CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125293

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	September 14, 2010
From:	Badrul A. Chowdhury, MD, PhD Badrul A. Chowdhury Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
BLA Number:	125293
Applicant Name:	Savient Pharmaceuticals, Inc.
Date of Submission:	March 15, 2010
PDUFA Goal Date:	September 14, 2010
Proprietary Name:	Krystexxa
Established Name:	Pegloticase
Dosage form:	Injection for intravenous infusion
Strength:	8 mg pegloticase/mL
Proposed Indications:	Treatment of chronic gout in patients refractory to conventional therapy
Action:	Approval

1. Introduction

Savient Pharmaceuticals originally submitted this BLA on October 31, 2008, for the use of Krystexxa (pegloticase) Injection for the treatment of chronic gout in adult patients refractory to conventional therapy. This is an orphan indication and an orphan designation was granted in 2001. The proposed dose is 8 mg administered as intravenous infusion every 2 weeks. A complete response action was taken on July 31, 2009, primarily due to deficiencies related to product quality and manufacturing. The applicant submitted a response the complete response action on March 15, 2010, adequately addressing these and other deficiencies. This summary review provides an overview of the application and the complete response. The reader is referred to the previous Division Director's review dated July 30, 2009, for details of the original review cycle findings and Agency conclusion.

2. Background

Gout is an inflammatory arthritis associated with hyperuricemia and caused by the deposition of monosodium urate crystals in and around the tissues of joints. Symptomatic crystal deposition includes attacks of acute inflammatory arthritis, a chronic destructive arthropathy, and soft tissue accumulation of monosodium urate crystals. Management of gout involves two primary components: (1) Treatment and prophylaxis of acute joint and bursal inflammation. Drugs used to treat with this intent include non-steroidal anti-inflammatory agents, corticosteroids, ACTH, and colchicine. (2) Lowering serum urate levels with the aim of avoiding recurrent inflammatory flares and progression of joint damage, and complications from deposition of monosodium crystals in various

tissues and organs. Drugs used to treat with this intent include the uricosuric agent probenecid, and the xanthine oxidase inhibitors allopurinol and febuxostat.

Pegloticase will be another treatment option for lowering serum urate levels in patients with gout. Pegloticase is a uricase that reduces serum urate levels by metabolizing uric acid to allantoin and hydrogen peroxide. Humans, unlike some lower animals, lack endogenous uricase and lack a metabolic pathway to handle uric acid. Pegloticase is not be the first uricase to be approved in the United States. Rasburicase (Elitek), also a uricase, was approved in the United States for management of plasma uric acid levels in patients receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid. Rasburicase is produced in a genetically modified *Saccharomyces cervisiase* strain with cDNA coding sequence cloned from a strain of *Aspergillus flavus*. Administration of this unmodified uricase beyond single dose or short-term course is limited by hypersensitivity reactions including anaphylaxis. To reduce this risk of similar immunologic response, pegloticase was developed from mammalian cDNA and as a PEGylated product since addition of PEG to foreign proteins is expected to reduce the risk of antibody formation.

3. Chemistry, Manufacturing, and Controls

The proposed commercial product Krystexxa is a sterile clear colorless solution containing 8 mg pegloticase per mL in phosphate-buffered saline. Pegloticase is a PEGylated recombinant uricase protein. The uricase protein 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 cDNA for the uricase protein is derived from the porcine uricase gene, with a (b) (4) (b) (4) derived from the baboon uricase gene, (b) (4) (b) (4) and transfected into *Escherichia coli* to produce the uricase protein. The homotetrameric uricase protein is (b) (4) estimated molecular weight of the pegylated homotetrameric uricase protein is (b) (4)

The pegloticase drug substance will be manufactured at Bio-Technology General Ltd in Israel. The final formulated drug product will be manufactured, filled, labeled, and packaged at Enzon Pharmaceuticals in Indianapolis, Indiana. The proposed commercial product will be manufactured using processes that were used in the pivotal clinical studies. All manufacturing and testing facilities associated with this application have acceptable inspection status. Previous deficiencies related to product quality and manufacturing processes for the proposed commercial product have been resolved. The proposed 24 month expiry from the date of manufacture of the product is supported by adequate stability data.

There are seven product manufacturing and quality-related post-marketing commitments that are listed in CMC reviews and the action letter.

