CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-542Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

COMPLETE RESPONSE

Axcan Pharma U.S., Inc.
Attention: Guy Rousseau, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
22 Inverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) dated October 29, 2009, received October 30, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viokace (pancrelipase) Tablets.

We acknowledge receipt of your amendments dated October 30, 2009, November 2, 2009, November 19, 2009, November 23, 2009, November 27, 2009, December 11, 2009, January 27, 2010, January 28, 2010, March 1, 2010, March 9, 2010, March 22, 2010, May 27, 2010, June 21, 2010, June 30, 2010, July 8, 2010, July 9, 2010, July 12, 2010, August 13, 2010, August 20, 2010, August 27, 2010, September 15, 2010, September 17, 2010, and October 8, 2010.

We also acknowledge receipt of your amendments dated October 26, 2010, November 19, 2010, and November 23, 2010, which received a preliminary review for this action. You may incorporate these amendments by specific reference as part of your response to the deficiencies cited in this letter.

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. [redacted] (b) (4) DMF [redacted] (b) (4) has been reviewed in support of NDA 022542 and found to contain deficiencies. A letter dated October 27, 2010, was sent to [redacted] (b) (4) listing several deficiencies regarding the drug substance manufacturing process. FDA conveyed additional information requests at a face-to-face meeting held on November 15, 2010, with you and representatives from [redacted] (b) (4) should address all deficiencies by directly submitting information to their DMF, or, if the information was previously submitted, then by specific reference to the appropriate submissions. Please notify us when [redacted] (b) (4) has submitted the requested information. Satisfactory resolution of the deficiencies identified is required before this application may be approved.

FACILITY INSPECTIONS

2. During an inspection of a manufacturing facility referenced in this application, [redacted] conducted between [redacted] and [redacted] the FDA investigator conveyed deficiencies to a representative of the facility. [redacted] response dated [redacted], addressing the deficiencies listed on FDA form 483 dated [redacted], was not adequate. Satisfactory resolution of these deficiencies is required before this application may be approved.

LABELING

3. Please submit draft labeling revised as follows:

   A. Package Insert

      i. Per the insert labeling, you have proposed imprinting the [redacted] on the 10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease strength tablets. However, we note that the [redacted] We recommend that you remove the imprinted [redacted] replace it with an imprint code.

   Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling 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.

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

   A. RETAIL CONTAINER LABELS (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)

      i. Per 21 CFR 201.6 and the United States Pharmacopoeia, 10/1/10-2/1/11, USP 33/NF 28 Monograph-Pancrelipase Tablets, please remove the statement, [redacted] which follows the established name. [redacted] does not appear in the Official USP monograph title for this product.

ii. As currently presented, the font utilized for the established name appears to be too thin. Revise the established name to be in accordance with 21 CFR 201.10 (g)(2) so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

B. RETAIL CARTON LABELING (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/ 39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)

i. Per 21 CFR 201.6 and the United States Pharmacopoeia, 10/1/10-2/1/11, USP 33/NF 28 Monograph-Pancrelipase Tablets, please revise the established name from (b) (4) to (pancrelipase) Tablets. (b) (4) does not comply with the official USP monograph title for Pancrelipase Tablets per the United States Pharmacopoeia, 12/1/09-10/1/10, USP 32/NF 27 and 10/1/10-2/1/11, USP 33/NF 28.

ii. As currently presented, the "Axcan Pharma" logo on the principle display panel appears large and is more prominent than the strength presentation. Minimize or remove this logo.

iii. See comment 3(A)(ii) above.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS will be necessary for Viokace (pancrelipase), if it is approved, to ensure that the benefits of the drug outweigh the possible risks of fibrosing colonopathy and transmission of viral disease to patients. The REMS, should it be approved, will create enforceable obligations.

We acknowledge receipt of your proposed REMS, included in your submission dated October 29, 2009, amended on August 20, 2010 and September 17, 2010, which contains a Medication Guide, and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA 22542**."

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

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.

An unexpected serious risk of pancreatic enzyme products (PEPs) including Viokace (pancrelipase) Tablets in patients with chronic pancreatitis or pancreatectomy is fibrosing colonopathy (a stricture process of the colon); the magnitude of this risk in these patients is unknown. In addition, there is an unexpected serious risk of transmission of viral disease to patients from porcine-derived PEPs such as Viokace (pancrelipase) Tablets.

Based on the above, FDA has determined that if NDA 022542 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the unexpected serious risks of fibrosing colonopathy and transmission of viral disease to patients taking Viokace (pancrelipase) Tablets.

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

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 022542 is approved, you will be required to conduct the following:

1. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with chronic pancreatitis or pancreatectomy treated with Viokace (pancrelipase) Tablets in the US and to assess potential risk factors for the event.

2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Viokace (pancrelipase) Tablets.

Any additional specific details of these required postmarketing studies, 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 one or both of these studies prior to re-submitting your application, you may include the final report(s) 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 314.65. 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's "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, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JULIE G BEITZ
11/28/2010