# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**125293**

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

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| **Date** | September 2, 2010 |
| **From** | Sarah Okada, M.D. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA #**<br>**Supplement#** | BLA 125293/Complete Response Submission |
| **Applicant** | Savient Pharmaceuticals, Inc. |
| **Date of Submission** | March 15, 2010 |
| **PDUFA Goal Date** | September 14, 2010 |
| | |
| **Proprietary Name / Established (USAN) names** | Krystexxa™ / Pegloticase |
| **Dosage forms / Strength** | IV/8 mg |
| **Proposed Indication(s)** | 1. Treatment of chronic gout in patients refractory to conventional therapy |
| **Recommended:** | *Approval* |

## 1. Introduction

Krystexxa (pegloticase) is a PEGylated porcine/baboon urate oxidase produced in E. coli, intended "to control the clinical consequences of hyperuricemia in patients with severe gout in whom conventional therapy is contraindicated or has been ineffective;" an indication granted orphan designation in 2001. BLA 125293 was originally submitted 10-3-08, and received a Complete Response action on 7-31-09 because of multiple product quality/manufacturing issues. The major issue resulting in the Complete Response (CR) was that the manufacturing process was changed after Phase 3, (b) (4) the to-be-marketed formulation compared to the Phase 3 material. Thus the products made by these 2 processes were not comparable in terms (b) (4) (b) (4). In order to address this deficiency, the Applicant reverted back to the Phase 3 material process (named Process C) (b) (4) Three validation runs have been performed, and a comparability study was performed comparing Process C product with the Phase 3 process material. These results were submitted with the CR resubmission.

Other major issues included multiple deficiencies in microbial control processes for the drug substance and an unacceptable facilities inspection of Bio-Technology General Ltd. in Israel, which is responsible for drug substance (DS) manufacturing, as well as release-testing for the DS and the drug product (DP). This facility was inspected June 3-10, 2009 and was classified Official Action Indicated (OAI).

No nonclinical, clinical pharmacology/biopharmaceutics, or clinical issues precluded approval in the first cycle of BLA 125293, although certain issues of note were identified and discussed at Advisory Committee (June 16, 2009). These are summarized below, and the reader is also referred to the first-cycle reviews for further detail. In addition to the information addressing

the product quality deficiencies, this CR resubmission contains approximately 13 additional months of clinical safety data that have accrued since the 1st cycle 120-day safety update.

## 2. Background

Humans and higher apes do not possess the metabolic pathway by which most other animals handle uric acid—i.e., creation of allantoin by oxidation of uric acid, using urate oxidase. Intravenous rasburicase, a recombinant urate oxidase produced by a genetically modified Saccharomyces cerevisiae strain (and initially cloned from a strain of Aspergillus flavus), was approved July 12, 2002 for the indication of "initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid." It is now also approved for adults with a similar indication. Repeated use of rasburicase is limited by the immunogenic responses to it, which can result in serious infusion reactions, hypersensitivity and anaphylaxis; pegloticase was developed as a PEGylated product in the hopes of reducing the immunogenic response.

The clinical trials submitted in support of this application were two replicate, randomized Phase 3 trials in gout patients who had failed or who were intolerant to allopurinol, one of which (Study C0405) was the subject of a Special Protocol Assessment (SPA) agreement (May 3, 2006). Patients were randomized 2:2:1 to pegloticase 8 mg IV every 2 weeks, pegloticase 8 mg IV every 4 weeks or placebo, respectively. As noted in the first-cycle clinical reviews, these two trials demonstrated convincing evidence of the efficacy of IV pegloticase over placebo for the primary endpoint of lowering serum uric acid to less than 6 mg/dL.

The primary safety issues of concern pertained to the risk of serious infusion reactions, hypersensitivity/anaphylaxis, and an imbalance of cardiovascular serious adverse events. During the first cycle, these issues were discussed in the context of pegloticase's efficacy and the underlying patient population at the Arthritis Advisory Committee meeting of June 16, 2009. The panel for this meeting included members of the Cardiovascular and Renal Drug Products Advisory Committee and the Drug Safety Advisory Committee. The panel voted 14 to 1 in favor of approval. Although there was no consensus from the panel regarding whether the imbalance of cardiovascular SAE represented a true signal, there was general agreement that additional postmarketing safety information in this regard should be collected, possibly via an observational epidemiologic study. Panel members also considered it important to limit the use of the product to patients who were truly refractory to conventional therapy. There was also support for a sponsor proposal to incorporate instructions in labeling regarding cessation of treatment when uric acid rises above 6 mg/dL in order to minimize the risk of infusion reactions. These issues will be discussed in further detail below.

## 3. CMC/Device

*Product Quality Review Team: Howard Anderson, Ph.D.—drug substance, Richard Ledwidge, Ph.D.—drug product, Emanuela Lacana, Ph.D. and Gibbes Johnson, Ph.D., team leaders Office of Compliance, Manufacturing Assessment and Pre-Approval Compliance Branch reviewers: Bo Chi, Ph.D., Patricia Hughes, Ph.D., team leader*

- **General product quality considerations**

Pegloticase is a pegylated recombinant uricase (urate oxidase) produced in Escherichia Coli. (b) (4) modified by (b) (4) and inclusion of baboon uricase sequences (b) (4) and transformed into E. Coli to generate the cell bank.

Uricase is a homotetrameric molecule of 136.8 kDa, with each monomeric subunit comprised of a (b) (4) and a molecular weight of 34.2 kDa. The homotetramer is (b) (4). An average of 9 molecules of PEG are attached per monomeric subunit (36/tetramer), for an estimated molecular weight of (b) (4) for the pegylated homotetramer.

The drug product is supplied as a sterile, clear, colorless solution for intravenous infusion. Each single-use vial contains 8 mg of uricase protein and 24 mg of monomethoxypoly (ethylene glycol) (mPEG). Pegloticase is formulated with disodium hydrogen phosphate dehydrate, sodium hydrogen phosphate dehydrate, sodium chloride and water for injection (WFI). KRYSTEXXA™ is packaged in 2-ml Type I (b) (4) glass vials, stoppered with a (b) (4) grey Teflon 13 mm stopper and sealed with an aluminum cap with a purple flip off cap. A drug product shelf life of 24 months when stored at 2-8°C is recommended. Drug product should be designated as "protect from light." Krystexxa is administered by intravenous infusion after dilution in infusion bags containing saline. The product should be administered within (b) (4) hours of dilution when stored at controlled room temperature.

- **Facilities review/inspection**

Companies involved in the production/storage/release of Krystexxa are as follows:

1) Savient Pharmaceuticals, New Jersey
    - The BLA sponsor, responsible for all quality oversight and for the decision of final release of drug substance and drug product
2) Bio-Technology General (BTG), Israel
    - Responsible for manufacture of the drug substance, in-process and release quality control (QC) testing, and storage
    - This site was inspected June 3-4 and June 7-10, 2009, with 13 deficiencies noted precluding approval. These included the following:
        1. Multiple lots of DS released with unacceptably high levels of bioburden during (b) (4), and lack of bioburden limit specification for each purification step.

2. (b) (4) lots with (b) (4) present in the (b) (4) harvest culture instead of (b) (4). Root cause investigation inadequate.
3. (b) (4) process was not conducted using adequate (b) (4).
4. Hold times for (b) (4) column eluates, intermediates, and process buffers were not adequately validated.
5. Membrane storage conditions and reuse times were not formally validated.
6. (b) (4) equipment was not always cleaned using validated procedures.
7. Dirty hold times for process equipment were inadequately validated.
8. Shipping of bulk drug substance from BTG to drug product facility was not adequately validated.
9. Buildings and facilities were not properly maintained, repaired, and kept clean.
10. Pest control program was inadequately managed.
11. Materials stored in cold rooms were not always adequately segregated.
12. A package of released-for-use sterile TSA plates was lying on the floor under an electrical panel.
13. Bioburden assay results for PEGuricase were not reported in CFU per volume tested.

- ***BTG responses to 483 items were submitted and determined to be acceptable.***

3) Enzon Pharmaceuticals, Indiana

- Responsible for manufacture of the drug product, in-process and release QC testing, and storage
- Surveillance inspection occurred on June 9-12, 2009 with initial classification of VAI, which would not preclude approval.

4) (b) (4)

- Responsible for storage of Krystexxa and distribution to wholesalers
- This shipper did not meet predetermined temperature acceptance criteria for the maximum load at summer and winter profiles, and minimum load at winter profile during validation runs. OC/MAPCB recommended a post-marketing requirement for the Applicant to develop and validate a shipper that is suitable to transport the finished product vials within the continental US.

