

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125293

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs II
Division of Pulmonary, Allergy, and Rheumatology Products

BLA #: 125293
Products: Krystexxa™ (pegloticase) 8 mg/mL for Intravenous Use
SPONSOR: Savient, Inc.
FROM: Sally Seymour, MD
Deputy Director for Safety *SmS 9/14/10*
THROUGH: Curtis Rosebraugh, MD, MPH *CR 9/14/10*
Office Director
DATE: September 14, 2010

The purpose of this memorandum is to document the rationale for removing the safety issue of major cardiovascular events from the REMS for Krystexxa™ (pegloticase) that was outlined in the July 9, 2009, REMS memorandum. Krystexxa™ (pegloticase) is proposed for the treatment of chronic gout refractory to conventional urate lowering therapy.

In the July 9, 2009, REMS memorandum, FDA determined Krystexxa™ (pegloticase) was required to have a REMS to ensure the benefits of the drug outweigh the risks of severe infusion reactions and anaphylaxis, severe adverse events in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and major cardiovascular events. The elements of the REMS included a Medication Guide, Communication Plan, and timetable for assessments.

A Complete Response action was taken on July 31, 2009. A response to the Complete Response action was submitted on March 15, 2010. Since that time, the review team has received input from various consultants that CV events cannot be clearly attributed to Krystexxa™ (pegloticase). A consult was submitted to the Office of Surveillance and Epidemiology to assess the possible safety signal of cardiovascular (CV) adverse events and to make recommendations on monitoring and evaluating the CV events post-marketing. According to the June 3, 2010, OSE consultation, the OSE Division of Epidemiology (OSE/DEPI) agreed with the sponsor's blinded CV adjudication committee, the consultation from the Division of Cardiovascular and Renal Products (Dr. Stephen Grant), and the Division of Risk Management (DRISK) that CV events cannot be clearly attributed to Krystexxa™ (pegloticase). OSE/DEPI did not recommend an epidemiology study, but recommended routine pharmacovigilance as OSE is aware of the potential risk and will monitor AERS accordingly. Based upon the input from OSE and the DCRP, major cardiovascular events is not considered a safety signal that warrants a REMS to ensure the benefits of Krystexxa™ (pegloticase) outweigh the risks.

A REMS is still required for the risks of severe infusion reactions and anaphylaxis and severe adverse events in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency as outlined in the July 9, 2009 REMS memorandum. The elements of the REMS are unchanged - Medication Guide, Communication Plan, and timetable for assessments. However, the REMS memo will no longer contain the risk of major cardiovascular events.

The following is the revised REMS memorandum:

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Krystexxa™ (pegloticase) to ensure that the benefits of the drug outweigh the risks of severe infusion reactions and anaphylaxis, and severe adverse events associated with use of Krystexxa™ (pegloticase) in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In reaching this determination, we considered the following:

- A. Krystexxa™ (pegloticase) is indicated for chronic gout refractory to conventional urate lowering therapy. The FDA estimates that the number of patients in the United States with chronic gout refractory to conventional urate lowering therapy is 50,000 to 100,000 individuals.
- B. Chronic gout refractory to conventional urate-lowering therapies is characterized by recurrent attacks of painful, inflammatory arthritis and deposits of urate crystals in tissues, termed tophi. The recurrent attacks of arthritis and tophi make this condition a serious and, in some cases, a debilitating condition.

(b) (4)

- D. The expected duration of treatment with the product will be from months to years.

- E. The most common of the known serious adverse events associated with Krystexxa™ (pegloticase) are infusion reactions and anaphylaxis, which would have a very low background incidence that would depend on which drugs the individual was receiving. There is also a risk of severe reactions associated with G6PD deficiency, which would have a very low background incidence that would depend on which drugs the individual was receiving.
- F. Krystexxa™ (pegloticase) is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Krystexxa™ (pegloticase). FDA has determined that Krystexxa™ (pegloticase) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Krystexxa™ (pegloticase). FDA has determined that Krystexxa™ (pegloticase) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Krystexxa™ (pegloticase).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

FINAL REMS REVIEW

Date: September 14, 2010

To: Badrul Chowdhury, MD, Director
Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)

Through: Claudia Karwoski, Pharm D., Director
Division of Risk Management (DRISK)

From: **Scientific Lead**, Elizabeth A. Donohoe, M.D, DRISK
Risk Management Analyst (RMA)

