of planned validation testing. However, no testing has been included and the list of planned testing does not state specifically what is to be tested. Please perform the following validation testing:

   a. You have mentioned conducting transit testing. However, there is no transit testing data included in the submission. Please perform shipping and transit testing mentioned in your submission (ASTM D4169). This is needed in order to ensure a viable product after shipping has consistent performance. Variability of the device after shipping and transit impacts the safety and effectiveness.

b. Actuation force testing should be conducted to demonstrate that the amount of force needed is not excessive as it could impede the ability of the user to deliver the drug formulation and lead to improper dosage which is critical for safety and effectiveness.

c. Leak testing should be performed (b) (4)

d. Performance testing to confirm that the device does deliver (b) (4) of fluid with each actuation and that there is a low variance of volume delivered.

e. Further performance testing to demonstrate consistent performance of the device over the product lifetime. It is important that the device not suffer fatigue over the recommend use life and deteriorate in performance. The deterioration of the device may result in improper or no dosage of the drug formulation.

f. You mention conducting accelerated aging (ASTM F1980). However, there is no testing data included. Furthermore, there is no real-time aging data or real-time aging protocol as well. This is essential to demonstrate consistent performance and stability of the device over the shelf life. The testing to confirm the viability of the device should be a comparison of the previously mentioned performance tests at time point zero and compare it to the testing for devices at the end of the shelf life after undergoing real-time and accelerated aging, sterilization, and transit testing.

8. You have not submitted human factors validation study data to demonstrate that your user interface supports the safe and effective use of your product by the intended users, for intended uses, and in the intended use environment. We recommend you include a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable. The risk analysis can be used to inform the design of a human factors validation study protocol for your product. You can consider submitting your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments

on the HF validation study protocol. Note that submission of a protocol for review is not a requirement. Guidance on human factors procedures to follow can be found in the following guidance documents: Applying Human Factors and Usability Engineering to Medical Devices Guidance on Safety Considerations for Product Design to Minimize Medication Errors.

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 Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] 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 FDA.gov.[3]

CARTON AND CONTAINER LABELING

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

PROPRIETARY NAME

Please refer to correspondence dated, March 15, 2021, which addresses the proposed proprietary name, MYDCOMBI. 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

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[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
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies 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 deficiencies 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 drug 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 Michael Puglisi, Regulatory Project Manager, at michael.puglisi@fda.hhs.gov or at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

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/

WILEY A CHAMBERS
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