5) Quality Control Testing

- Performed at (b) (4)–responsible for DP release testing, Enzon, (b) (4)
- (b) (4) was inspected October 25-27, 2006 and classified NAI. Re-inspection was not considered necessary.

- **Other notable issues (resolved or outstanding)**

Product Quality issues described in the Complete Response Action letter, dated July 31, 2009:

1) 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 (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.

***Applicant Response and Product Quality Review Team Conclusions:***
*Savient has reverted back to the Phase 3 process (b) (4) (named Process C). Three validation runs have been performed, and a comparability study has been performed comparing Process C Krystexxa with Phase 3 process material (historical data). The Product Quality review team has concluded that these data support the physico-chemical comparability of the Phase 3 clinical trial lots and the to-be-marketed lots made by Process C. Therefore this deficiency has been adequately addressed.*

2) Release testing program for drug substance and drug product is inadequate. Specifically:
   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)
   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. Include an assay to measure (b) (4) in your drug substance release testing program.

3) Stability program for drug substance and drug product is inadequate. Specifically:
   A. Provide updated acceptance criteria that reflect the manufacturing history, process capability, and clinical experience for $K_m$, $k_{cat}$, (b) (4) and (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.

***Applicant Response and Product Quality Review Team Conclusions:***
*To address the deficiencies listed in item numbers 2 and 3 above, the Applicant has responded as follows:*

- *A peptide map assay (b) (4) has been developed and validated for lot release (DP) to monitor lysine site occupancy with PEG.*
- *A LC-MS peptide (b) (4) identity test has been developed and validated.*
- *A SEC-HPLC assay has been developed and validated for DS and DP degradation products.*
- *Acceptance criteria for multiple assays ($K_m$, $k_{cat}$, enzyme potency assays) have been tightened for the DS and DP.*
- *A validated quantitative PCR method to measure (b) (4) has been introduced for the DS testing program and a specification has been established for lot release.*

*The product quality review team believes these responses are adequate to address the stated deficiencies but recommends the following PMCs:*

*1) To revise the acceptance criteria for the peptide map assay used to quantify lysine site occupancy with PEG molecules, to specify a numerical range for all the polypeptides identified.*

*2) To conduct a study to evaluate the sensitivity of the LC-MS Peptide Mapping Assay to detect over and under pegylated uricase molecules.*

*3) To re-evaluate the release and stability acceptance criteria for the following assays;*
*a. enzymatic activity*
*b. Km and kcat determination by product accumulation and substrate depletion*
*c. monomer and HMW forms by SEC-HPLC Abs220*
*d. monomer HMW and LMW forms by Abs220*
*The acceptance criteria for the drug substance and drug product will be reevaluated and after a certain number of (to be negotiated) lots are manufactured and the revised specifications submitted in a supplement to the license.*

4) Release testing program for the uricase intermediate is inadequate. Specifically:

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 $K_{cat}$.

***Applicant Response and Product Quality Review Team Conclusions:***
*The Applicant has modified the specifications for the RP-HPLC assay to include an acceptance criterion for the ratio of the* (b) (4)

*To address item B, the Applicant has implemented the Edman degradation assay to confirm the identity of the first 10 amino acids of the Uricase Intermediate N-terminus. Regarding item C, the Applicant has provided justification for why they are currently unable to improve the $K_m$ and $k_{cat}$ assays but commit to further attempts to improve this assay. Until an appropriate assay is developed, they will continue to use an assay that measures $K_m$ and $k_{cat}$ based on loss of the substrate (UV assay). They have, however, adjusted the acceptance criteria for $K_m$ and $k_{cat}$. The product quality review team believes this response is adequate to address the stated deficiencies but recommend—*
*PMC #4: To develop and implement an enzymatic assay, based on a measure of product accumulation, that determines Km and kcat values for release of uricase intermediate.*

5) Stability program for the 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.

***Applicant Response and Product Quality Review Team Conclusions:***

*To address items # 5 and 6 above, the Applicant has updated the reference standard qualification program to include specific enzyme activity, $K_m$ and $k_{cat}$, and other assays for qualification and stability testing of the uricase intermediate and pegloticase reference standards. The product quality review team believes this response is adequate to address the stated deficiencies, but recommends an additional PMC—*
*PMC#5: To include stress conditions in the annual stability program for drug substance and drug product.*

7) Address 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.

***Applicant Response and Product Quality Review Team Conclusions:***
*A container-closure extractable study on the DS container and an accelerated leachable screening study for the DS and DP containers have been performed, and no extractable compounds were detected. The product quality review team believes this response is adequate to address the stated deficiency.*

8) The in-use stability study conducted on the drug product following dilution in infusion bags is inadequate. Perform additional studies to address protein aggregation and degradation.

***Applicant Response and Product Quality Review Team Conclusions:***
*The Applicant provided stability data to support the stability of Krystexxa in infusion bags for up to 8 hours. The product quality review team believes this response is adequate to address the stated deficiency, but recommends additional PMCs—*
*PMC#6: To evaluate in-use stability of the drug product by assessing the impact dilution of 1.0 mL drug product (pH 7.0) into 250mL saline solution (pH 4.5) has on the final pH of the infusion solution. The results of the study and risk mitigation strategies, if the final pH is below 6.2, will be submitted to the license.*
*PMC#7: To provide the results of studies supporting the proposed drug product overfill.*

9) Regarding analytical techniques:

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 free uricase in the drug substance release testing, as assessed by the ELISA assay, is low. Redevelop the ELISA assay to increase recover and improve assay accuracy.
C. During validation of the SEC-HPLC assay, the recovery of dimers and high molecular weight forms was (b) (4) and (b) (4), respectively. Improve the accuracy of the SEC-HPLC method for the detection of high molecular weight species.
D. Provide data to support the suitability of the assay to detect Host Cell Protein (HCP) at release.

***Applicant Response and Product Quality Review Team Conclusions:***

*The Applicant has responded by including SDS-PAGE destain control in the assay SOP, uricase ELISA sensitivity has been increased, SEC-HPLC assay sensitivity for uricase aggregates has been increased, and anti-Host Cell Protein antibody reactivity has been confirmed via 2-D gel analysis of HCP. The product quality review team believes this response is adequate to address the stated deficiencies.*

10) In your RP-HPLC profile, uricase appears in (b) (4) Provide characterization data addressing the nature of the (b) (4) found in these distinct peaks.

***Applicant Response and Product Quality Review Team Conclusions:***
*The Applicant has not been able to provide any further physico-chemical analysis that would account for the (b) (4) detected by RP-HPLC. However, the product quality review team believes this item is not critical, since current biochemical methods may not be able to definitively define (b) (4). The believe that the response to item 4A has now established satisfactory acceptance criteria for the (b) (4) and that there is therefore adequate quality control to ensure the consistency of manufacture. They therefore conclude that the concern giving rise to this item has been satisfactorily addressed.*

11) Develop an assay to measure sub-visible protein particulates in the (b) (4) range, and include it in your release and stability protocols.

***Applicant Response and Product Quality Review Team Conclusions:***
*The Applicant has developed and validated a method based on a modification of the USP<788> light obscuration method. This method will be used to test DP on release and stability. The product quality review team believes this response is adequate to address the stated deficiencies.*

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.

***Applicant Response and Product Quality Microbiology Review Team Conclusions:***
*The applicant has now introduced (b) (4) in the manufacturing process to better control bioburden. The bioburden action limits for in-process steps of DS manufacturing were established as (b) (4) and revised to (b) (4) (the entire sample volume) per FDA request. (b) (4)*

*Validation data for these tests and limits were provided from 3 batches of uricase intermediate and pegloticase DS. The product quality microbiology review team believes this response is adequate to address the stated deficiencies.*

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.

***Applicant Response and Product Quality Microbiology Review Team Conclusions:***
*The applicant has now introduced* (b) (4) *in the manufacturing process to better control bioburden. In addition, they have implemented the use o* (b) (4)- (b) (4) *batches were manufactured to validate these processes, with the first 3 batches used for data for the basis of setting in-process bioburden and endotoxin limits. The product quality microbiology review team believes this response is adequate to address the stated deficiencies.*

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) 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.

***Applicant Response and Product Quality Microbiology Review Team Conclusions:***
*The requested hold-time validation study was performed for crude uricase and uricase intermediate using three runs at scale. Hold times for the* (b) (4) (b) (4) *column eluates were validated in the same runs. Samples were collected prior to and after the corresponding hold period and tested for bioburden and endotoxin, with minimal to no increase in bioburden and endotoxin after holds. Hold times and acceptance criteria were proposed based on these data and were determined to be acceptable. The product quality microbiology review team believes this response is adequate to address the stated deficiencies listed in items 14 and 15.*

16) Conduct a growth promotion study for the final formulation buffer.

