

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125293

OTHER ACTION LETTERS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125293/0

COMPLETE RESPONSE

Savient Pharmaceuticals, Inc.
One Tower Center Boulevard
14th Floor
East Brunswick, NJ 08816

July 31, 2009

Attention: Murad Husain
Vice President of Regulatory Affairs

Dear Mr. Husain:

Please refer to your biologics license application (BLA), dated and received October 31, 2008, submitted under section 351 of the Public Health Service Act, for Krystexxa (pegloticase).

We acknowledge receipt of your amendments dated November 14 and December 5, 9, 22, and 30, 2008, and January 16 and 28, February 4, 6, and 27, March 10 and 19, April 3, 8, 21, 22, and 29, May 12, June 11, 18, 22, 23, 25, and 26, and July 9, 10, and 17, 2009.

The February 4, 2009, amendment constituted a major amendment.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY (CHEMISTRY, MANUFACTURING AND CONTROLS)

1. Based on the data you have provided in the submission, and in subsequent information request amendments, we have concluded that the material manufactured with the commercial process is not representative of the Phase 3 material used to establish the safety and efficacy profile of pegloticase. Products manufactured with the two processes differ in terms of (b) (4) and we cannot assess the impact of these differences on clinical safety and efficacy. Additional clinical studies are necessary to support the use of pegloticase manufactured with the commercial process or, alternatively, you may validate the Phase 3 process for commercialization.
2. Your release testing program for drug substance and drug product is inadequate. Specifically, we have the following requests and comments:

- a. Include peptide mapping to assess lysine site occupancy with PEG and develop acceptance criteria for the lysine most frequently occupied.
 - b. Tighten acceptance criteria to reflect the manufacturing history, process capability, and clinical experience for K_m , k_{cat} , (b) (4)
(b) (4)
 - c. Include an assay(s) that monitors drug substance and product degradation.
 - d. Include an appropriate identity test such as peptide mapping or N-terminal sequencing.
 - e. You did not appropriately validate removal of (b) (4); therefore, include an assay to measure (b) (4) in your drug substance testing program.
3. Your stability program for drug substance and drug product is inadequate. Specifically, we have the following requests:
- a. Provide updated acceptance criteria that reflect the manufacturing history, process capability, and clinical experience for K_m , k_{cat} , (b) (4) (b) (4)
 - b. Include an assay(s) that monitors drug substance and product degradation.
 - c. Include an appropriate identity test such as peptide mapping or N-terminal sequencing.
4. Your release testing program for the uricase intermediate is inadequate. Specifically, we have the following requests:
- a. Develop acceptance criteria for each peak identified in the RP-HPLC assay.
 - b. Include an appropriate identity test for the uricase intermediate (e.g., peptide mapping or N-terminal sequence).
 - c. Tighten the acceptance criteria for K_m and k_{cat} .
5. The stability program for your reference standard is inadequate. Include measurements of potency using specific activity and K_m and k_{cat} , and establish acceptance criteria for these tests.
6. A robust qualification program should be developed for your reference standard. The protocol should include release and characterization assays, and acceptance criteria/limits should be established to minimize variations and drift of the reference standard.

7. You have not addressed the effects of leachables and extractables on the quality of your product. Provide studies that investigate the effect of material released by storage containers and container closures on uricase intermediate, drug substance, and drug product.
8. The in-use stability study you have conducted on drug product following dilution in infusion bags is inadequate. Perform additional studies to address protein aggregation and degradation.
9. In regard to your analytical techniques, we have the following comments and requests:
 - a. Your SDS-PAGE does not provide adequate control for destaining. Implement a system suitability control for the SDS-PAGE and establish quantitative acceptance criteria for the major band and additional bands.
 - b. The percent mean recovery of (b) (4) in the drug substance release testing, as assessed by the ELISA assay, is low. Redevelop the ELISA assay to increase recovery and, hence, improve assay accuracy.
 - c. During validation of the SEC-HPLC assay, the recovery of dimers and high molecular weight forms was 75-85% and 49-55%, respectively. Improve the accuracy of the SEC-HPLC method for the detection of high molecular weight species.
 - d. You have not provided sufficient information to characterize the antibody used in the assay that measures Host Cell Protein (HCP) at release. Provide data to support the suitability of the assay to detect HCP.