S. Robottom
9.14.10
on behalf of
C. Karwoski

Team Leader, Suzanne Robottom, Pharm D, DRISK

DRISK Review Team

Jodi Duckhorn, Senior Social Science Reviewer, DRISK
Kate Heinrich, Health Educator, DRISK

Subject: Final Risk Evaluation and Mitigation Strategy (REMS)
Review for Krystexxa (pegloticase)

Drug Name

(Established Name): Krystexxa (pegloticase)

Therapeutic Class: Pegylated uric acid specific enzyme

Dosage and Route: 8mg IV infusion every two weeks

Application Type/Number: BLA 125293

Applicant: Savient Pharmaceuticals, Inc.

OSE RCM #: 2010-633

1 INTRODUCTION

Pegloticase has a proposed indication for the treatment of chronic gout in adult patients refractory to conventional therapy. Pegloticase is a PEGylated uric acid specific enzyme administered as an intravenous infusion, 8mg every two weeks. It is not recommended for the treatment of asymptomatic hyperuricemia.

DRISK was initially consulted to review the proposed Risk Management Plan for pegloticase. That review was completed in June 2009 with a recommendation for a Risk Evaluation and Mitigation Strategy (REMS) program including a Medication Guide (MG) and Communication Plan (CP) to address the risks of severe infusion reactions and anaphylaxis, severe adverse events associated with the use of Krystexxa in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and major cardiac events. The sponsor received a CR letter in July 2009, in part due to the REMS requirement.

OSE's Division of Epidemiology was subsequently consulted to address the cardiovascular (CV) events. That review, dated June 3, 2010, concluded that there is not a clear association of Krystexxa with a CV risk. For that reason, it was decided to remove CV adverse events from the REMS and related materials.

The Krystexxa REMS addresses the risks of anaphylaxis, infusion reactions, and contraindication of use of KRYSTEXXA in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. The Krystexxa REMS includes the REMS document, MG, Dear Healthcare Provider (DHCP) Letter, Dear Infusion Site Medical Personnel (DISMP) Letter, REMS website landing page and a Journal Informational Piece.

DRISK has reviewed the sponsor's REMS submissions and provided Interim Comments (dated Sept. 2, 10 and 14) to DPARP. This review is OSE's final review of the proposed REMS for Krystexxa (pegloticase). This review does not address any potential response by the sponsor to comments from DRISK's 3rd Interim Review, forwarded to DPARP on September 14, 2010.

2 MATERIALS REVIEWED

- Proposed REMS, Dear Healthcare Provider (DHCP) Letter, DISMP Letter, REMS website landing page, Journal Informational Piece and REMS Supporting Document (SD) forwarded to DPARP on September 14, 2010 as Attachment 1 to the Interim Comments #3 review.
- Proposed label forwarded by DPARP via email on Sept. 14, 2010.

3 RESULTS OF REVIEW OF PROPOSED KRYSTEXXA RISK EVALUATION AND MITIGATION STRATEGY

3.1 Goals

The goals of the KRYSTEXXA Risk Evaluation and Mitigation Strategy (REMS) are:

1. To inform healthcare providers about anaphylaxis, infusion reactions, and contraindication of use of KRYSTEXXA in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency.
2. To inform patients about the serious risks associated with use of KRYSTEXXA.

3.2 REMS Elements

3.2.1 Medication Guide

A Medication Guide will be distributed to all patients receiving Krystexxa.

3.2.2 Communication Plan

The Krystexxa Communication Plan consists of: a Dear Healthcare Provider Letter, a Dear Infusion Site Medical Personnel Letter, a journal information piece to appear in a number of professional societies' journals and a REMS-dedicated landing page on the Krustexxa website.

3.2.3 Timetable for Submission of Assessments

The sponsor will submit REMS Assessments to the FDA at 1 year, 2 years, 3 years, 5 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. The sponsor will submit each assessment so that it will be received by the FDA within 60 days of the due date. The due date is calculated from the date of launch or 60 days from the approval of the BLA, whichever is sooner.

(b) (4)



Additionally, the Office of Compliance has requested the following with regard to the communication plan:

1. The date of product launch and the launch of the communication plan.
2. The date(s) of mailing and number of recipients of the Dear Healthcare Provider letter (DHCP) and the Dear Infusion Site Medical Personnel letter (DISMP).
3. The number of mailings returned.
4. The sources of the recipient lists.
5. The dates of the annual meetings attended and number of materials distributed.
6. The names of the journals that published the Journal information piece and the dates of publication.