4. Nonclinical Pharmacology and Toxicology

The Applicant submitted a nonclinical toxicology program for pegloticase consisting of a single-dose and repeat-dose toxicity studies in rats and dogs via subcutaneous or intravenous route of administration. Repeat-dose studies up to 54 days in rats and 39 weeks in dogs were performed. Nonclinical safety issues relevant to clinical use were identified in the dog studies. In the 12-week intravenous dog toxicity study, irreversible vacuolation of the spleen was observed. In the 6-month chronic intravenous toxicology study in dogs, irreversible vacuolation was observed in the adrenal cortex, duodenum, heart, jejunum, liver, and spleen. The vacuoles in duodenum, jejunum, liver, and spleen were located with macrophages and contained PEG or uricase or both. However, the vacuoles in the adrenal gland and intima of the heart were not associated with macrophages. The potential long-term consequences of accumulation of these vacuoles in the heart and the adrenal glands are unknown. 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. In addition, the applicant has not performed carcinogenicity studies since they were not required given the nature of the product and the indication.

The Applicant has agreed to conduct the following studies, which will be post-marketing requirements: 1. fertility study in rats; 2. embryo-fetal development study in rabbits; 3. peri-natal and post-natal development study in rats; and 4. eighteen-month study in dogs to evaluate the impact of cytoplasmic vacuoles in adrenal gland and aortic outflow of heart.

5. Clinical Pharmacology and Biopharmaceutics

The Applicant submitted a clinical pharmacology program evaluating the key pharmacokinetic profile of pegloticase. Following a single dose intravenous infusion, pegloticase exposure increased in a dose-proportional manner. Terminal half-life ranged from approximately 150 to 300 hours. Population PK analysis showed that age, gender, weight, and creatinine clearance did not influence the PK parameters of pegloticase. Formal drug-drug interaction, renal impairment, hepatic impairment, or thorough QT studies were not required since the product being a biologic, and with consideration of the indication and projected use of the product did not warrant these studies.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of the review and regulatory decision for this application are shown in Table 1. The design and conduct of

these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant clinical studies

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups#	N (ITT)	Primary efficacy variables	Countries
402 2003	Dose finding	Single dose	28 - 73	Kry 0.5 mg Kry 1 mg Kry 2 mg Kry 4 mg Kry 8 mg Kry 12 mg	24	Plasma uric acid level	US
403 0004	Proof of concept	12 weeks	22 - 83	Kry 4 mg every 2 weeks Kry 8 mg every 2 weeks Kry 8 mg every 4 weeks Kry 12 mg every 4 weeks	7 8 13 13	Plasma uric acid level	US
405 2006	Efficacy and Safety	6 months	23 - 85	Kry 8 mg every 2 weeks Kry 8 mg every 4 weeks Placebo	43 41 20	Patients with plasma uric acid below 6 mg/dL	US, Canada
406 2006	Efficacy and Safety	6 months	28 - 80	Kry 8 mg every 2 weeks Kry 8 mg every 4 weeks Placebo	42 43 23	Patients with plasma uric acid below 6 mg/dL	US, Mexico
407 2007	Open Label Safety	24 months	23-85	Kry 8 mg every 2 weeks Kry 8 mg every 4 weeks Observation	82 67 2	Safety	US, Canada, Mexico

*Year study subject enrollment ended
Kry = Krystexxa (pegloticase) Injection, for intravenous infusion

b. Design and conduct of the studies

Study 402 was a dose finding study evaluating the effect of single intravenous doses of pegloticase on plasma uric acid level in adult patients with gout. Time profile analysis of serum uric acid was done after single dose up to 500 hours.