***Applicant Response and Product Quality Microbiology Review Team Conclusions:***
*The requested growth promotion study was conducted using the formulation buffer and 5 challenge microorganisms, with corresponding negative and positive controls. After 3-5 days of incubation (depending on the organism) no microbial growth was detected in test samples and the negative control, whereas growth was noted in the positive control samples. The product quality microbiology review team believes this response is adequate to address the stated deficiency.*

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.

***Applicant Response and Product Quality Microbiology Review Team Conclusions:***

*The Applicant responded that the requested buffer hold time studies at scale were not feasible due to space, time, and equipment constraints in the clean rooms of BTG, Inc. In lieu of these studies the Applicant has implemented rules that* (b) (4) (b) (4) *The product quality microbiology review team believes this response is adequate to address the stated deficiency.*

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.

***Applicant Response and Product Quality Microbiology Review Team Conclusions:***
*The Applicant validated the* (b) (4) *shipping container system during 3 shipments in the summer from BTG in Israel to Enzon in Indianapolis* (b) (4) *The system was also validated in environmental chambers using ISTA* (b) (4) *Results and acceptance criteria from these validation studies were reviewed and determined to be acceptable. The product quality microbiology review team believes this response is adequate to address the stated deficiency.*

19) The current selected small shipper for finished product vial did not meet the predetermined 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.

*The applicant compared validation reports prepared by a number of biologics distributors in the U.S. and has selected a biologics distributor,* (b) (4), *based on results suggesting that the temperature profiles and product load configurations used by this group reflect what would be expected during shipments of Krystexxa finished product. Shipping validation studies were performed in environmental chambers using summer and winter temperature profiles and acceptance criteria defined as maintaining product load temperatures between 2 to 8° C for 48 hours (worst-case shipping duration). This temperature range was actually maintained for 58 hours and 60 hours for the maximum load and minimum load, respectively. The product quality microbiology review team believes this response is adequate to address the stated deficiency.*

In summary, the product quality review team and the product quality microbiology review team have evaluated the responses to the items listed as deficiencies in the BLA 125293 Complete Response Action letter of July 31, 2009, and have determined that the responses to all these items are adequate. In addition, they have not identified any new issues that would preclude approval of this BLA resubmission.

# 4. Nonclinical Pharmacology/Toxicology

*First-Cycle Pharmacology-Toxicology Reviewer: BeLinda Hayes, Ph.D.*
*First-Cycle Pharmacology-Toxicology Supervisor: R. Daniel Mellon, Ph.D.*
*Second-Cycle Pharmacology-Toxicology Reviewer: Asoke Mukherjee, Ph.D.*
*Second-Cycle Pharmacology-Toxicology Supervisor: Molly Topper, Ph.D.*

- **General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).**
- **Carcinogenicity**
- **Reproductive toxicology**
- **Other notable issues (resolved or outstanding)**

No new nonclinical data were submitted with this BLA re-submission, as there no nonclinical deficiencies identified as precluding approval.

The nonclinical toxicology program consisted of single-dose and repeat-dose toxicity studies in rats and dogs administered either via subcutaneous or via intravenous route. Repeat-dose studies of up to 54 days duration in rats or up to 39 weeks in dogs were performed. The 39-week dog study is the primary chronic long-term toxicity study; this was not done in a second species as per previous agreements between the Applicant and the Agency. Both 12-week and 39-week dog studies demonstrated vacuolation of spleen; other organs affected in the 39-week study only included adrenal cortex, duodenum, heart, jejunum, and liver. No reversibility after a 12-week recovery period was observed. Dr. Mukherjee believes these vacuoles to be expected histological effects of pegylated protein degradation, and that these had not demonstrated toxicological effects. The hypothesis that these vacuoles contained PEG was not reassuring to Dr. Hayes, Dr. Mellon, and Dr. Topper, in light of the lack of demonstrated clearance of these vacuoles and the potential for continued accumulation of PEG with increasing exposure. Nonetheless, in response to the Agency's preliminary discipline comments associated with the first-cycle BLA, the Applicant submitted a proposal to 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. This study proposed dosing dogs for 12-months, at up to 5-fold the human dose every 14 days, followed by a recovery period of 6 months. This had been accepted by the review team involved at that time. Since the majority of the Pharmacology-Toxicology review team has determined this study to be necessary, and agreement has already been reached with the Applicant, this study will remain as a post-marketing requirement.

No carcinogenicity studies were submitted or required.

Reproductive toxicology was assessed in a single embryofetal development study in Sprague-Dawley rats and showed no evidence of maternal or fetal toxicity, or teratogenicity. A full battery of reproductive toxicology studies was not conducted, but this had been agreed to by the Agency earlier in the clinical development program of pegloticase. Therefore Agency Pharm-Tox reviewers decided that this would not be a barrier to approval, but that these studies should be completed as post-marketing requirements.

In summary, the first-cycle and second-cycle pharmacology-toxicology review teams agree that BLA 125293 may be approved. The following studies are being required post-marketing, as follows:
PMR#1: Conduct a fertility study in the rat model.
PMR#2: Conduct an embryo-fetal development study in the rabbit model (Segment 2).
PMR#3: Conduct a peri-natal and post-natal development study in the rat model (Segment 3)
PMR#4: Conduct an 18-month study in the dog to evaluate the impact of cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart.

# 5. Clinical Pharmacology/Biopharmaceutics

*First Cycle Clinical Pharmacology Reviewer: Ping Ji, Ph.D.*
*First Cycle Clinical Pharmacology Team Leader: Suresh Doddapaneni, Ph.D.*
*First Cycle Pharmacometric Reviewers: Atul Bhattaram, Ph.D., and Ping Ji, Ph.D.*
*First Cycle Pharmacometric Team Leader: Yaning Wang, Ph.D.*

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**
- **Drug-drug interactions**
- **Pathway of elimination, effects of intrinsic factors**
- **Demographic interactions/special populations**
- **Thorough QT study or other QT assessment**
- **Other notable issues (resolved or outstanding)**

No new clinical pharmacology/biopharmaceutics data were submitted in this BLA resubmission, as no discipline-specific deficiencies were identified in the original BLA. Agency reviewers had recommended approval, with revisions to proposed labeling. No postmarketing commitments were recommended.

To briefly summarize the clinical pharmacology/biopharmaceutics findings (from Dr. Ji's first-cycle review):

"Following single 1-hour i.v. infusions of 0.5 to 12.0 mg of pegloticase in 23 patients with symptomatic gout (study C0402), pegloticase exposure increased approximately proportionally to the dose administered. Mean terminal half-life ranged from 152 to 332 hours... After multiple dose administrations, the accumulation index was 1.42 for AUC and 1.86 for Cmax at the dose of 8 mg every 2 weeks, and the accumulation was minimal for the dose of 8 mg every 4 weeks (study C0403).

A population PK analysis was conducted based on data from the two phase 3 studies (studies C0405 and C0406). A one-compartment model with linear elimination was found to best fit the plasma pegloticase concentration time profiles. Body surface area and overall anti-pegloticase antibody response were identified as significant covariates for PK parameters clearance (CL) and volume of distribution (V). An increase in anti-pegloticase antibody

response led to 32% increase in CL and 25% increase in V. Body surface area was found to be positively related with CL and V."

# 6. Clinical Microbiology – N/A

# 7. Clinical/Statistical- Efficacy

*First Cycle Clinical Review: Rosemarie Neuner, M.D., M.P.H.*
*First Cycle Clinical Team Leader: Jeffrey Siegel, M.D.*
*First and Second Cycle Statistical Reviewer: Ruthanna Davi, Ph.D.*
*Second Cycle Statistical Team Leader: Joan Buenconsejo, Ph.D.*

The details of the Phase 3 trials submitted to support this BLA, and the regulatory interactions during the clinical development program, may be found in Dr. Neuner's and Dr. Siegel's first cycle reviews of this BLA. In summary, the Applicant submitted two replicate studies, C0405 and C0406, in adults 18 years of age or older with symptomatic gout and inadequate control with or intolerance to optimal therapy with allopurinol. Symptomatic gout was defined as either 3 or more gout attacks in the preceding 18 months, or a documented tophus, or gouty arthritis. Patients were also required to have a screening uric acid of 8 mg/dL or higher. The study excluded patients with uncontrolled cardiac disease or end-stage renal disease.