3.4 Proposed Postmarketing Studies (as applicable)

A number of Post-Marketing Requirements (PMRs) are included in the Approval Letter for Krystexxa. Adverse events are the focus of a clinical PMR. The sponsor will be required to conduct an observational safety study enrolling 500 patients treated with Krystexxa (pegloticase) for one year duration. Patients enrolled should have hyperuricemia and gout and be refractory to standard uric acid lowering therapies (e.g., allopurinol). The frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events will be evaluated. Additionally, serious adverse events associated with Krystexxa (pegloticase) therapy will be identified.

4 DISCUSSION

The OSE Krystexxa review team has worked with the review division to develop a MG/CP REMS for Krystexxa to address the risks of anaphylaxis, infusion reactions, and contraindication of use of KRYSTEXXA in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency.

OSE and DPARP are in agreement that the Krystexxa REMS should consist of a MG and CP and the CP materials are aligned with the goals of the Krystexxa REMS. The sponsor has voluntarily put in place a distribution system that utilizes Specialty Distributors for prescribers that choose to administer Krystexxa; this was not a requirement in the REMS. Only Specialty Distributors under contract with the sponsor will have access to Krystexxa.

5 CONCLUSION

In conclusion, the amended REMS for Krystexxa (pegloticase), based on edits provided by DRISK in the Interim Comments #3 review of September 14, 2010, contains the appropriate and agreed upon revisions on the REMS components as stipulated by the Agency. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of the Krystexxa REMS in achieving the goals. DRISK has not yet received the final clean versions of the REMS document and attachments or the SD from the sponsor.

6 RECOMMENDATIONS

DRISK recommends that DPARP approve Krystexxa with the MG/CP REMS attached to this review, pending edits as indicated.

ATTACHMENTS (REMS document and all appended materials. This is the track changes version forwarded to DPARP as Attachment 1 in the Interim Comments #3 review.)

18 Pages has been withheld in full immediately following this page as B4 (CCI/TS)

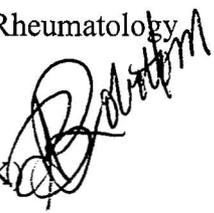
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK INTERIM REMS REVIEW

REMS Comment Set #1

Date: September 2, 2010

To: Badrul Chowdhury, MD, Director
Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)

Through: Suzanne Robottom, Team Leader
Division of Risk Management (DRISK) 

From: **Scientific Lead**, Risk Management Analyst (RMA)
Elizabeth A. Donohoe, M.D., DRISK

DRISK Review Team

Jodi Duckhorn, Senior Social Science Reviewer, DRISK
Kate Heinrich, Health Educator, DRISK

Roberta Szydlo, Regulatory Review Officer, Division of
Drug Marketing, Advertising and Communications
(DDMAC)

Subject: Interim REMS Review Comments for Krystexxa
(pegloticase)

**Drug Name
(Established Name):** Krystexxa (pegloticase)

Therapeutic Class: Pegylated uric acid specific enzyme

Dosage and Route: 8mg IV infusion every two weeks

Application Type/Number: BLA 125293

Applicant: Savient Pharmaceuticals, Inc.

OSE RCM #: 2010-633

1 Materials Reviewed

- Proposed label after initial edit by DPARP, received via email August 26, 2010.
- Review by the Division of Epidemiology (DEpi) in OSE, dated June 3, 2010.
- Review by the Division of Cardiovascular and Renal Products (DCRP), dated May 19, 2010.
- Proposed REMS, Dear Healthcare Professional (DHCP) letter, Dear Infusion Site Medical Personnel Letter, and REMS Supporting Document, submitted March 15, 2010.
- Proposed REMS Journal Informational Piece (Word version), received via email from DPARP April 13, 2010.
- Complete Response (CR) letter dated July 31, 2009.
- Review of Pegloticase Risk Management Plan (RMP) by DRISK, dated June 26, 2009.