Studies 405 and 406 were pivotal efficacy and safety studies similar in design and conduct. Both studies were randomized, double-blind, parallel group in design, and conducted in patients 18 years of age and older. The subjects enrolled in the studies were patients who had 3 or more gouty attacks in the prior 18 months, a documented tophus or gouty arthritis, a screening uric acid level of 8 mg/dL or higher, and a documented intolerance to allopurinol or failure to normalize uric acid despite maximal recommended dose of allopurinol. Patients were washed out of other urate lowering treatments for 1 week before enrollment. Patients were randomized to three treatment arms as shown in Table 1. Since gouty flares, anaphylaxis, and infusion reactions were expected during treatment, all patients were required to take colchicine or NSAIDs, and all patients were pre-treated before study drug treatment with a parenteral corticosteroid, oral antihistamine, and acetaminophen. The primary efficacy endpoint was the proportion of patients with a plasma uric acid level below 6 mg/dL at least 80% of the time during months 3 and 6. Several secondary efficacy variables were studies including the resolution of tophi assessed by digital photographs. Safety assessments included recording of adverse events, vital signs, physical examination, gouty flares, clinical

laboratory evaluation, antibody formation, and 12-lead ECG.

Patients completing these studies had the option to enroll in a long-term extension study (study 407).

c. Efficacy findings and conclusions

The submitted clinical program supports efficacy of pegloticase at a dose of 8 mg every 2 weeks for the treatment of chronic gout in adult patients refractory to conventional therapy.

The dose of pegloticase was selected from a single dose study that showed dose-dependent decrease of plasma uric acid with doses ranging from 0.4 mg to 12 mg. Sustained decrease in uric acid for more than 300 hours was observed with doses of 8 mg and 12 mg (Figure 1). Based on these data, the 8 mg dose was studied further in pivotal efficacy and safety studies.

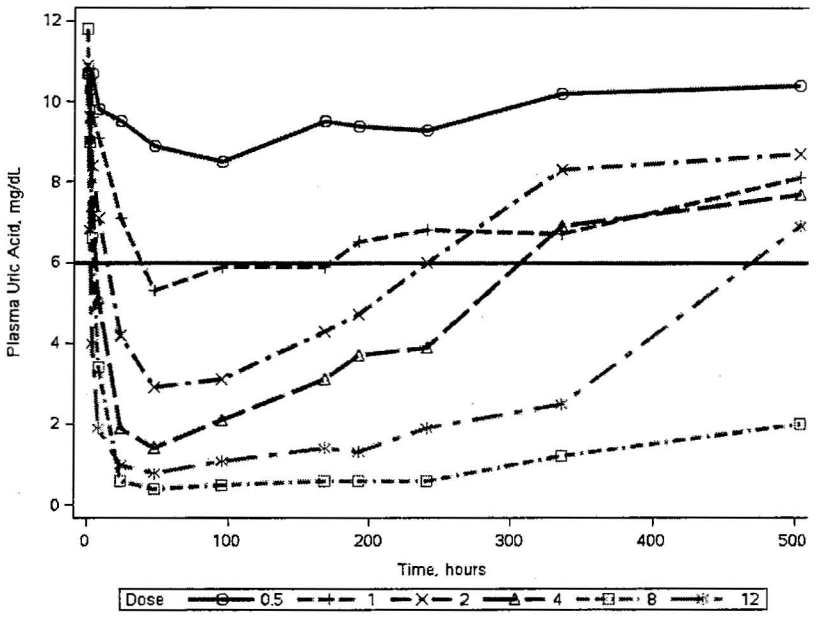

Figure 1. Mean plasma uric acid concentrations after a single intravenous dose of 0.5, 1, 2, 4, 8, and 12 mg of pegloticase (study 402).

In the pivotal studies, pegloticase 8 mg at both dose frequencies, every 2 weeks and every 4 weeks, resulted in a higher proportion of patients maintaining a plasma uric acid level below 6 mg/dL for at least 80% of the time during months 3 and 6 combined (i.e., the primary endpoint, data shown in Table 2). The differences between both dosing frequencies of pegloticase and placebo were also statistically significant for the two studies at both the 3 month and 6 month time points tested. Secondary analyses were conducted pooling data from the two studies. The pooled data showed improvement for the major secondary endpoint of resolution of tophi, but the differences were statistically

significant only for the every 2 weeks dosing regimen (Table 3). The applicant's proposal to recommend dosing every 2 weeks is reasonable since the primary endpoint at the 2-week frequency provided numerically higher and consistent results across the two studies (Table 2), and for the endpoint of resolution of tophi the difference between pegloticase and placebo was statistically significant for the 2 weeks frequency but not for the 4 weeks frequency (Table 3).