A total of 100 subjects was planned for each of the Phase 3 trials. Randomization was carried out in a 2:2:1 ratio for the pegloticase 8 mg every 2 week, pegloticase 8 mg every 4 week and placebo study arms, respectively. Randomization was stratified for the presence/absence of tophi. The primary endpoint was the proportion of patients with a plasma uric acid below 6 mg/dL at least 80% of the time during months 3 and 6. The prespecified primary analysis was the intent-to-treat (ITT) population analyzed based on Fisher's exact test. A non-responder imputation was specified for missing data. No multiplicity adjustment was specified for the two treatment arms. As previously mentioned, the Agency entered into SPA agreement with the Applicant regarding these details as proposed for Study C0405.

As shown in Table 1 below, treatment with pegloticase was associated with a higher proportion of patients maintaining a plasma uric acid level below 6 mg/dL at least 80% of the time during months 3 and 6. Approximately 40-50% of patients treated with pegloticase 8 mg every 2 weeks were able to achieve this magnitude of response. Interestingly, the 8 mg every 4 week dose was associated with a lower proportion of responders compared to 8 mg every 2 week regimen in Study C0405 but not Study C0406. In either case, a treatment effect in favor of pegloticase was clearly demonstrated, as no placebo patients were able to achieve this target, and differences between pegloticase and placebo were statistically significant for either dosing regimen.

The 8 mg every 2 week dose regimen also demonstrated effectiveness for the major secondary endpoint of resolution of tophi. The reader is referred to first-cycle clinical and statistical reviews for additional details of the efficacy findings.

**Table 1**

| Primary Endpoint Results for Studies C0405 and C0406: Plasma Uric Acid < 6 mg/dL for at Least 80% of the Time in Months 3 and 6 (ITT Population) | | | |
|---|---|---|---|
| | **Pegloticase 8 mg every 2 weeks** | **Pegloticase 8 mg every 4 weeks** | **Placebo** |
| **Study C0405, total n = 104** | **n = 43** | **n = 41** | **n = 20** |
| **PUA < 6 mg/dl for at Least 80% of the Time in Month 3** | | | |
| Number (%) | 25 (58) | 13 (32) | 1 (5) |
| 95% Confidence Interval[1] | [35.6, 70.7] | [9.6, 43.9] | |
| P-Value[2] | <0.001 | 0.024 | |
| **PUA <6 mg/dL for at Least 80% of the Time in Month 6** | | | |
| Number (%) | 20 (47) | 11 (27) | 0 |
| 95% Confidence Interval[1] | [31.6, 61.4] | [13.3, 40.4] | |
| P-Value[2] | <0.001 | 0.011 | |
| **PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined** | | | |
| Number (%) | 20 (47) | 8 (20) | 0 |
| 95% Confidence Interval[1] | [31.6, 61.4] | [7.4, 31.6] | |
| P-Value[2] | <0.001 | 0.044 | |
| **Study C0406, total n = 108** | **n = 42** | **n = 43** | **n = 23** |
| **PUA < 6 mg/dl for at Least 80% of the Time in Month 3** | | | |
| Number (%) | 19 (45) | 21 (49) | 1 (4) |
| 95% Confidence Interval[1] | [23.7, 58.1] | [27.4, 61.6] | |
| P-Value[2] | <0.001 | <0.001 | |
| **PUA <6 mg/dL for at Least 80% of the Time in Month 6** | | | |
| Number (%) | 17 (41) | 18 (42) | 0 |
| 95% Confidence Interval[1] | [25.6, 55.3] | [27.1, 56.6] | |
| P-Value[2] | <0.001 | <0.001 | |
| **PUA <6 mg/dL for at Least 80% of the Time in Months 3 and 6 Combined** | | | |
| Number (%) | 16 (38) | 21 (49) | 0 |
| 95% Confidence Interval[1] | [23.4, 52.8] | [33.9, 63.8] | |
| P-Value[2] | <0.001 | <0.001 | |

[1]95% confidence interval for differences in responder rate between corresponding pegloticase groups vs. placebo
[2]P-value using Fisher's exact test to compare corresponding pegloticase group vs. placebo.
Sponsor's Table 11; p. 57-58

At the Arthritis Advisory Committee Meeting of June 16, 2009 pertaining to Krystexxa, the Applicant presented analyses that showed that the risk of infusion reactions could be reduced if patients whose uric acid levels rose to above 6 mg/dL were discontinued from further treatment. (See Section 8 below regarding infusion reactions). Per their accounting, 49 of 56 (88%) of subjects had infusion reactions after their serum uric acid (SUA) levels had risen to above 6 mg/dL. In the pegloticase every 2 week group, 20/22 (>91%) who had infusion reactions had their pre-infusion serum uric acid level above 6 mg/dL. Therefore the Applicant proposed to label pegloticase with the recommendation that it should be discontinued in patients whose serum uric acid levels have risen above 6 mg/dL.

Dr. Ruthanna Davi, the primary FDA statistical reviewer for the first and second cycle application, was concerned that efficacy results from the trial would be different had such a stopping rule been in place during the conduct of the trial. She also noted that the Applicant's post-hoc analyses utilized the serum uric acid level the day of the infusion, whereas it is more likely in clinical practice that preceding visit values, rather than same-day values, would be used. Using preceding visit values, Dr. Davi calculated the effect of various stopping rules on both incidence of infusion reactions and efficacy results. Her analyses are presented in Table 2 below.

**Table 2**

| Benefit-Risk of Stopping Pegloticase (8 mg every 2 weeks) Early | | | | | | |
|---|---|---|---|---|---|---|
| | Infusion Reaction Observed Before Reaching Criteria | | | Efficacy Responder [1,2] | | |
| Pegloticase Stopping Rule | C405 (N=43) | C406 (N=42) | Pooled (N=85) | C405 (N=43) | C406 (N=42) | Pooled (N=85) |
| No Stopping Criteria | 11 (26%) | 11 (26%) | 22 (26%) | 20 (47%) | 16 (38%) | 36 (42%) |
| One SUA >6 mg/dL | 3 (7%) | 4 (10%) | 7 (8%) | 15 (35%) | 16 (38%) | 31 (36%) |
| One SUA >7 mg/dL | 3 (7%) | 4 (10%) | 7 (8%) | 16 (37%) | 16 (38%) | 32 (38%) |
| One SUA >8 mg/dL | 4 (9%) | 5 (12%) | 9 (11%) | 17 (40%) | 16 (38%) | 33 (39%) |
| Two consecutive SUA >6 mg/dL | 6 (14%) | 6 (14%) | 12 (14%) | 19 (44%) | 16 (38%) | 35 (41%) |
| Two consecutive SUA >7 mg/dL | 6 (14%) | 6 (14%) | 12 (14%) | 19 (44%) | 16 (38%) | 35 (41%) |
| Two consecutive SUA >8 mg/dL | 7 (16%) | 6 (14%) | 13 (15%) | 20 (47%) | 16 (38%) | 36 (42%) |

1. Efficacy responder was defined in the study protocols as a subject who achieved and maintained plasma uric acid concentrations less than 6 mg/dL for at least 80% of the time during months 3 and 6 combined.
2. No placebo subjects in either C405 or C406 were efficacy responders. Two subjects who received placebo experienced an infusion reaction while their serum uric acid levels were each above 10 mg/dL.
Source: Table 3 of Dr. Davi's 2nd cycle statistical review

These analyses suggest that the incidence of infusion reactions would have been reduced the most had single values of SUA above 6 mg/dL or 7 mg/dL at the preceding visit been used to discontinue further treatment with pegloticase. However, the proportion of patients meeting the primary endpoint is also reduced the most, suggesting some patients had isolated elevations that resolved with continued treatment. The proportion of efficacy responders drops only slightly if two consecutive elevated SUA values are utilized as a stopping rule, but the reduction in infusion reactions is also less.

- **Statistical review and the clinical efficacy review conclusions, disagreements and how they were addressed**

The first-cycle statistics and clinical reviewers were in agreement that the submitted studies provided adequate evidence of a treatment benefit associated with pegloticase. The difference compared to placebo is larger for the 8 mg every 2 week dosing regimen, for the primary endpoint of plasma urate level less than 6 at least 80% of the time in months 3 and 6, and for the secondary endpoint of tophi resolution.

- **Notable efficacy issues both resolved and outstanding**

No new efficacy data were provided in this CR resubmission. No unresolved efficacy issues remain. The statistical team recommends the label contain some annotation regarding the change in efficacy if stopping rules were applied, as the study results would have been less impressive.