2 Introduction and Background

This review is OSE's preliminary review of the proposed REMS for Krystexxa (pegloticase). The application for pegloticase (BLA 125293) was initially submitted to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) and DRISK was consulted to review the proposed RMP; that review was completed in June 2009 with a recommendation for a REMS program including a Medication Guide (MG) and Communication Plan (CP) to address the risks of severe infusion reactions and anaphylaxis, severe adverse events associated with the use of Krystexxa in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and major cardiac events.

DAARP sent the sponsor a CR letter in July 2009 requiring, among other issues, submission of a MG/CP REMS. The CP must include: Dear Healthcare Provider letters for prescribers and infusion center medical personnel; non-promotional print service announcements (journal information pieces); and non-promotional information at major internal medicine and rheumatology meetings.

DCRP was consulted by DAARP to "assess the significance of a greater proportion of subjects in the active treatment arms experiencing cardiovascular (CV) deaths and other CV serious adverse events (SAEs)...and recommend if additional information is needed to define the CV safety of product administration. That review was completed May 19, 2010 and stated: "None of the cardiac adverse events identified appeared unusual...and there are too few cardiac SAEs to be able to allow detection of any pattern."

Recently, BLA 125293 was moved to the newly formed DPARP which includes rheumatology products. DPARP consulted OSE/DEPI to assess a possible safety signal of CV adverse events and to make recommendations on monitoring and

evaluating CV events post-marketing. That review, dated June 3, 2010, referenced the DCRP review and concluded that the “usual practice of reporting AEs...should suffice at this time when it is not clear that causality of the CV events is due to pegloticase.no additional postmarketing activities ...are recommended at this time.”

Given this new information, DPARP has decided that the risk for CV events does not need to be included in the REMS but will be included in the labeling under the Highlights section and Warnings and Precautions regarding congestive heart failure. This review includes edits to remove CV adverse events from the REMS and associated materials.

The sponsor responded to the CR letter on March 15, 2010. This review addresses the March 15 submission, including the REMS document, Dear Healthcare Provider (DHCP) Letter, Dear Infusion Site Medical Personnel (DISMP) Letter, REMS Journal Informational Piece, and REMS Supporting Document. This review also provides some standard guidance to the sponsor regarding the patient and provider surveys. These comments include input from DDMAC regarding the DHCP letter and the Journal Information Piece.

3 Recommendations for the Review Division

We recommend that the following comments on the pegloticase REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review in order to meet the action date for this BLA re-submission.

The comments below are based on DRISK’s preliminary review of the REMS proposal for pegloticase. Attached to this review are the edited (with track changes) Proposed REMS and proposed Dear Health Care Provider Letter. The changes to the DHCP Letter also apply to the Dear Infusion Site Medical Personnel (DISMP) Letter.

4 Recommendations for the Applicant

We have reviewed the submission and have the following comments. Be aware that we anticipate additional comments as your submission(s) undergoes further review. Also, see the attached WORD version of the REMS (with track changes) and the Dear Health Care Provider (DHCP) Letter (with track changes).

- The changes to the DHCP Letter also apply to the DISMP Letter; please make the appropriate changes with your re-submission.
- Comments regarding the Journal Information Piece and the Supporting Document are below; track changes are not provided.
- Comments on the Medication Guide are provided separately.

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs II
Division of Anesthesia, Analgesia, and Rheumatology Products

BLA #: 125293
Products: Krystexxa™ (pegloticase) 8 mg/mL for Intravenous Use
SPONSOR: Savient, Inc.
FROM: Rosemarie Neuner, M.D., M.P.H. 
Medical Officer
THROUGH: Bob Rappaport, M.D. 
Division Director
DATE: July 9, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Krystexxa (pegloticase) to ensure that the benefits of the drug outweigh the risks of severe infusion reactions and anaphylaxis, severe adverse events associated with use of Krystexxa (pegloticase) in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and major cardiovascular events. In reaching this determination, we considered the following:

- A. Krystexxa (pegloticase) is indicated for chronic gout refractory to conventional urate lowering therapy. The FDA estimates that the number of patients in the United States with chronic gout refractory to conventional urate lowering therapy is 50,000 to 100,000 individuals. .
- B. Chronic gout refractory to conventional urate-lowering therapies is characterized by recurrent attacks of painful, inflammatory arthritis and deposits of urate

crystals in tissues, termed tophi. The recurrent attacks of arthritis and tophi make this condition a serious and, in some cases, a debilitating condition.