Table 2. Plasma uric acid <6 mg/dL for at least 80% of the time during months 3 and 6 combined

Treatment Groups	n	Number (%) of patients who met the criteria	95% Confidence interval	P-value
Study 405				
Kry 8 mg every 2 weeks	43	20 (47%)	32%, 61%	<0.001
Kry 8 mg every 4 weeks	41	8 (20%)	7%, 32%	0.044
Placebo	20	0 (0%)		
Study 406				
Kry 8 mg every 2 weeks	42	16 (38%)	23%, 53%	<0.001
Kry 8 mg every 4 weeks	43	21 (49%)	34%, 64%	<0.001
Placebo	23	0 (0%)		
# Kry = Krystexxa (pegloticase) Injection, for intravenous infusion				

Table 3. Tophus response at week 25 shown as pooled data from studies 405 and 406, shown as number of patients (% of patients)

	Krystexxa 8 mg every 2 weeks	Krystexxa 8 mg every 4 weeks	Placebo
Subjects with evaluable tophi at week 25*	40	42	25
Complete response	18 (45%)	11 (26%)	2 (8%)
Partial response	8 (20%)	10 (24%)	6 (24%)
Stable disease	10 (25%)	16 (38%)	11 (44%)
Progressive disease	4 (10%)	5 (12%)	6 (24%)
p-value, Wilcoxon test	0.002	0.061	
P-value, Fisher's exact test	0.002	0.109	

* Tophi were categorized by the central reader as "unable to evaluate" if an individual tophi could not be assessed for any reason at week 25 (e.g., image missing or of poor quality, obvious infection of the tophus) subjecting these results to bias. A sensitivity analysis considering the "unable to evaluate" cases as failures leads to the followng proportions of subjects with complete response at week 25: 29% (18 of 62), 17% (11 of 64) and 7% (2 of 29) for the pegloticase every 2 weeks groups, every 4 weeks groups, and placebo groups, respectively.

Pegloticase is highly immunogenic and causes a high frequency of anaphylaxis and infusion reaction (discussed further in section 8 below). Efficacy was further analyzed taking into consideration the possibility of stopping dosing in patients with high uric acid levels at previous clinic visit(s). (Previous visit data was used to simulate real world use scenario.) Various stopping rules for dosing of pegloticase (i.e., above 6 to 8 g/dL at one or two consecutive time points) and the impact of these on the risks of anaphylaxis and infusion reaction as well as efficacy were considered. These post-hoc analyses suggest that the incidence of infusion reactions would be reduced if patients with one or two consecutive serum uric acid values above 6 mg/dL discontinued pegloticase. However, it

should be noted that the stopping rules may affect the efficacy results in that dosing of patients who eventually achieved efficacy but who also had transiently high SUA levels at previous visits would be discontinued. (Table 4). This information will be included in the product label to support the recommendation to discontinue pegloticase when serum uric acid levels increase above 6 mg/dL, particularly on two consecutive occasions.

Table 4. Number (%) of patients at various stopping rules on infusion reactions (includes anaphylaxis) and efficacy, shown for the pegloticase 8 mg every 2 weeks group and as pooled from the studies 405 and 406

Stopping rule (UA = uric acid)	**Infusion reaction (includes anaphylaxis) before reaching stopping rule, n=85**	**Efficacy: Plasma uric acid <6 mg/dL at least 80% of time during months 3 and 6 combined, n=85**
No Stopping Rule	22 (26%)	36 (42%)
One UA > 6 mg/dL	7 (8%)	31 (36%)
One UA > 7 mg/dL	7 (8%)	32 (38%)
One UA > 8 mg/dL	9 (11%)	33 (39%)
Two consecutive UA > 6 mg/dL	12 (14%)	35 (41%)
Two consecutive UA > 7 mg/dL	12 (14%)	35 (41%)
Two consecutive UA > 8 mg/dL	13 (15%)	36 (42%)

8. Safety

a. Safety database

The safety assessment of pegloticase was primarily based on the two pivotal efficacy and safety studies shown in Table 1. Although the safety database is small, given that the prevalence of patients for this orphan indication is about 100,000, the safety database is acceptable for review and regulatory action.

b. Safety findings and conclusion

The safety data do not raise concerns that would preclude approval. There was one death that occurred in the pegloticase treatment arm, but the death was not related to gout or its treatment. The patient had multiple serious comorbidities (AIDS, chronic renal disease, type II diabetes) and died of respiratory failure from pneumonia. Serious adverse events and adverse events in general were common, which is expected because the patients had refractory gout and other multiple serious medical conditions. Safety findings of concern with pegloticase are anaphylaxis, infusion reaction, gout flares, immunogenicity, and cardiovascular events. These are further discussed below.