# 8. Safety

*2nd Cycle Clinical Review of Updated Safety Data: Keith Hull, M.D., Ph.D.*

- **Adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing**

A total of 212 subjects were randomized and received at least one dose of study drug in C0405 or C0406. Of these, 157 (74%) completed the double-blind studies and 151 of these subjects continued into the open-label extension (OLE) study, C0407. At the time of the first cycle submission, the safety database included information on up to 19 months of pegloticase treatment in the OLE (a total maximum of up to 25 months of pegloticase treatment). For the current safety update, with data-lock of September 16, 2009, approximately 10 additional months of data are provided, which include 110 subjects treated for ≥12 months, 102 subjects treated for ≥18 months, and 71 subjects treated for ≥24 months. With respect to number of infusions, 91 subjects have had more than 30 doses of pegloticase, and 40 subjects have had more than 50 doses of pegloticase (Source: Table 50, Module 5 ISS, p. 127).

Interpretation of safety findings by treatment group for the OLE period is complicated by the fact that subjects were allowed to select their treatment in the OLE, and switch up to 2 times. Overall, more patients elected treatment with pegloticase 8 mg every 2 weeks (see Table 3 below).

**Table 3 Treatment Arm Selection in OLE by Double-Blind Study Assignment**

| | Study Arm Selection in C0407 | | | |
|---|---|---|---|---|
| | 8 mg Pegloticase | | | |
| Treatment assignment in C0405/C0406 | Every 2 Weeks n (%) | Every 4 Weeks N (%) | Observational Arm n (%) | Total n (%) |
| Pegloticase 8 mg/2 weeks | 34 (22.5) | 23 (15.2) | 0 | 57 (37.7) |
| Pegloticase 8 mg/4 weeks | 25 (16.6) | 28 (18.5) | 2 (1.3) | 55 (36.4) |
| Placebo | 23 (15.2) | 16 (10.6) | 0 | 39 (25.8) |
| Total | 82 (54.3) | 67 (44.4) | 2 (1.3) | 151 (100) |

Source: Table 47 of ISS

The numbers of patients and duration of exposure were agreed upon by the Agency as adequate for the BLA for the orphan indication of refractory gout patients. However, this safety database is clearly limited, and a postmarketing long-term observational study may be needed to provide information on rare adverse events and adverse events that may require prolonged exposure to develop, such as immune-complex mediated adverse effects.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Studies C0405 and C0406 targeted refractory gout patients, most of had multiple serious comorbidities. As shown in Table 4 below, all but one patient experienced at least one AE during the trial and long-term follow up, and most experienced multiple AEs. The proportion of patients experiencing an SAE or discontinuing due to an AE has slowly risen over time, as might be expected with increasing duration of observation and exposure.

**Table 4**

| Treatment Emergent Adverse Events in the Pegloticase Pivotal Trials and Open-Label Extension | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6-month controlled period | | | 1st cycle OLE | | Updated OLE | |
| | Placebo, n = 43 | Pegloticase q2wk, n=85 | Pegloticase q4wk, n=84 | Pegloticase q2wk, n=85 | Pegloticase q4wk, n=84 | Pegloticase q2wk, n=85 | Pegloticase q4wk, n=84 |
| Deaths n(%) | 1 (2) | 3 (4) | 1 (1) | 0 (0) | 2 (2) | 1(1)* | 0 (0) |
| Subjects with AE n(%) | 41 (95) | 80 (94) | 84 (100) | 83 (98) | 84 (100) | 84 (99) | 84 (100) |
| Number of AE | 370 | 693 | 870 | 1044 | 1411 | 1546 | 1930 |
| Subjects with SAE n(%) | 5 (12) | 20 (24) | 19 (23) | 24 (28) | 27 (32) | 33 (39) | 36 (43) |
| Subjects Discontinuing due to AE n(%) | 1 (2) | 16 (19) | 17 (20) | 18 (21) | 21 (25) | 20 (24) | 27 (32) |

*Pt was on q2wk regimen in controlled period, switched to q4wk in the OLE
Sources: Table 47 of Dr. Neuner's review, Table 53 of ISS, Section 11.11 of ISS

A single additional death occurred from the data cut-off of the 1st cycle application through the current data cut-off—a 54 year old African American male who received pegloticase 8 mg every 2 weeks in the controlled period and switched to 8 mg every 4 weeks in the OLE. This patient had multiple serious comorbidities to include AIDS (HIV-2), chronic renal disease, and Type II diabetes mellitus. He died of pneumonia requiring mechanical ventilation and associated multiple organ failure. His last uric acid value before the infectious event was below 6 mg/dL suggesting the pegloticase had not lost therapeutic efficacy, as might be expected if the patient had developed anti-product antibodies. Given his underlying immunodeficiency, serious, potentially fatal, infectious events would not be unexpected.

As discussed in Dr. Hull's clinical review, the frequency and type of both SAEs and common AEs has been consistent with that noted in the data from the original BLA submission. The overall rate of SAE since the previous data cut-off has been 0.51 events/person-years, whereas the rate was 0.58 events/person-years in the original BLA through the 120-day safety update. The rate of common AE has also decreased to 7.1 events/person-years vs. 14.4 events/person-years in the original BLA. These decreases are not unexpected given that patients who are not tolerating the drug are removed from treatment; thus patients tolerating the drug represent more and more of the dataset as clinical experience accrues.

The most common SAE during the controlled period were infusion reactions (5% for the q2wk regimen and 8% for the q4wk regimen, vs. 0% for placebo) and gout flares (5% for the q2wk regimen and for placebo, 1% for q4wk regimen)[Source: Table 49 of Dr. Neuner's first-cycle clinical review]. The most common adverse reactions by preferred term (Table 62 of Dr. Neuner's review) which occurred in ≥5% of subjects (q2wk regimen) and at least 1% more than in placebo included nausea, headache, contusion, nasopharyngitis, vomiting, pruritis, chest pain, and constipation.

- **Immunogenicity**

*Immunogenicity Assays reviewed by João Pedras-Vasconcelos, Ph.D., DTP/OBP/CDER in the first-cycle submission of this BLA; DTP team leader: Susan Kirshner, Ph.D.*

Immunogenicity-related assays were reviewed in the first-cycle BLA submission by Dr. Pedras-Vasconcelos. He concluded that the anti-pegloticase and anti-uricase IgM and IgG binding assays were suitable for the clinical analyses. The definition of high titer (>1:7920 dilution) was derived empirically by the Applicant based on thresholds observed for correlations between antibody titers and clinically observed responses, which is appropriate. The anti-PEG binding assay is very sensitive to the presence of drug in serum and is extremely variable. The anti-pegloticase IgE assay did not include a suitable positive control, as the Applicant was unable to develop one. The assay to detect neutralizing antibodies was not properly validated, also because the Applicant could not develop positive control antibodies that neutralize pegloticase. Therefore results for the anti-PEG assay, the anti-pegloticase IgE assay, and the neutralizing anti-pegloticase assay are considered unreliable.

Approximately 90% of patients in both the pegloticase every 2 week and pegloticase every 4 week treatment arms developed anti-product antibodies in the controlled period of the pivotal trials, compared to 20% of placebo-treated patients. The impact of immunogenicity on efficacy and safety results is summarized in Table 5 below. The presence of high titer anti-pegloticase antibodies was associated with lack of achievement of the primary endpoint, and was also associated with the proportionally highest incidence of infusion reactions.

**Table 5**

| Immunogenicity Results and Impact on Efficacy and Safety | | | |
|---|---|---|---|
| | **pegloticase q 2 week n = 83*** | **pegloticase q 4 week n = 81*** | **placebo n = 40*** |
| **Overall anti-pegloticase antibody testing results** | | | |
| Anti-pegloticase ab level | n(%) | n(%) | n(%) |
| None | 10 (12) | 9 (11) | 32 (80) |
| Low | 24 (29) | 24 (30) | 5 (13) |
| Moderate | 19 (23) | 21 (26) | 3 (8) |
| High | 30 (36) | 27 (33) | 0 |
| Total anti-pegloticase ab positive | 73/83 (88) | 72/81 (89) | 8/40 (20) |
| **Proportion of pts achieving primary endpoint, by antibody status** | | | |
| Anti-pegloticase ab level | | | |
| None | 7/10 (70) | 6/9 (67) | 0 |
| Low | 19/24 (79) | 13/24 (54) | 0 |
| Moderate | 10/19 (53) | 9/21 (43) | 0 |
| High | 0 | 1/27 (4) | 0 |
| **Proportion of pts experiencing infusion reaction, by antibody status** | | | |
| Anti-pegloticase ab level | | | |
| None | 1/10 (10) | 1/9 (11) | 2/32 (6) |
| Low | 1/24 (4) | 4/24 (17) | 0 |
| Moderate | 3/19 (16) | 9/21 (43) | 0 |
| High | 16/30 (53) | 18/27 (67) | 0 |

Sources: Tables 37 and 38, Module 2.7.4 and Table A10.13 of ISE, Original BLA submission
*Note: Denominators used for the proportions in this table are patients who had ELISA results for both anti-pegloticase and anti-PEG antibody assays. Numerators could include patients who were single-assay positive, thus proportions may be slightly lower than represented here.