(b) (4)

- D. The expected duration of treatment with the product will be from months to years.
- E. The most common of the known serious adverse events associated with Krystexxa (pegloticase) are infusion reactions and anaphylaxis, which would have a very low background incidence that would depend on which drugs the individual was receiving. There is also a risk of severe reactions associated with G6PD deficiency, which would have a very low background incidence that would depend on which drugs the individual was receiving. Finally, there have been cases of major cardiac events associated with the use of Krystexxa (pegloticase). Major cardiac events are not uncommon in this patient population and may occur at a rate as high as 1-2% per year.
- F. Krystexxa (pegloticase) is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Krystexxa (pegloticase). FDA has determined that Krystexxa (pegloticase) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Krystexxa (pegloticase). FDA has determined that Krystexxa (pegloticase) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Krystexxa (pegloticase).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

Bob Rappaport, M.D.

Director, Division of Anesthesia, Analgesia, and Rheumatology Products



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 26, 2009
To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology
Products (DAARP), CDER
Through: Claudia Karwoski, Pharm.D., Acting Director
Division of Risk Management (DRISK) *Claudia Karwoski*
Office of Surveillance and Epidemiology (OSE) *7/7/09*
From: OSE Pegloticase Risk Management Team

Scientific Lead:

Kathryn O'Connell, MD, PhD, Medical Officer (DRISK)

Team Members

- Suzanne Berkman Robottom, Pharm.D., Senior Drug Risk Management Analyst, Team Leader (DRISK)
- Mary Dempsey, Risk Management Coordinator (DRISK)
- Peter Diak, PharmD, Division of Pharmacovigilance II
- Christopher Wheeler, Pharm.D., Regulatory Project Manager (OSE)

Subject: Review of Risk Management Plan
Drug Name(s): pegloticase
Submission Number: Original BLA October 31, 2008
Application Type/Number: BLA 125293
Applicant/sponsor: Savient Pharmaceuticals, Inc.
OSE RCM #: 2008-1798

1. INTRODUCTION

This memorandum responds to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) request for Office of Surveillance and Epidemiology (OSE) to review and comment on the sponsor's proposed Risk Management Plan (RMP) for pegloticase, monomethoxypolyethylene glycol modified uricase [PEG-uricase]. The plan was included in the original BLA 125293 submission by Saviant Pharmaceuticals on October 31, 2008. It was subsequently updated in an "addendum" dated January 29, 2007. An advisory committee meeting was held June 16, 2009.

2. BACKGROUND

Pegloticase is a bio-uricolytic with a proposed indication for "treatment failure gout" (TFG), specifically, to control hyperuricemia and manage the signs and symptoms of gout. The sponsor defines TFG as gout in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with allopurinol at the maximum medically appropriate dose or for whom allopurinol is contraindicated. The product is an intravenous infusion given over a 2 hour period every 2 weeks.

Pegloticase, which has Orphan product designation in the US, is a PEG-modified recombinant mammalian (porcine) uricase that catalyzes the conversion of uric acid (UA) to the highly water-soluble end-stage metabolite, allantoin. The sponsor hypothesizes that by eliminating tissue pools of monosodium urate, the clinical manifestations of gout can be controlled or reversed, claiming that the TFG population currently has no effective treatment available other than medications to manage acute flares.

There is a similar product on the U.S. market, rasburicase (recombinant uric oxidase), indicated for tumor lysis syndrome in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in elevation of plasma uric acid. However, the recommended duration of treatment with rasburicase is only 5 days. The most serious adverse reactions in the labeling for rasburicase are anaphylaxis (<1%), rash (1%), hemolysis (<1%), and methemoglobinemia (<1%). According to the sponsor, longer duration rasburicase treatment has been reported in two cases of tophaceous TFG. Both patients experienced an increase in flare activity early in therapy that tapered off with continued dosing. Rasburicase is approved with no additional risk management options beyond labeling and routine pharmacovigilance.

