

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125293

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	September 14, 2010
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II <i>CR</i> 9/14/10
Subject	Summary Review
NDA/BLA #	BLA 125293
Supp #	
Applicant Name	Savient Pharmaceutical
Proprietary / Established (USAN) Names	Krystexxa pegloticase
Dosage Forms / Strength	IV infusion 8 mg/ml every two weeks
Proposed Indication(s)	Treatment of refractory gout
Action:	<i>Approval</i>

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding pegloticase and the reader should refer to the reviews in the action package for a more detailed discussion. As noted in my memorandum from the first review cycle for this product, pegloticase is a recombinant PEGylated uricase (uric acid oxidase) enzyme produced by E. Coli and developed for the orphan population of patients with chronic gout that have failed conventional uric acid-lowering therapies. Pegloticase was found to be very effective at reducing plasma uric acid (PUA) levels and, for some subjects, causes total resolution of tophi in a short time frame. It was felt by the review team and I that pegloticase had the potential to be a very important agent in the treatment of refractory gout. There were several areas of concern with the initial application that my review identified including:

- 1) The Division of Therapeutic Proteins had determined that the product proposed for commercial use has not been demonstrated to be physicochemically equivalent to the material used in the Phase 3 trial which was used to establish the safety and efficacy profile
- 2) The Product Quality Microbiology team had determined that there are multiple deficiencies at the drug substance manufacturing facility related to microbial control and good manufacturing practices. Additionally the sponsor had not been able to meet the typical standard of being able to produce three lots of product meeting requirements for microbial control
- 3) There was an imbalance of cardiovascular serious events associated with the use of pegloticase
- 4) Pegloticase treatment is associated with serious infusion reactions and anaphylaxis despite prophylactic pretreatment

5) Pharmacology-Toxicology review of animal studies demonstrated vacuolation of several organs

At the time of the initial review, issues 1 and 2 above led to a complete response on August 1, 2009, while it was felt that issues 3, 4, and 5 could be address post-approval should the application ever be approved.

Regarding the issues that led to the CR action with the original submission, the sponsor has reverted back to manufacturing the final formulated drug product using processes that were the same as those used in the pivotal clinical studies. Therefore, the sponsor now plans on marketing the substance that was shown to be safe and effective in clinical trials (validated the Phase 3 process for commercialization). This successfully resolves of the first issue. Regarding the second issue, all manufacturing and testing facilities now have acceptable inspection status with resolution of all previous deficiencies related to product quality and manufacturing process.

Therefore, since the two reasons for a CR action have now been resolved, with appropriate labeling, this application should receive an approval action.

Regarding the other issues above, for the cardiovascular concerns, the original studies were small in size (approximately 200 subjects in total) with 2:2:1 randomization to pegloticase 8 mg every two weeks, 8 mg every four weeks, and placebo. There were few cardiovascular (CV) events (one or two events for some categories), but those that did occur provide a numerical disadvantage for pegloticase use (although as noted above, there was 4x the exposure to drug compared to placebo so much greater chance for the limited events to occur in a subject taking drug). As with any issue where there are few events, it is difficult to know whether this represented a true difference or not as there were also imbalances in confounders. For a drug which would be used in a large population, this issue could be sorted out with a traditional cardiovascular safety outcome trial. However, pegloticase will be used in a limited population (qualifies for orphan drug status) so there are not enough patients available to perform an outcome study. Discussion internally with our OSE/DEPI colleagues has led to the conclusion that a dedicated post-marketing observational study or a registry based study would probably not be useful to further define if there are cardiovascular risks. As such, our OSE colleagues recommend that we follow the usual practice of analyzing AEs reported to the manufacturer and to us.

Anaphylaxis is expected as uricase is a foreign protein derived from other mammals. The frequency noted was approximately 7% for the every two week dosing interval and occurred in subjects that were pretreated with antihistamines and corticosteroids. Since this is a serious reaction that should be weighed in any decision regarding therapy and can be monitored for, the risk of anaphylaxis will be highlighted in a boxed warning and will be described in a medication guide. Infusion reactions also occurred frequently. It was noted that almost all infusion reactions occurred in subjects that had uric acid levels of 6 mg/dL or greater. Antibody levels were also greater in patients with higher levels of uric acid. One could speculate that for those subjects whose uric acid levels rose above 6 mg/dL during therapy most likely formed a neutralizing antibody as rising uric acid levels indicates loss of efficacy of pegloticase. In any event, patients that do not achieve uric acid levels < 6 mg/dL, or those

that had low uric acid levels (initial responders) that increase to >6 mg/dL over time, should discontinue therapy as they are not benefiting from therapy, but are at risk for anaphylaxis/infusion therapy. Dr. Davi has performed some very elegant analyses to explore different stopping criteria and their effect on the initial responder group. Dr. Okada has a very nice discussion of this in her review, and I agree with her conclusions that when considering efficacy and safety together, for initial responders, treatment should be discontinued when two consecutive uric acid levels are greater than 6 mg/dL. I think this is a good balance of not sacrificing possible efficacy in a particular patient while still minimizing potential infusion reactions and anaphylaxis.

Finally, there were histological observations of vacuolation of various organs. It is felt that this likely due to pegylated protein degradation. These findings were not associated with tissue injury or toxicological effects. The applicant will conduct an 18-month study in dogs to further evaluate the impact of the vacuoles for future labeling, but at present they are not felt to be a significant safety risk in the use of pegloticase in patients.

Pegloticase will have a REMS that includes a Medication Guide and Communication Plan highlighting the anaphylaxis and infusion reactions. Because the size and duration of exposure represented in the premarket safety database was limited (though acceptable for an orphan indication), a clinical postmarketing requirement will be enacted for an observational safety study enrolling 500 patients in the approved indication treated with pegloticase for one year duration. The purpose of this study would be to evaluate the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events, as well as to further assess for serious adverse events that may be associated with pegloticase therapy.