CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207987Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207987

COMPLETE RESPONSE

Belcher Pharmaceuticals, LLC.
Attention: Mihir Taneja
Vice President
6911 Bryan Dairy Road
Largo, FL 33777

Dear Mr. Taneja:

Please refer to your New Drug Application (NDA) dated and received February 12, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ablysinol (Dehydrated Alcohol Injection, USP).

We have completed our review of this application and have determined that we cannot approve the application at the present time. We describe our reasons for this action below and, where possible, provide suggestions for addressing these issues.

CLINICAL

1. Because the effect of Ablysinol is usually manifest rapidly, we feel confident that it is effective, despite the absence of the usual level of trial evidence. However, we have less good information on instructions for use (particularly dose) and on the expected rates for adverse events. We acknowledge receipt of your proposal dated November 2, 2015, containing your proposed postmarketing study design to address these issues. You are encouraged to initiate the registry while remediating the issues outlined in this Complete Response Letter.

PRODUCT QUALITY

2. From the chemistry, manufacturing and controls (CMC) perspective, NDA 207987 cannot be recommended for approval because of unresolved CMC deficiencies, resulting in the 'withhold' recommendation issued by the Office of Process and Facility for the drug substance manufacturing facility. Additional issues are listed below:

    A. **Drug Product Specification:** You need to provide CMC information concerning the validated analytical methods to be included in the revised drug product specification.

    B. **Drug Product Stability:** In the absence of including quantitative analytical methods for monitoring product attributes, the drug product stability data

provided are inadequate. You will need to generate product stability data using the revised product specification, which includes monitoring product critical quality attributes using validated quantitative analytical methods.

C. **Microbiological Aspects:** You have not adequately specified the number and types of runs that will be performed (b) (4) as part of the revalidation/requalification program for (b) (4) With regard to the endotoxin testing, you have not provided adequate validation information regarding the chromogenic kinetic method.

D. **Labeling:** You need to revise the carton and container labels using the approved trade name.

PRESCRIBING INFORMATION

3. Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you revise your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit 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.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

PROPRIETARY NAME

4. Please refer to correspondence dated, March 30, 2015 which addresses the proposed proprietary name, Ablysinol. 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.

FACILITY INSPECTIONS

5. Our field investigator could not complete inspection of the (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this application may be approved. Please notify us in writing when this facility is ready for inspection.

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.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

The use of Ablysinol during percutaneous transluminal septal myocardial ablation (PTSMA) may cause heart block, cardiac arrhythmias, myocardial infarction, and coronary artery dissection. Because your application for Ablysinol relies heavily on data from publications containing limited safety information, a reliable estimation of these risks is impossible.

Based on the above, FDA has determined that if NDA 207987 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of peri- and post-procedural adverse events following PTSMA with Ablysinol.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 207987 is approved, you will be required to conduct the following:

> *A registry of patients undergoing PTSMA with Ablysinol. The patients will be prospectively enrolled, and data collected on the number and type of peri/post-procedural adverse events attributed to Ablysinol.*

Any additional specific details of this required postmarketing study, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete this study prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

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.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Draft Labeling

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

NORMAN L STOCKBRIDGE
12/09/2015