In February 2009 FDA approved Uloric, an orally administered xanthine oxidase inhibitor indicated for the chronic management of hyperuricemia in patients with gout. The product has a Patient Package Insert. The sponsor also has a post-marketing commitment to conduct clinical trials to delineate theophylline interactions and a possible cardiovascular signal. The Warnings and Precautions for Uloric note the following adverse reactions:

- *Gout Flare: An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug (NSAID) or colchicine upon initiation of treatment) may be beneficial for up to six months.*
- *Cardiovascular Events: A higher rate of cardiovascular thromboembolic events was observed in patients treated with ULORIC than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke.*
- *Liver Enzyme Elevation: Transaminase elevations have been observed in ULORIC-treated patients. Monitor liver function tests periodically.*

3. MATERIAL REVIEWED

- Proposed Risk Management Plan submitted for pegloticase, BLA 125293, dated October 31, 2008; revised amendment dated February 4, 2009 ('Risk Management Plan Addendum')
- Filing meeting clinical presentation December 15, 2008
- Mid-cycle clinical presentation January 27, 2009
- Proposed pegloticase package insert dated October 31, 2008; revised amendment dated February 4, 2009
- Rasburicase package insert September 2007
- Uloric package insert February 2009
- Division of Allergy and Pulmonary Products consult re: anaphylaxis dated June 1, 2009
- Internal meetings: Post-advisory committee review, June 17 and 22, 2009

3 RESULTS OF REVIEW

3.1 Overview of clinical program

The pegloticase clinical development patient population consisted of 273 patients exposed to intravenous pegloticase in five clinical studies. Only 169 of these patients were in a randomized, placebo controlled double-blind, Phase 3 trial. These trials used parallel groups of pegloticase 8 mg every 2 weeks for 6 months, pegloticase 8 mg every 4 weeks (plus placebo every 4 weeks to maintain blinding) for 6 months, or placebo every 2 weeks for 6 months. There is also an ongoing open-label extension study for total exposure of 24 months. Currently there are 101 patients who have been exposed to continuous pegloticase for at least 12 months. The sponsor states that the RMP is primarily based on safety data from both the randomized controlled trials and this open label study.

It is important to note that all patients in the pegloticase Phase 3 studies received pretreatment prophylaxis for gout flares (colchicine or NSAIDs) *and* infusion reactions (non-sedating antihistamine, acetaminophen, i.v. corticosteroid). Subjects in the extension study continued with gout flare prophylaxis for at least 3 months, after which it could be discontinued at the discretion of the Principal Investigator. All of these subjects also received the standardized pre-treatment prophylaxis regimen.

A total of 129 patients had some history of cardiovascular disease/hypertension, but patients were excluded for unstable angina, uncontrolled arrhythmia, non-compensated congestive heart failure, and 'uncontrolled' hypertension (above 150/95 mmHg). Hepatic disease was present in 23 patients; there were no specific hepatic exclusion criteria. Renal insufficiency and frank renal disease was present in 81 and 63 subjects, respectively. Patients with a history of end stage renal disease requiring dialysis were excluded. No trial subject had hyposplenism or splenectomy. This is noted because the spleen is involved in removal of pegloticase from the circulation. Other exclusion criteria included significant anemia (due to frequent blood draws in the trials) and G6PD deficiency. Patients were also excluded for past history of allergy to PEGylated products or recombinant proteins.

There were no pregnancies among the treated patients and no lactating women (animal reproductive and developmental toxicology studies did not demonstrate any pegloticase-related abnormalities).

3.2 Safety concerns

3.2.1 The sponsor identified three categories of safety issues for post-marketing risk management:

Identified risks

- Infusion reactions (hypersensitivity and "other" infusion reactions)
- Gout flares

Potential risks

- Anaphylaxis
- Delayed hypersensitivity reactions
- "Use in patients with uncompensated heart disease"
- Acute effects on red blood cells in glucose-6-phosphate dehydrogenase (G6PD) deficiency (methemoglobinemia and hemolytic anemia)
- Immunogenicity (loss of efficacy and association with infusion reactions)

Important missing information

- Effects of long-term exposure

- Withdrawal of therapy
- Patients with hyposplenism/splenectomy
- Patients with hepatic impairment

3.2.2 At the filing and mid-cycle review meetings, the review division emphasized the following safety issues:

- Antibody formation and infusion reactions present safety and long-term efficacy issues (7% of subjects had a severe reaction despite pre-medication versus none in the placebo arm). The review division obtained a consult from DPAP regarding anaphylaxis. That consult concluded as follows:

An estimated rate of anaphylaxis of 5% is not unusually high compared to similar porcine-derived biologic products. However, we note that the proposed product label does not explicitly describe the risk for anaphylaxis. Also, we note that the BLA does not contain a proposal for further evaluation of potential screening tests, including skin testing, graded challenges, and serum antibody assays. Such tests could potentially identify patients at risk for anaphylaxis and improve the risk:benefit ratio for the drug.

