DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125293/S-034
BLA 125293/S-040

SUPPLEMENT APPROVAL
REMOVE REMS ELEMENT

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

Attention: Murad Hussain
Vice President, Regulatory Affairs

Dear Mr. Hussain:

Please refer to your Supplemental Biologics License Applications (sBLA), dated September 14, 2011, received September 14, 2011, and dated December 9, 2011, received December 9, 2011, submitted under section 351 of the Public Health Service Act for Krystexxa (pegloticase).

We acknowledge receipt of your amendments dated December 20, 2011, February 24, and April 6, and 12, 2012, and your risk evaluation and mitigation strategy (REMS) assessment dated September 14, 2011.

Supplement 125293/S-034 to your biologics license application contains your assessment of the Krystexxa (pegloticase) risk evaluation and mitigation strategy (REMS).

Prior Approval supplement 125293/S-040 to your biologics license application proposes to revise the package insert (PI) and the Medication Guide (MG) to incorporate important treatment guidance related to concomitant use of oral urate lowering agents. This supplement also proposes to eliminate the required MG as an element of the approved Krystexxa (pegloticase) REMS and to modify the REMS to include revised safety information.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the

labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125293/S-040**."

Also within 14 days, amend all pending supplemental applications for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Krystexxa (pegloticase) was originally approved on September 14, 2010, and the most recent REMS modification was approved on October 19, 2010. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of eliminating the requirement for the Medication Guide as an element of the REMS, and revisions to the REMS document and the appended REMS materials as follows:

- Removal of the REMS goal "to inform patients about the serious risks associated with the use of Krystexxa," to be consistent with removal of the Medication Guide as an element of the REMS
- Inclusion in the healthcare professional letters, journal information pieces, and Krystexxa web pages of new safety information about increased risk of anaphylaxis and infusion reactions with concomitant use of Krystexxa and oral urate-lowering therapy.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of the Krystexxa (pegloticase) outweigh the risks.

Therefore, we agree with your proposal, and a Medication Guide is no longer required as part of the REMS for Krystexxa (pegloticase).

Your proposed modified REMS, submitted on February 24, 2012, and appended to this letter, is approved.

The modified REMS consists of a communication plan, and a timetable for submission of assessments of the REMS.

We remind you that the Medication Guide will continue to be part of the approved labeling for Krystexxa (pegloticase) in accordance with 21 CFR 208.

The timetable for submission of assessments of the REMS will remain the same as that approved on September 14, 2010.

The revised REMS assessment plan should include, but is not limited to, the following:

a. Healthcare providers' understanding (i.e., surveys) of the serious risks of KRYSTEXXA (pegloticase).

b. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.

c. Periodic summaries of adverse reporting of infusion reactions, including an analysis of anaphylaxis and whether appropriate therapy was instituted promptly.

d. With regard to communication plan:

    1. Date of product launch and launch of the communication plan.

    2. The date(s) of mailing of the Dear Healthcare Provider letter (DHCP) and the Dear Infusion Site Medical Personnel letter (DISMP).

    3. The number of DHCP and DISMP letters sent.

    4. Number of mailings returned.

    5. Sources of the recipient lists.

    6. The dates of the annual meetings attended and number of materials distributed.

    7. The names of the journals that published the Journal information piece and the dates of publication.

e. Information on the status of any postapproval study or clinical trial required under section 505(o)(3) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS

assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125293 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 125293 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125293
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125293
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Colette Jackson, Senior Regulatory Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Sally Seymour, M.D.
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

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

/s/

SALLY M SEYMOUR
04/16/2012