



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

Our STN: BL 125293/0

**BLA APPROVAL**  
September 14, 2010

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

Attention: Steve Hamburger, Ph.D.  
Group Vice President, Quality and Regulatory Affairs

Dear Dr. Hamburger:

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) Injection, for intravenous infusion.

We acknowledge receipt of your amendments dated November 14 and December 5, 9, 22, and 30, 2008, 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, and March 15, April 23, June 1, 7, and 16, July 2 and 28, August 4, and September 2 (2) 3, 8(2), 9 and 14, 2010.

The March 15, 2010, submission constituted a complete response to our July 31, 2009, action letter.

We are issuing Department of Health and Human Services U.S. License No. 1801 to Savient Pharmaceuticals, East Brunswick, New Jersey, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce into, or deliver for introduction into, interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product pegloticase. Pegloticase is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Under this license, you are approved to manufacture pegloticase drug substance at BTG, Ltd., in Kiryat Malachi, Israel. The final formulated product will be manufactured, filled, labeled, and packaged at Enzon Pharmaceuticals, Inc., Indianapolis, Indiana. You may label your product with the proprietary name Krystexxa and market it in vials containing (b) (4) of pegloticase corresponding to 8 mg uricase protein conjugated to 24 mg of 10 kDa mPEG.

The dating period for pegloticase shall be 24 months (2 years) from the date of manufacture when stored at 4° to 8°C. The date of manufacture shall be defined as the date of (b) (4) (b) (4) the formulated drug product. The dating period for your drug substance shall be 6 months when stored at 2° to 8°C. The dating period for the uricase intermediate shall be 54 days when stored at 2° to 8°C.

You are not currently required to submit samples of future lots of pegloticase to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of pegloticase, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

### **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 [21 601.14(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 and Medication Guide. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. For administrative purposes, designate this submission “**Product Correspondence – Final SPL for approved BLA STN 125293/0.**”

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.

### **CARTON AND IMMEDIATE-CONTAINER LABELS**

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications*

*and Related Submissions Using the eCTD Specifications.* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125293/0.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product has an orphan drug designation for this indication, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of severe infusion reactions, anaphylaxis, and immune complex-related adverse events, as well as to identify unexpected risks related to fertility, pre-, peri-, and post-natal development, and cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart.

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 is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. An observational safety study enrolling 500 patients treated with Krystexxa (pegloticase) for one year duration. Patients enrolled should have hyperuricemia and gout and be refractory to standard uric acid-lowering therapies (e.g., allopurinol). The study should include the following objectives:

- a. An evaluation of the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events.
- b. Identification of serious adverse events associated with Krystexxa (pegloticase) therapy.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: February 2011  
Study Completion Date: July 2015  
Final Report Submission: December 2015

2. Conduct a male and female fertility study in rats per ICH-S5A and ICH-S5B.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 2011  
Study Completion Date: November 2011  
Final Report Submission: June 2012

3. Conduct an embryo-fetal development study in the rabbit model (Segment 2) according to ICH-S5A guidance.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission (Main Study): September 2011  
Study Completion (Main Study): March 2012  
Final Report Submission (Main Study): September 2012

4. Conduct a peri-natal and post-natal development study in the rat model (Segment 3)

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 2011  
Study Completion: February 2012  
Final Report Submission: October 2012

5. Conduct an 18-month study in dogs to evaluate the impact of cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: May 2011  
Study Completion Date: November 2012  
Final Report Submission: July 2013

6. The current anti-PEG antibody ELISA shows a very high degree of intra-and inter-assay variability possibly related to the PEG coating of the ELISA plate. This indicates either that the assay is not sufficiently optimized or that the format is unsuitable. Redevelop the anti-PEG antibody assay to address these concerns.

Final Report Submission: April 2011

7. The sensitivity of your IgE assay, as currently designed, is insufficient to detect IgE antibodies to the product. For an antigen-specific IgE assay to be useful, it should have sensitivity in the nanogram to sub-nanogram range, and there are technologies currently available that can meet this criterion. Develop a more sensitive antigen-specific IgE assay. Consider using ECL technology.

Final Report Submission: October 2012

8. Your IgE assay was not properly validated due to a lack of positive control antibody. Develop a suitable positive control for the IgE ELISA. Cross-linking the current rabbit polyclonal to a human IgE may be an option.