- There appears to be an excess of cardiovascular events in the treatment arms compared to placebo, but the population size and duration of exposure are insufficient to address causality. There does not appear to be an imbalance in effect on overall mortality, nor did a clear trend in types of cardiovascular events emerge in clinical review by the CardioRenal Division or in statistical analysis.
- The product is associated with gout flares, possibly because it mobilizes urate in tophi and tissues. This also underscores a unique feature of the product, in that it is the only gout therapy to date that has been shown to actually decrease the size of existing tophi¹.

3.2.3 06/17/2009 and 6/22/2009 Internal Meetings: Post-advisory committee review

As summarized by the reviewing division, the committee's two main safety concerns were the indeterminate cardiovascular risk and the established infusion reactions. As such, the committee suggested a risk management strategy with the following two safety objectives:

¹ Both pivotal trials showed statistical significance for the primary efficacy endpoint: 47% and 38% response for 8 mg every 2 weeks, versus no responders for placebo.

- 1) The product should be reserved for patients for whom the risks are justified by the benefit. For example, the product should not be used to normalize serum urate levels).
- 2) Collect more data on cardiovascular outcomes among patients using the product.

At an internal meeting held with the DAARP review team and OSE, REMS were discussed as a possible approach to addressing the infusion reactions.

The role of an observational study or voluntary registry (outside of a REMS) was discussed as an approach to collecting more data on cardiovascular outcomes.

In addition to AC follow-up discussion, new data analysis was discussed suggesting that patients who develop neutralizing antibodies to the product are more likely to experience infusion reactions. Since these antibodies also interfere with the product's efficacy, the review division seeks a risk mitigation strategy to prevent continued exposure among these patients, who stand to gain no benefit.

3.3 Sponsor's risk management proposal



(b) (4)

4 DISCUSSION

Considerations in Determining the Need for REMS

REMS are intended to meet specific risk mitigation goals for a product that requires strategies beyond professional labeling to ensure safe use in the post-marketing setting. If the review division finds that the risks of pegloticase are justified by benefit for gout patients, it is important to determine if such additional measures are feasible, appropriate, and necessary to mitigate the risks. This determination by FDA is particularly important if the additional measures include ETASU that restrict distribution and thus pose considerable burden on the healthcare system and patients.

Cardiovascular events

Cardiovascular events possibly associated with pegloticase are not amenable to REMS monitoring strategy, since the observed numbers of cardiovascular events are too low to identify the at-risk population and/or a monitoring schema to prevent events. *If* the cardiovascular signal reflects actual risk, events could be “prevented” by limiting the number of patients exposed to the product, by restricting pegloticase to the approved indication. This approach however would potentially deny treatment to patients who do not meet the stated indication, but who, in their physician’s best judgment, would benefit. Furthermore, Uloric, an orally administered xanthine oxidase inhibitor indicated for the chronic management of hyperuricemia in patients with gout, was approved in February 2009 without a REMS. According to

Uloric's labeling², it too appeared to have a cardiovascular signal. In our internal meeting with DAARP, they agreed that a REMS that includes a plan to restrict the drug to address the cardiovascular events or to require cardiovascular monitoring of all patients was not warranted and that the cardiovascular signal could be further assessed in a postmarketing study. Any labeling regarding the cardiovascular risk could be addressed in patient labeling.

Gout flares

Gout flares are frequently observed during initiation of anti-hyperuricemic agents and none of these products have REMS. If the gout flares observed with pegloticase are consistent with what is known about other anti-hyperuricemic agents, we would not recommend REMS with ETASU to address this safety concern.

Infusion reactions

Infusion reactions may be amenable to REMS with ETASU and may be warranted if the infusion reactions are life-threatening and if it is felt that the medical supervision and routine emergent management as per standard of care in the usual infusion center setting is insufficient.

ETASU aimed at limiting the number of patients initially chosen for treatment are not necessary unless significant off label use is anticipated. Patients with mild gout or asymptomatic hyperuricemia would have no incentive to undergo frequent, lengthy infusions and significant reactions. Unnecessary use by unscrupulous and/or incompetent prescribers will not be stopped by ETASU short of requiring laboratory/clinical/radiographic documentation of need, followed by authorization, and closed-loop dispensing.