Anaphylaxis was expected for pegloticase since humans do not possess endogenous uricase, and the uricase protein sequence in pegloticase is derived from other mammals (described in section 3 CMC, above). Using generally accepted diagnostic criteria of anaphylaxis,[1] there were a total of at least 14 cases of anaphylaxis in the clinical program

[1] Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, Brown SG, Camargo CA, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006; 117:391-7.

giving a frequency of 5.1% of patients (14 out of 273 patients). The frequency was 6.5% for the 2 week dosing frequency (8 out of 123) [studies included were 403 with 15 patients, 405 with 43 patients, 406 with 42 patients, and 407 with 23 patients who previously received placebo], and 4.8% for the 4 week dosing frequency (6 out of 126) [studies included were 403 with 26 patients, 405 with 41 patients, 406 with 43 patients, and 407 with 16 patients who previously received placebo]. This frequency was in spite of all patients being pre-treated with parenteral corticosteroids and antihistamine before dosing. The risk of anaphylaxis will be highlighted in a boxed warning and described in a Medication Guide.

Infusions reactions occurred with a frequency of 26% in the 2 week dosing regimen and 41% in the 4 week dosing regimen. Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with anaphylaxis, but did not occur together in any given patient to satisfy the clinical criteria of anaphylaxis. These reactions may or may not be related to type I hypersensitivity. Infusion reactions are thought to result from release of various mediators, such as cytokines.

Gouty flares were expected because pegloticase is intended to dissolve clumps of uric acid crystals and release crystals that unlike native crystals would not be coated with proteins and therefore may have an increased propensity to precipitate and cause inflammation. All patients were pre-treated with NSAIDS or colchicine due to this risk of gouty flares. The frequency of gouty flares was high in all treatment groups, but more so in the pegloticase treatment group during the first 3 months, the frequency seemed to decrease in the subsequent 3 months. The number (%) of patients with any flare for the first 3 months were 63 (74%), 68 (81%), and 22 (51%), for pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks, and placebo, respectively. The number (%) of patients with any flare for the subsequent 3 months were 28 (41%), 39 (57%), and 29 (67%), for pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks, and placebo, respectively.

Immunogenicity is a concern for pegloticase because the uricase enzyme sequence in pegloticase is derived from other mammals and because of the presence of PEG in the product (described in section 3, CMC, above). The applicant has developed anti-uricase and anti-pegloticase assays for IgM and IgG antibodies, but not for IgE antibody. Approximately 90% of patients receiving pegloticase developed anti-pegloticase antibody. Presence of high titre antibody was associated with lack of achievement of the primary efficacy endpoint, and was also associated with high frequency of anaphylaxis or infusion reaction. Most of the anti-pegloticase antibody seemed to be directed against PEG and only a small frequency to the uricase. The consequences of presence of anti-PEG antibody to other PEG containing molecules are not known.

Cardiovascular adverse reactions showed an imbalance favoring placebo. Events occurring with higher frequency in pegloticase arms compared to placebo included ischemic cardiovascular events, heart failure, cardiac arrhythmias, and death. The

numbers of events in each category were generally small, mostly on in the order of one or two events. In the face of the high background rate expected in the study subjects, these small numerical imbalances are not remarkable. The product label will note these findings. Routine post-marketing events will be closely monitored as a tool for surveillance for cardiovascular events. A dedicated post-marketing observational study or a registry based study would not be useful to further understand these events.

The applicant has reasonably characterized the safety of pegloticase as described above, but the safety database is small, and is insufficient to identify rare adverse reactions. Additionally, the long-term immunological consequence (such as anaphylaxis, serum sickness, and infusion reaction) of continued treatment with pegloticase in the presence of anti-pegloticase antibody is not known. The applicant is required to conduct a post-marketing safety study to better characterize the safety of pegloticase.

c. REMS/RiskMAP

Pegloticase will have a REMS limited to a Medication Guide and a Communication Plan to address the safety concerns of anaphylaxis and infusion reaction. These are adequate to address the safety concerns. Further restrictions, such as restricted distribution and Elements to Assure Safe Use (ETASU) are not necessary. Anaphylaxis and infusion reaction are fairly common for biologic products derived from foreign protein. Other comparable products do not have restricted distribution or ETASU. Additionally, the nature of the disease and indication will limit the use of this drug to a medical setting with supervised dosing.