Final Report Submission: January 2012

Submit the protocols to your IND 010122, with a cross-reference letter to this BLA 125293. Submit all final reports to your BLA 125293. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments in your submission dated September 14, 2010. These commitments are listed below.

9. Revise the acceptance criteria for the peptide map assay used to quantify Krystexxa lysine site occupancy with PEG molecules, to specify a numerical range for all the polypeptides identified. Submit the new acceptance criteria for the assay.

Final Report Submission: September 2012

10. Conduct a study to evaluate the sensitivity of the LC-MS Peptide Mapping Assay to detect over- and under-pegylated uricase molecules and submit the results.

Final Report Submission: January 2011

11. Reevaluate the release criteria for the following assays. Submit the revised acceptance criteria and supporting data for the drug substance and drug product after 30 lots of Krystexxa (pegloticase) are manufactured.

- a. Enzymatic activity
- b.  $K_m$  and  $k_{cat}$  determination by product accumulation and substrate depletion
- c. Monomer and HMW forms by SEC-HPLC Abs<sub>220</sub>
- d. Monomer HMW and LMW forms by Abs<sub>214</sub>

Final Report Submission (for release acceptance criteria): Sept 2012

12. Reevaluate the stability acceptance criteria for the following assays. Submit the revised criteria and supporting data for the drug substance and drug product after 30 lots of Krystexxa (pegloticase) are manufactured.

- a. Enzymatic activity assay
- b.  $K_m$  and  $k_{cat}$  determination by product accumulation and substrate depletion assay
- c. Monomer and HMW forms by SEC-HPLC Abs<sub>220</sub> assay
- d. Monomer HMW and LMW forms by Abs<sub>214</sub> assay.

Final Report Submission (for stability acceptance criteria): June 2013

13. Develop and implement an enzymatic assay, based on product accumulation that determines  $K_m$  and  $k_{cat}$  values for release of uricase intermediate and submit the new specification and supporting data.

Validation Report Completion: June 2011  
Final Report Submission (Acceptance Criteria): December 2012

14. Include stress conditions in the annual stability program for drug substance and drug product. Submit the revised stability protocols.

Final Protocol Submission: January 2011

15. Evaluate in-use stability of the drug product by assessing the impact dilution of 1.0 mL drug product (pH 7.0) into 250 mL saline solution with the worst case scenario pH (4.5) has on the final pH of the infusion solution. Submit the results of the study and risk mitigation strategies if the final pH is below 6.2.

Study Completion Date: April 2011  
Final Report Submission: July 2011

16. Provide the results of aseptic fill validation and results of stability studies on three batches of Krystexxa (pegloticase) held for at least six months to support the reduction of the drug product vial overfill to that recommended in the USP.

Final Protocol Submission: November 2010  
Study Completion Date: March 2011  
Final Report Submission: January 2012

Submit clinical protocols to your IND 010122 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA 125293. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA 125293. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the 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)). The details of the REMS requirements were outlined in our complete response letter dated July 31, 2009.

Your proposed REMS, submitted on September 14, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

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

- a. An evaluation of the patients' and prescribers' understanding of the serious risks of Krystexxa (pegloticase).
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance with 21 CFR 208.24.
- d. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.
- e. Summaries of adverse event reporting of infusion reactions, including an analysis of anaphylaxis, and whether appropriate therapy was instituted.
- f. With regard to the communication plan:
  1. The dates of product launch and the launch of the communication plan
  2. The date(s) of mailing and number of recipients of the Dear Healthcare Provider letter (DHCP) and the Dear Infusion Site Medical Personnel letter (DISMP).
  3. The number of mailings returned.
  4. The sources of the recipient lists.  
The dates of the annual meetings attended and number of materials distributed.
  5. The names of the journals that published the journal information piece and the dates of publication.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any post approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post approval 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 updates to the status information since the annual report was prepared. Failure to comply with the REMS assessment provisions in section 505-1(g) could result in enforcement action.

We remind you that 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.



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

**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 five copies of REMS-related submissions.

### **REPORTING REQUIREMENTS**

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding, and distribution. If the deviation

involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
10903 New Hampshire Avenue, Bldg. 51, Room 4206  
Silver Spring, MD 20992-0002

### **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 to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, 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 Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (e.g., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

**POST-ACTION FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Ramani Sista, Regulatory Project Manager, at (301) 796-1236.

Sincerely,

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

Enclosures:

Package Insert with Medication Guide  
REMS documents  
Carton and Container Labels