Despite the lack of reliability of the anti-PEG assay (only 40% of patients tested positive for anti-PEG antibodies), the fact that almost 90% of patients developed anti-pegloticase antibodies, but only a small subset had anti-uricase antibodies, suggests that most of the anti-pegloticase antibodies are directed against the PEG portion of the molecule. Whether these anti-PEG antibodies would cross-react with PEG on other molecules, and thus increase the risk of an allergic reaction to other PEG-containing molecules, is unknown.

- **Special safety concerns**

*Cardiovascular Adverse Events*

As detailed in the first-cycle clinical reviews of this BLA, an imbalance of major cardiovascular adverse events was noted during the double-blind period of the pivotal studies. The ratio between treatment arms differed depending on the analysis—several were done, including Anti-Platelet Trialist Collaborative (APTC) vs. non-APTC events, done by the Applicant's cardiac adjudication committee, and a mechanism-based analysis done by FDA cardiologist, Dr. Stephen Grant. Regardless of the analysis, few to no events occurred in the placebo treatment arm.

These two analyses are recapitulated in Table 6 below, limited to the controlled period. Additional cases from the OLE, also adjudicated by the Applicant's cardiac adjudication committee, are provided for comparison. Interpretation of the OLE data is complicated by the

fact that patients switched treatments up to two times, although there was more exposure to the 8 mg every 2 week regimen overall. There were few ischemic cardiovascular events or APTC events—3 additional cases; most of the additional cases were related to congestive heart failure or deep venous thrombosis (DVT)/pulmonary embolism (PE). Two cases of revascularization were not included in Table 6—a single case of femoral artery revascularization occurring in a patient receiving the every 2 week regimen in the OLE and a single case of coronary revascularization occurring in a patient who was on observation only, but whom had received the every 4 week regimen in the double-blind portion.

Review of the case narratives reveals no trends in temporal relationship to treatment. More events occurred with the pegloticase 8 mg every 2 week regimen, but this is in part reflective of the greater exposure to that regimen. Cases were confounded by comorbid conditions that are known to increase the risk of cardiovascular disease, and often by a history of cardiovascular disease as well.

**Table 6**

**Major Cardiovascular Adverse Events in the Pegloticase Pivotal Trials and Open-Label Extension**

| | 6-month controlled period | | | OLE | | |
|---|---|---|---|---|---|---|
| | Placebo, n = 43 | Pegloticase q2wk, n=85 | Pegloticase q4wk, n=84 | Previous Placebo, n=39[a] | Pegloticase q2wk, n=59[b] (total inc pbo=82) | Pegloticase q4wk, n=51[b] (total inc pbo=67) |
| **FDA DCRP-Adjudicated Analysis:** | | | | | | |
| Subjects with Major CV AE, n(%) | 1 (2) | 5 (6) | 3 (4) | 3 (8) | 6 (10) | 1 (2) |
| **Ischemic CVD** | | | | | | |
| Sudden death | 0 | 2 | 0 | 0 | 0 | 0 |
| Nonfatal MI | 0 | 0 | 1 | 0 | 2 | 1 |
| "Troponin leak" | 1 | 0 | 0 | 0 | 0 | 0 |
| TIA | 0 | 0 | 1 | 0 | 0 | 0 |
| **Heart Failure** | | | | | | |
| Heart Failure | 0 | 2 | 0 | 2 | 4 | 0 |
| **Cardiac Arrhythmias** | | | | | | |
| Supraventricular tachycardia | 0 | 0 | 1 | 1 | 0 | 0 |
| Ventricular tachycardia | 0 | 1 | 0 | 0 | 0 | 0 |
| **Applicant Adjudicated Analysis:** | | | | | | |
| Subjects with Major CV AE, n(%) | 0 | 4 (5)[c] | 6 (8) | 5 (13) | 8 (14)[c] | 1 (2) |
| **APTC Events** | | | | | | |
| Cardiovascular Death | 0 | 2 | 0 | 0 | 0 | 0 |
| Nonfatal MI | 0 | 0 | 1 | 0 | 2 | 1 |
| Nonfatal Stroke | 0 | 0 | 0 | 0 | 0 | 0 |
| **Non-APTC CV Events** | | | | | | |
| Angina | 0 | 0 | 1 | 0 | 0 | 0 |
| CHF | 0 | 2 | 1 | 2 | 4 | 0 |
| Arrhythmia | 0 | 1 | 1 | 1 | 0 | 0 |
| DVT/PE | 0 | 0 | 1 | 2 | 3 | 0 |
| TIA | 0 | 0 | 1 | 0 | 0 | 0 |

[a]23 placebo pts went to q2wk, 16 to q4wk, 2 to observation only; 4/5 subjects in this column were on pbo q2wk; the other on obs.
[b]Patients were allowed to select their dose regimen in OLE and switch up to 2 times. See Table 47 of ISS for transition numbers.
[c]One subject experienced more than one event
Source: Dr Neuner's Tables 53 and 54, Sponsor Table 65 from the ISS

Based on the OLE data submitted, I am of the opinion that Dr. Grant's (FDA, Division of Cardio-Renal Products) conclusions are still applicable. Specifically, that the population

enrolled in these trials appears to have had a high prevalence of cardiovascular disease and that occurrence of cardiovascular adverse events would not be unexpected, and that there are too few patients and SAEs to allow detection of any pattern in occurrence that would result in conclusions about the cardiac safety of pegloticase. Nonetheless, as heart failure events were the most common cardiac SAE, and there is a plausible mechanism by which treatment may exacerbate CHF via the additional fluid and protein load, I believe a warning in the label in this regard may be appropriate.

The Office of Surveillance and Epidemiology (OSE) Division of Epidemiology (DEPI) was consulted during this review cycle for their opinion regarding the utility of a postmarketing observational epidemiology study, such as a registry, as suggested by the June 16, 2009 Advisory Committee panel. OSE/DEPI's view, as expressed in their June 6, 2010 consult, is that the usual practice of reporting AEs to the manufacturer and FDA should be sufficient, and an epidemiology study unlikely to be helpful, given that the causality of the CV events is so confounded by the underlying comorbidities, small sample size, and long duration of exposure to other gout treatments. They also expressed concern regarding the possibility of posing an undue burden due to the small group of refractory patients targeted.

*Anaphylaxis and Infusion Reactions*

In light of the fact that humans do not possess urate oxidase, and thus the enzyme sequences had to be derived from other mammals (specifically pig), an increased risk for immunogenicity and allergic reactions was anticipated for this product, and this expectation has largely held true. The first-cycle review team consulted the Division of Pulmonary and Allergy Products regarding cases of anaphylaxis, which were not explicitly sorted from other cases of infusion reactions.

Based on review of individual line listings, the allergy consultant, Dr. Susan Limb, identified at least 14 cases meeting the NIAID/FAAN clinical criteria for anaphylaxis (See Table 7 below, from Sampson HA et al. J Allergy Clin Immunol 2006;117:391-7).

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Using these criteria, the estimated frequency of anaphylaxis is 5.1% (14 of 273 patients who received IV pegloticase in the clinical development program). For the Q2wk regimen, the frequency is 7.3% (9 out of 123); for the Q4wk regimen, the frequency is 3.9% (4 out of 126), which is a reverse of the trend observed for infusion reactions as a whole, but may just be random chance given the small numbers involved. The true rate of anaphylaxis and hypersensitivity may be underestimated due to the mandatory prophylactic administration of antihistamines, acetaminophen and IV corticosteroids prior to pegloticase infusion. Based on the cases Dr. Limb reviewed, the presence of IgE, IgG or IgM antibodies against the drug did not appear to have a predictive effect. Other screening assessments such as skin test or graded challenge were not performed. Dr. Limb concluded that an estimated rate of anaphylaxis of 5% is not unusually high compared to similar porcine-derived biologic products. Because it may not be readily apparent to prescribers that pegloticase is a foreign protein, I believe a boxed warning is warranted to draw attention to this life-threatening risk.