9. Advisory Committee Meeting

An advisory committee was held on June 16, 2009, with members from the Arthritis Advisory Committee, Cardiovascular and Renal Drug Products Advisory Committee, and Drug Safety Advisory Committee. The panel voted 14 to 1 in favor of approval. The safety issues of concerns noted by the combined Committee were anaphylaxis, infusion reaction, and imbalance in cardiovascular adverse reactions. The Committee considered it important to limit the use of pegloticase to patients who were truly refractory to conventional treatment, and cease treatment in patients whose uric acid level rises above 6 mg/dL in order to minimize the risk of anaphylaxis and infusion reaction. There was no consensus regarding whether the imbalance of cardiovascular adverse reactions was a true signal or not. The general opinion was that post-marketing safety information for cardiovascular events should be collected, possibly via an observational epidemiologic study.

10. Pediatric

The Pediatric Research Equity Act (PREA) is not triggered due to the orphan status of the application. Furthermore, gout is an adult disease and rarely occurs in children; therefore, specific pediatric studies are not feasible. In children, gout occurs almost exclusively in the setting of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency (also known as Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome),

which are rare diseases. This application was not discussed at the Center's Pediatric Review Committee (PeRC) meeting because PREA was not triggered.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited 3 investigator sites selected based on high enrollment and result trends, an analytical site that analyzed all patient uric acid levels, and the Applicant for study conduct and analyses. Some minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity. During review of the submission, no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. The applicant certified that no investigator entered into any financial arrangements that could affect the outcome of the study.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name Krystexxa. The proposed proprietary name is acceptable to DMEPA.

b. Physician Labeling

The Applicant submitted a label in the Physician's Labeling Rule format that contained information generally supported by the submitted data. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to health care providers. The labeling contains a Boxed Warning for anaphylaxis and a Medication guide. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, and DDMAC. Changes to different sections of the label were done to reflect the data accurately and better communicate the findings to health care providers. The Division and the Applicant have agreed on the final labeling language.

c. Carton and Immediate Container Labels

The carton and immediate container labels were reviewed by various disciplines of this Division, OBP, and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

A Medication Guide was required as discussed in section 8C above. The Medication Guide has been reviewed by DRISK.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Krystexxa (pegloticase) Injection at a dose of 8 mg given as intravenous infusion every 2 weeks for the treatment of chronic gout in adult patients refractory to conventional therapy. The recommended action on this application is Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment of pegloticase for the treatment of chronic gout in patients refractory to conventional therapy supports its approval. Chronic gout is a serious and debilitating disease. There are no treatment options available for patients who do not tolerate or respond to currently available uric acid lowering drugs including uricosurinc agents (e.g., probenecid) and xanthine oxidase inhibitor (e.g., allopurinol, febuxostat). The direct action of pegloticase in breaking down uric acid provides for the possibility of control of the disease in patients failing the other two treatment options. Given the lack of treatment options available for refractory patients, the risk of anaphylaxis, infusion reaction, and gouty flares with the reported frequency (section 8, Safety, above) is an acceptable risk for pegloticase. To reduce the possibility of anaphylaxis and infusion reaction, and to provide acceptable risk-benefit ratio, patients whose uric acid level rise above 6 mg/dL will not be suitable for continued treatment with pegloticase. With the REMS, consisting of a Medication Guide and Communication Plan (discussed in section 8c, REMS/RsikMap, above) in place for the safety risks, the overall risk-benefit assessment of pegloticase for the proposed indication is favorable.

c. Post-marketing Risk Management Activities

Discussed in section 8c, REMS/RiskMap, above.

d. Post-marketing Study Commitments

There are several studies that the applicant has agreed to conduct as post-marketing commitment or required studies. These are mentioned in section 3 (Chemistry, Manufacturing, and Controls), section 4 (nonclinical pharmacology and toxicology), and section 8 (Clinical Safety) above.