CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211950Orig1s000

OTHER ACTION LETTERS

NDA 211950

COMPLETE RESPONSE

Clearside Biomedical, Inc.
Attention: Barbara Bauschka
Senior Director, Regulatory Operations
900 North Point Parkway
Suite 200
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) dated and received December 19, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for XIPERE (triamcinolone acetonide ophthalmic suspension) for suprachoroidal injection.

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.

COMPLETE RESPONSE

1. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing and holding of the drug substance and the drug product must comply with the current good manufacturing practice (cGMP) regulations in 21 CFR 210 and 211. During the pre-approval inspection of (b) (4) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved or alternative manufacturing facilities which are in compliance with cGMPs must be included in the application.

2. There is insufficient information about the drug product to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling. Clinical use data should be submitted to support the use of the final to-be-marketed SCS Microinjector Delivery System. The final to-be-marketed configuration should be evaluated by at least three physicians and in at least 30 patients.

3. Please provide data generated from three new registration batches using the proposed commercial process to demonstrate process robustness and product meeting quality standards of efficacy, stability, and safety. Please provide at least one registration batch with 3 months stability data at long term storage and 3 months stability data at accelerated condition.

4. One or more amendments to your pending application does not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

   Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

   - To add a new indication or other condition of use;
   - To add a new strength;
   - To make other than minor changes in product formulation; or
   - To change the physical form or crystalline structure of the active ingredient.

   If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, you must verify that the proposed change described in the amendment is not one of the types of amendments described above.

   Please provide a list of your amendments submitted to FDA on or after December 5, 2016, clearly referencing each amendment by submission date, and either:

   i. state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

   ii. 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.

   The cover letter for your Complete Response and all future amendments to your unapproved 505(b)(2) application should continue to address the requirements under 21 CFR 314.60(f).

ADDITIONAL COMMENTS

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

5. The drug product is an ophthalmic suspension. We recommend that for quality control purposes, you develop an *in vitro* drug release method and include the dissolution test in the specifications of the product. We recommend that you submit the development and validation report for the proposed *in vitro* drug release method including justifications and enough data supporting the selection of the dissolution testing conditions (equipment/apparatus, in vitro drug release media, agitation/rotation speed, pH, sink conditions, use of surfactant if applicable, etc.). Please provide data/information supporting the discriminating ability of the method with respect to the most relevant critical material attributes (CMAs, e.g., PSD), critical formulation variables, and critical process parameters (CPPs).

6. Update manufacturing process flow diagram to include all individual process step enhancements described below.

(b) (4)

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(b) (4)

[redacted]

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 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 FDA.gov.

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 314.65. 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, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of New Drugs
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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