(b) (4)

11. Develop an assay to measure sub-visible protein particulates in the (b) (4) range, and include it in your release and stability protocols.
12. Interim bioburden action limits for column eluates from in-process steps were not established. The interim bioburden action limits for all in-process steps should be specified.
13. You have not provided data from at least three lots of pegloticase that demonstrate that the manufacturing process is able to meet reasonable standards for microbial control. Provide data from at least three lots of pegloticase that demonstrate that the manufacturing process is able to meet the interim bioburden and endotoxin limits.

14. The hold times for crude uricase and uricase intermediate have not been adequately validated. Conduct a hold time validation study of crude uricase and uricase intermediate using three production-scale runs that are tested for bioburden and endotoxin before and after the claimed hold time.
15. You did not conduct a hold time validation study of the column eluates. Conduct a hold time validation study of the (b) (4) column eluates using three production scale runs that are tested for bioburden and endotoxin before and after the claimed hold time.
16. You did not conduct a growth promotion study for the final formulation buffer. Conduct a growth promotion study for the final formulation buffer.
17. Your buffer hold time studies were inadequate. Conduct buffer hold time studies using a bracketing approach for buffer selection and include measurement of endotoxin as well as other microbial and biochemical parameters.
18. The shipping validation for shipment of bulk drug substance is inadequate. Conduct a study to validate the shipping practices for bulk drug substance from BTG to Enzon. This study should evaluate the temperature of at least three packed shipping boxes of material for both the summer and winter conditions.
19. The current selected small shipper for finished product vial did not meet the pre-determined temperature acceptance criteria in shipping validation studies. Develop and validate a shipper that is suitable to transport the finished product vials within the continental United States. The worst-case conditions should be used in the shipper validation studies.

LABELING

Submit draft package insert labeling that incorporates the revisions in the enclosed draft labeling. We reserve further comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include 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>.

Submit draft carton and container labels that incorporate the proprietary name Krystexxa.

FACILITY INSPECTIONS

During the pre-license inspection of BioTechnology General (Israel), Ltd., the manufacturer for drug substance for this application, the inspection team conveyed deficiencies to the representative of the facility. Satisfactory inspection reports for all facilities are required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies 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 for the proposed indication using the same format as the initial submission.
 - Present tabulations of the new safety data combined with the initial data.
 - Include tables that compare frequencies of adverse events in the initial data 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 study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 initial data.
6. Provide updated exposure information for the clinical 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Krystexxa (pegloticase) to ensure that the benefits of the drug outweigh the risks of severe infusion reactions and anaphylaxis, severe adverse events associated with use of Krystexxa (pegloticase) in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and major cardiac events. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR part 208. Pursuant to 21 CFR part 208, FDA has determined that Krystexxa (pegloticase) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Krystexxa (pegloticase). FDA has determined that Krystexxa (pegloticase) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Krystexxa (pegloticase).

Under 21 CFR part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Krystexxa (pegloticase).

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Krystexxa (pegloticase) will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about the risks of severe infusion reactions and anaphylaxis, severe adverse events associated with use of Krystexxa (pegloticase) in individuals with G6PD deficiency, and major cardiovascular events.

The communication plan must include, at minimum, the following:

- Dear Healthcare Provider letters describing safety concerns with Krystexxa (pegloticase) and key aspects of recommended management for prescribers and infusion center medical personnel
- Non-promotional print service announcements describing safety concerns with Krystexxa (pegloticase) and key aspects of recommended management. Such announcements could be published in rheumatology journals
- Non-promotional information about safety concerns with Krystexxa (pegloticase) and key aspects of recommended management at major internal medicine and rheumatology meetings.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 1 year, 2 years, 3 years, and 5 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the

planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31 should conclude no earlier than June 1.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Enclosed is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Krystexxa (pegloticase). Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an enclosure to the approval letter that includes the REMS.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

(b) (4)



Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked-up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125293
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125293
PROPOSED REMS-AMENDMENT**

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

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed 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 can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm153222.pdf>).

Please refer to <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Diana L. Walker, Ph.D., Regulatory Project Manager, at 301-796-4029.

Sincerely,



Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

- Appendix A: REMS Template
- Appendix B: Supporting Document
- Package Insert Label
 - Clean Copy
 - Track-changes Copy

42 Pages of Draft Labeling has been withheld in full immediately following this page as B4
(CCI/TS)