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RESEARCH**

APPLICATION NUMBER:

204734Orig1s000

OTHER ACTION LETTERS



NDA 204734

COMPLETE RESPONSE

Shire Development, LLC
Attention: Sabrina R. Girty, JD
Director, Global Regulatory Affairs
725 Chesterbrook Blvd
Wayne, PA 19087

Dear Ms. Girty:

Please refer to your New Drug Application (NDA) dated February 28, 2013, received February 28, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate) Oral Powder 750 mg and 1000 mg.

We acknowledge receipt of your amendments dated March 15, April 10, May 15, June 26, July 15, September 5, 18, October 2, November 1, 18, December 5 and 20, 2013.

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.

PRODUCT QUALITY

1. The provided dissolution method development data do not support the selection of (b) (4)% Tween 80 as the surfactant concentration in the dissolution medium of proposed method PA E-086 and is not acceptable. The provided dissolution profiles with lower Tween 80 concentrations showed complete dissolution (e.g., (b) (4)% dissolution in (b) (4) minutes with (b) (4)% surfactant) and are likely to demonstrate adequate discriminating power.
2. Necessity for the (b) (4) rpm agitation speed for the proposed dissolution method PA E-086 has not been established. Data for the alternative paddle speed of (b) (4) rpm were only provided with (b) (4)% surfactant and the results indicate that (b) (4) rpm suffices there, so it may also suffice at lower surfactant levels, too.
3. The formulation approach adopted in the investigation of the discriminating ability of the proposed dissolution method is not acceptable. (b) (4)
(b) (4) applicable to this product and should be investigated for its impact on the discriminating ability after the dissolution method has been modified as appropriate.

In summary of the above items 1-3:

- Conduct further experiments with paddle speeds of 50 and 75 rpm (as needed) and surfactant concentrations of 0.25%, 0.5%, 0.75%, and 1% Tween 80. Provide the individual vessel data at 15, 20, 30, 45, and 60 minutes and the descriptive statistics. Also provide the individual dissolution plots, including the mean dissolution profiles for both 50 and 75 rpm at each surfactant concentration in each individual plot.
 - Based on the results from the above, revise (as appropriate) the dissolution method for your drug product.
 - Provide the complete dissolution profile data from the new experiments investigating the discriminating power of the revised dissolution method.
4. Using the revised dissolution method, collect dissolution profile data (15, 20, 30, 45, and 60 minutes, n=12) from the registration and other available stability batches at the current stability time points. Provide the individual vessel data and the descriptive statistics. Based on the overall data, submit a proposal for the dissolution acceptance criterion of your drug product.

LABELING

6. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(1)(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 Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

7. Please submit draft carton and container labeling revised as follows:

Carton Labeling

- 1) Increase the prominence of the “Mix with small quantity... immediately” statement by using bold font
- 2) Debold the net quantity “9 cartons, each carton...” and “10 stick packs” statements.
- 3) Revise the equivalency statement in the “Active Ingredient” section of back panel to read:
750 mg carton: “Each stick pack contains 1431 mg lanthanum carbonate hydrate equivalent to 750 mg lanthanum”
1000 mg carton: “Each stick pack contains 1908 mg lanthanum carbonate hydrate equivalent to 1000 mg lanthanum”

Foil Label

- 1) Increase the font size of the proprietary name, established name, and strength for increased prominence. In addition, decrease the size of the company logo.

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.

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. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 the 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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Draft Labeling

10 Page(s) 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/

NORMAN L STOCKBRIDGE
12/24/2013