**Table 8**

| Summary of Infusion Reaction Incidence, Overall and by Dose | | | |
|---|---|---|---|
| | Pegloticase 8 mg | | Placebo |
| | Every 2 weeks | Every 4 weeks | |
| | n = 85 | n = 84 | n = 43 |
| | n (%) | n (%) | n (%) |
| Any Infusion Reaction | 22 (26) | 34 (41) | 2 (5) |
| Serious Infusion Reaction | 4 (5) | 7 (8) | 0 |
| **Percentage* of Subjects with Infusion Reactions, by Dose** | | | |
| Week 1 (Dose 1) | 1 (1.2) | 4 (4.8) | 1 ( 2.3) |
| Week 3 (Dose 2) | 4 (4.8) | 1 (1.2) | 1 ( 2.3) |
| Week 5 (Dose 3) | 6 (7.5) | 16 (20.3) | 1 ( 2.3) |
| Week 7 (Dose 4) | 7 (9.1) | 0 | 1 ( 2.3) |
| Week 9 (Dose 5) | 5 (6.8) | 15 (20.3) | 0 |
| Week 11 (Dose 6) | 3 (4.2) | 0 | 0 |
| Week 13 (Dose 7) | 1 (1.4) | 8 (11.1) | 0 |
| Week 15 (Dose 8) | 3 (4.4) | 2 ( 3.1) | 0 |
| Week 17 (Dose 9) | 4 (6.1) | 13 (20.3) | 0 |
| Week 19 (Dose 10) | 3 (4.6) | 1 (1.4) | 0 |
| Week 21 (Dose 11) | 2 (3.3) | 8 (13.3) | 0 |
| Week 23 (Dose 12) | 3 (5.0) | 1 (1.7) | 0 |
| **Percentage* of Subjects with First Infusion Reactions, by Dose** | | | |
| Week 1 (Dose 1) | 1 (4.5) | 4 (11.8) | 1 (50.0) |
| Week 3 (Dose 2) | 4 (18.2) | 1 (2.9) | NA |
| Week 5 (Dose 3) | 3 (13.6) | 15 (44.1) | NA |
| Week 7 (Dose 4) | 5 (22.7) | NA | 1 (50.0) |
| Week 9 (Dose 5) | 1 (4.5) | 6 (17.6) | NA |
| Week 11 (Dose 6) | 2 (9.1) | NA | NA |
| Week 13 (Dose 7) | 1 (4.5) | 2 (5.9) | NA |
| Week 15 (Dose 8) | 3 (13.6) | 1 (2.9) | NA |
| Week 17 (Dose 9) | NA | 4 (11.8) | NA |
| Week 19 (Dose 10) | 2 (9.1) | NA | NA |
| Week 21 (Dose 11) | NA | 1 (2.9) | NA |

Sources: Tables 28, 29, 31, and 33 of Resubmission ISS
*Denominators are remaining patients in the treatment group at each visit

As shown in Table 8 above, overall, infusion reactions occurred fairly commonly—26% of patients treated every 2 weeks and 41% of patients treated every 4 weeks experienced an infusion reaction. Infusion reactions and first infusion reactions could occur at any exposure during treatment, including the first exposure to pegloticase. The most common symptoms reported in the 8 mg/2 weeks group were urticaria (10.6%) and dyspnea (7.1%); in the pegloticase 8 mg/4 weeks group, chest discomfort, chest pain, erythema, and pruritus (all 9.5%) were reported by the greatest percent of subjects.

Most infusion reactions occurred during the planned 2-hour infusion time period, however a small number reported an infusion reaction after the infusion completed: 4 (4.7%) in the pegloticase 8 mg/2 weeks group, 4 (4.8%) in the 8 mg/4 weeks group, and 2 (4.7%) in the placebo group. Of the eight pegloticase-treated subjects who experienced infusion reactions after the infusion completed, six subjects had symptoms within 60 minutes after the infusion and 2 subjects had symptoms between 60 and 90 minutes after the completion of the infusion,

and none were serious. No infusion reactions were reported after 90 minutes from the completion of the pegloticase infusion.

(b) (4)

*Gout Flares*

Although the mechanisms underlying a flare are not completely clear, it is currently hypothesized that a gout attack may be triggered by a release of uncoated crystals (for example due to partial dissolution of microtophi caused by changing serum uric acid levels), or by precipitation of crystals in a supersaturated microenvironment. Stable uric acid crystals become coated with serum proteins that physically inhibit binding of crystals to cell receptors, thus do not precipitate the inflammatory response caused by naked crystals.[1] Because of pegloticase's mechanism of action, which would result in direct breakdown of existing uric acid stores, it would be expected to dissolve stable clumps of uric acid crystals and microtophi and thereby increase acute flares. In addition, the clinical trials targeted patients with severe refractory gout, with a high baseline history of flare (an average of 10 gout flares in the previous 18 months).

[1]Terkeltaub RA, Dyer CA, Martin J, et al. Apolipoprotein (apo) E inhibits the capacity of monosodium urate crystals to stimulate neutrophils. Characterization of intraarticular apo E and demonstration of apo E binding to urate crystals in vivo. *J Clin Invest.* Jan 1991;87(1):20-6;
Liu-Bryan R, Scott P, Sydlaske A, et al. Innate immunity conferred by Toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. *Arthritis Rheum.* Sep 2005;52(9):2936-46.

**Table 9**

| Summary of Gout Flares, by Treatment Group and Severity | | | |
|---|---|---|---|
| | Pegloticase 8 mg | | Placebo |
| | Every 2 weeks | Every 4 weeks | |
| Total Randomized | n = 85 | n = 84 | n = 43 |
| **Gout Flares During Month 1-3** | | | |
| Number of Subjects in Period, N | 85 | 84 | 43 |
| Number (%) with No Flare | 22 (26) | 16 (19) | 21 (49) |
| Number (%) with Mild Flare | 7 (8) | 14 (17) | 9 (21) |
| Number (%) with Moderate Flare | 37 (44) | 35 (42) | 11 (26) |
| Number (%) with Severe Flare | 19 (22) | 19 (23) | 2 (5) |
| Total Number (%) with any Flare | 63 (74) | 68 (81) | 22 (51) |
| **Gout flares During Month 4-6** | | | |
| Number of Subjects in Period, N | 69 | 69 | 43 |
| Number (%) with No Flare | 41 (59) | 30 (43) | 14 (33) |
| Number (%) with Mild Flare | 11 (16) | 12 (17) | 8 (19) |
| Number (%) with Moderate Flare | 12 (17) | 21 (30) | 15 (35) |
| Number (%) with Severe Flare | 5 (7) | 6 (9) | 6 (14) |
| Total Number (%) with any Flare | 28 (41) | 39 (57) | 29 (67) |

Source: Table 48 of Resubmission ISS

As shown in Table 9 above, both pegloticase treatment regimens were associated with an increased incidence of flares overall, primarily due to an increase in moderate and severe flares, in the first 3 months of treatment. This relative increase in flares appeared to resolve over time, with the number of flares in months 4 to 6 being lower in the pegloticase treatment groups compared to placebo (best in the every 2 week pegloticase treatment group).

- **Discussion of primary reviewer's comments and conclusions**

Dr. Hull has concluded that the additional safety data submitted in this complete response submission is consistent with the safety data in the original BLA submission. He has not identified any new safety signals.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

I concur with Dr. Hull's conclusion that the data in this submission are consistent with data submitted in the original BLA.

- **Discussion of notable safety issues (resolved or outstanding).**

The notable safety issues are the immunogenicity of this product and the risk of anaphylaxis and infusion reactions associated with treatment. Because the premarketing safety database for this product is so limited (though justified by the limited numbers in the target population), it is possible that rare adverse events and adverse events that might occur with prolonged exposure, such as immune-complex-mediated adverse effects, may not have been captured. Therefore a postmarketing observational study should be required to enable assessment of a larger, longer duration experience than has been provided in the BLA.

The imbalance of cardiovascular adverse events noted in the controlled period of the trials is difficult to interpret given the small number of events and the high underlying risk in the patient population. Because pegloticase is intended for the treatment of a small, refractory patient population, OSE/DEPI believes that an observational registry is unlikely to result in better data than postmarketing spontaneous adverse event reporting. I concur with their recommendation that standard postmarketing pharmacovigilance is warranted at this time.

# 9. Advisory Committee Meeting

During the first cycle, the primary safety issues of concern were identified as the risk of serious infusion reactions, hypersensitivity/anaphylaxis, and the imbalance of cardiovascular serious adverse events in the controlled period. These issues were discussed at the Arthritis Advisory Committee meeting of June 16, 2009, in the context of the efficacy of pegloticase and the refractory population targeted. The panel for this meeting included members of the Cardiovascular and Renal Drug Products Advisory Committee and the Drug Safety Advisory Committee. The panel voted 14 to 1 in favor of approval. Although there was no consensus from the panel regarding whether the imbalance of cardiovascular SAE represented a true signal, there was general agreement that additional postmarketing safety information in this regard should be collected, possibly via an observational epidemiologic study. Panel members also considered it important to limit the use of the product to patients who were truly refractory to conventional therapy. There was also support for a sponsor proposal to incorporate instructions in labeling regarding cessation of treatment when uric acid rises above 6 mg/dL in order to minimize the risk of infusion reactions.

