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APPLICATION NUMBER:

209529Orig1s000

OTHER ACTION LETTERS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209529

COMPLETE RESPONSE

Astellas Pharma US, Inc.
Attention: Jennifer M. LaMora
Associate Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Ms. LaMora:

Please refer to your New Drug Application (NDA) dated February 28, 2017, received February 28, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for solifenacin succinate oral suspension, 1 mg/mL.

We have completed our review of this application 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.

Deficiencies:

1. During a recent 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.
2. The quality of (b) (4) as currently supplied by (b) (4) (U) (4) is not adequately controlled, resulting in drug product batches that do not meet the proposed drug product specification.
3. The drug product specification and post-approval stability program do not include the test methods and acceptance criteria to demonstrate that the product is free, and remains free, of the objectionable microorganisms in the (b) (4).

Information Needed to Address the Deficiencies:

To address the first two deficiencies, submit the following information:

- Results from the ongoing (b) (4) characterization studies, including a summary of your investigations and the corrective and preventive actions taken to address the root cause.

- Establish and validate additional tests and acceptance criteria (b) (4).
- Batch analyses from three verification/validation batches demonstrating that drug product manufactured with (b) (4) meeting the NF and additional quality requirements, has the requisite quality (e.g., viscosity). Include executed batch records from the validation batches along with the validation protocol and the final summary report.

If suitable additional controls for (b) (4) cannot be identified and validated or if (b) (4) is unable to supply (b) (4) that meets the enhanced raw material specification, revision of the acceptance criteria for drug product viscosity may be proposed. Along with a justification for revising the (b) (4) limit, confirm, with release and stability data, that drug product quality and performance, including homogeneity, is not adversely impacted.

To address the third deficiency,

- Revise the drug product specification to include the test method(s) and acceptance criteria to assure that the product is free of the objectionable microorganisms in the (b) (4). Update the relevant sections of the application accordingly.
- Revise the post-approval stability program to include testing to confirm the absence of (b) (4).

ADDITIONAL COMMENTS

- Update *Table 12, Specifications for Solifenacin Succinate Oral Suspension* (in Module 2.3.P Drug Product Quality Overall Summary), to reflect that the microbial limit tests will be performed on every batch.
- Under the Best Pharmaceuticals for Children Act (BPCA) (21 U.S.C. 355a), FDA will publish a notice identifying any drug for which, on or after the date of the enactment of the BPCA of 2007, a pediatric formulation was developed, studied, and found to be safe and effective in the pediatric population (or specified subpopulation) that is not introduced onto the market. Such an action will be taken if the pediatric formulation for this drug is not marketed within one year of our public notification granting exclusivity on August 10, 2017.

PRESCRIBING INFORMATION

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 develop 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.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on our proposed revisions dated May 3, 2017, and May 24, 2017.

PROPRIETARY NAME

Please refer to correspondence dated, May 24, 2017, which addresses the proposed proprietary name, VESIcare LS. 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

During a recent inspection of the (b) (4) 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.

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 in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application 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 application 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.

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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.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 Nenita Crisostomo, Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, M.D.
Acting Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Labeling

18 Pages of Draft Labeling have been Withheld in Full as
B4(CCI/TS) Immediately Following this Page

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

/s/

CHRISTINE P NGUYEN
08/28/2017