# 10. Pediatrics

Gout is quite rare in children, occurring almost exclusively in the setting of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency (also known as Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome). Therefore it would not be possible to conduct studies in children due to the small number of patients available and the Applicant would qualify for a waiver to conduct studies in children under PREA. However, since the indication of gout refractory to conventional treatments was granted orphan designation, this application is exempt from PREA.

# 11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—N/A
- **Exclusivity or patent issues**—The Applicant is claiming orphan exclusivity as per the provisions of 21CFR, Part 316.31. Savient Pharmaceuticals, Inc. is the holder of an approved Orphan Drug Application for pegloticase (ODA 00-1356; granted on February 21, 2001)
- **Financial disclosures**—Submitted for all investigators; no issues identified.

- **DSI audits**—3 investigator sites were inspected (Bookbinder, Sundy, and Baraf) as well as the Applicant's site (because the product is a new molecular entity) and Charles River Laboratories (because the clinical sites were to be blinded to plasma uric acid concentrations which were performed here). No issues were identified that would have negatively impacted on the data integrity and interpretability of study results.
- **Other outstanding regulatory issues**—N/A

## 12. Labeling

*Reviewers from the Division of Drug Marketing, Advertising, and Communications (DDMAC), 1st cycle—Samuel Skariah, Ph.D., Michael Sauers; 2nd cycle—Roberta Szydlo, Twyla Thompson*
*Reviewers from the Division of Medication Error, Prevention, and Analysis (DMEPA), 1st cycle—Cathy Miller, M.P.H.,*

- **Proprietary name**—The Applicant proposed Krystexxa; this was reviewed by DDMAC and DMEPA and found to be acceptable.
- **Physician labeling**—

Major items to be revised from proposed labeling include the following:

- *Addition of Boxed Warning for Anaphylaxis*

  No boxed warning or separate warning for anaphylaxis was proposed by the Applicant, as they believe stopping treatment for uric acid levels greater than 6 mg/dL would ameliorate this risk. The Applicant's analysis is hampered by the fact that it is based on same-day uric acid values. In the likely clinical scenario of previous visit uric acid values being used, the risk for anaphylaxis and severe infusion reactions would not be as extensively reduced. The label should be revised to include a boxed warning, as discussed in Section 8 above. This warning should also address the need for infusion premedication, as the anaphylaxis and infusion reactions observed in the clinical trials were in spite of required premedication—lack of premedication could have resulted in increased rates.
- *Monitoring of serum uric acid*

  (b) (4) Based on the review team's assessment of the infusion reaction data, it appears that infusion reactions continued to occur throughout treatment with long term exposure. (b) (4)

  Because monitoring is being recommended to make a clinical decision with respect to possible discontinuation of treatment (see next bullet), it should also be noted that pegloticase could result in falsely low serum uric acid levels if blood samples are left at room temperature. Given the putative mechanism behind loss of therapeutic response (i.e. due to neutralizing antibodies), this may not be an impediment to using serum uric acid elevation to above 6 mg/dL as a stopping rule to minimize the risk of infusion reactions, as these neutralizing antibodies should prevent enzymatic activity in collected blood samples as well as in vivo.

- *Recommendation for discontinuation of treatment with a single uric acid level greater than 6 mg/dL to minimize risk of infusion reactions*

In order to allow for situations where the benefit might outweigh the risk of infusion reaction, I recommend the label be revised to state that treatment should be discontinued when two consecutive uric acid levels greater than 6 mg/dL are observed, as this is a more definitive sign of loss of therapeutic response. The relative safety benefit of using a single value to make this determination can only be determined on a case by case basis, depending on the severity of the patient's underlying condition.

- **Carton and immediate container labels**—Carton and container labeling was revised as per DMEPA's first-cycle comments, with the exception of two items that still need to be addressed: 1) The dilution statement that appears on the principal display panel of the carton labeling needs to be changed to read, "Must Be Diluted Prior to Administration," rather than the currently proposed, "Dilute Before Administration; and 2) the dilution statement, "Must Be Diluted Prior to Administration," must be added to the fold-out carton labeling and if space permits, to the container label.
- **Patient labeling/Medication guide**—DRISK comments for the proposed Medication Guide are pending.

# 13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval, with revisions to the proposed labeling.

- **Risk Benefit Assessment**

Because of its direct activity in breaking down uric acid, pegloticase targets a unique niche in the therapeutic armamentarium for gout. This distinct mechanism provides for the possibility of control of disease that has historically been difficult to control with uric acid lowering treatments (i.e. uricosurics and xanthine oxidase inhibitors), including tophaceous gout. As shown in Table 10 below, using the data from the controlled trials, only 2 patients needed to be treated to achieve a treatment benefit, as described by the primary endpoint of plasma uric acid less than 6 mg/dL over 80% of the time in months 3 and 6 combined. More remarkably, only 5 patients with tophi need to be treated for one to experience complete resolution of at least one tophus. However this is negatively balanced by the high rate of infusion reactions (all severities), which also approached 1 in 5. For the most severe reactions (i.e. anaphylaxis), 20 patients were treated for every case of anaphylaxis observed. This relative balance in risks vs. benefits should give pause to prescribers contemplating off-label use for patients with uncomplicated forms of gout. However, for the target population of patients who are refractory to conventional therapy, the lack of alternatives makes the risk:benefit balance clearly favorable.

**Table 10**

| Risk-Benefit Overview | | |
|---|---|---|
| **Clinical Activity** | **Proportion Responding** | **Number Needed to Treat** |
| PUA<6 mg/dL, over 80% of time in months 3 and 6 combined | 42% | 2 |
| Tophus Resolution | 29% | 5 |
| **Risks** | **Event Rate** | **Number Needed to Harm** |
| Anaphylaxis | 5% | 20 |
| Infusion Reaction, including anaphylaxis | 26% | 5 |

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

The risks of pegloticase are not insignificant, and a risk evaluation and mitigation strategy (REMS) consisting of a Medication Guide and Communication Plan, is warranted, as originally agreed upon by the original review team, OSE, and the Applicant in the first cycle. It was determined at that time that Elements to Assure Safe Use (ETASU) were not considered necessary, as the risk of life threatening infusion reactions has always been a concern with biologic products, and this has historically been adequately addressed by labeling and medical supervision/routine emergent management as per standard of care in the infusion center setting. The second cycle review team for DRISK concurs that this is reasonable. Therefore, in order to entail the least burden possible consistent with the safety goals, it is appropriate that the REMS consist of the Medication Guide and Communication Plan, focusing on the primary risks of anaphylaxis and infusion reactions as well as the need for premedication of infusions, monitoring and stopping treatment for loss of therapeutic response.

- **Recommendation for other Postmarketing Requirements and Commitments**

Clinical Postmarketing Requirement:

1) Conduct an observational study enrolling 500 patients with hyperuricemia and gout who are refractory to standard uric acid lowering therapies who are treated with pegloticase for 1 year, in order to evaluate the frequency and severity of infusion reactions, anaphylaxis, immune complex-related adverse events and serious adverse events.

Pharmacology/Toxicology Postmarketing Requirements:

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

2) Conduct an embryo-fetal development study in the rabbit model (Segment 2).

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

4) 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.

Product Quality Postmarketing Commitments:

1) To revise the acceptance criteria for the peptide map assay used to quantify lysine site occupancy with PEG molecules, to specify a numerical range for all the polypeptides identified.

2) To conduct a study to evaluate the sensitivity of the LC-MS Peptide Mapping Assay to detect over and under pegylated uricase molecules.

3) To re-evaluate the release and stability acceptance criteria for the following assays;
a. enzymatic activity
b. Km and kcat determination by product accumulation and substrate depletion
c. monomer and HMW forms by SEC-HPLC Abs220
d. monomer HMW and LMW forms by Abs220
The acceptance criteria for the drug substance and drug product will be reevaluated and after [number to be negotiated] lots are manufactured and the revised specifications submitted in a supplement to the license.

4) To develop and implement an enzymatic assay, based on a measure of product accumulation, that determines Km and kcat values for release of uricase intermediate.

5) To include stress conditions in the annual stability program for drug substance and drug product.

6) To evaluate in-use stability of the drug product by assessing the impact dilution of 1.0 mL drug product (pH 7.0) into 250mL saline solution (pH 4.5) has on the final pH of the infusion solution. The results of the study and risk mitigation strategies, if the final pH is below 6.2, will be submitted to the license.

7) To provide the results of studies supporting the proposed drug product overfill.

- **Recommended Comments to Applicant**

*N/A*