For patients undergoing pegloticase therapy, future infusion reaction risk could be mitigated if FDA/sponsor can identify a laboratory test value that predicts who will no longer benefit from the product and/or is at greater risk. Such information can be delivered in labeling, augmented by a REMS Communication Plan for healthcare providers (in this case prescribers and infusion centers), or 'documented' by an ETASU program that 'certifies' prescriber and infusion center understanding. This can be implemented with or without restricted distribution based on documentation that testing has

² Uloric's labeling has the following Warning: *A higher rate of cardiovascular thromboembolic events was observed in patients treated with ULORIC than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke.* The product also has a post-marketing commitment to conduct clinical trials to delineate the possible cardiovascular signal.

been performed, evaluated, and the patient authorized for continued infusion.

At this time, it is not known if HCP registration/certification as an isolated ETASU is superior to education supplied via a Communication Plan. Physician attestation of safe use conditions under the Tysabri risk management program appears to have had the intended effect on how the product is prescribed.³ Note, however, that physician attestation for Tysabri is accompanied by additional elements of a closed-loop restricted distribution program. It is unknown whether physician attestation as a means to ensure appropriate laboratory monitoring is effective. It is presumably more effective than labeling alone. Of note, it was not sufficiently effective to ensure pregnancy testing under the isotretinoin SMART program, which required physicians to attest to conducting pregnancy tests on a monthly basis.

While post-marketing adverse event reporting might detect some cases of lack of compliance with required monitoring in patients who experience adverse events, it would not suffice to assess ETASU effectiveness since voluntary reporting is biased and significantly under-ascertains events. A program requiring a laboratory test as documentation of safe use conditions would offer greater assurance that laboratory testing was being conducted if that laboratory test was required in order to receive another dose. It is crucial to note that in the absence of a closed-loop program, FDA will not receive detailed patient-level data needed to delineate whether the testing process is, in fact, mitigating the risk. Prescribers and infusion centers not following procedure despite attesting to cooperate are highly unlikely to participate in voluntary surveys or report adverse outcomes, much less link those outcomes to such behavior. Thus, ETASU without closed-loop restricted distribution must be accompanied by realistic assessment goals and data requests on the part of FDA. For this reason, we cannot over-emphasize the importance of clear, prospectively identified goals and expectations.

Lastly, it is important to consider the burdens of REMS with ETASU. Any REMS with ETASU options does entail possible hardship for patients in isolated areas who may be unable to locate 'certified' providers, as some providers may opt not to participate in the program and prescribe the product. Refusal to engage REMS certification programs will likely become more common as such programs proliferate, which underscores the need to reserve ETASU for products with exceptional safety issues. Restricted distribution based on documentation that testing has been performed, evaluated, and the patient authorized for continued infusion obviously entails much greater burden on patients, physicians and infusion centers since

³ Less than 1% of patients and prescribers report concomitant use of an immunosuppressant or chronic corticosteroid use, a condition felt by the Agency to put patients at greater potential risk of PML. Tysabri (natalizumab) RiskMAP 7th MS Submission, August 2008.

patient and infusion center registration are required, in addition to provider registration.

Sponsor's Proposed REMS

(b) (4)



5 RECOMMENDATIONS

- (1) If pegloticase is approved, prescribers and patients need non-promotional information to decide whether to use pegloticase despite the indeterminate risk of cardiovascular adverse effects and the established risk of infusion reactions and gout flares. We recommend a REMS consisting of a Medication Guide for patients and a Communication Plan for prescribers and infusion center medical personnel:
 - a. The PPI should be converted to a Medication Guide to improve patient compliance with important instructions to mitigate severe infusion reactions and gout flares.
 - Medication Guides trigger REMS and are therefore subject to assessment by the sponsor. The sponsor therefore will need to submit a plan for assessing the effectiveness of the Medication Guide in educating patients about the risk(s).
 - Medication Guide review is conducted after professional labeling is substantially completed.
 - b. The sponsor should submit a detailed Communication Plan consisting of, at minimum, Dear Healthcare Provider letters for prescribers and infusion center medical personnel, non-promotional print service announcements in rheumatology journals, and non-promotional information at major internal medicine and rheumatology meetings.
- (2) ETASU *may* be justified for pegloticase if there is reason to believe that the risk of life threatening infusion reactions cannot be adequately addressed by labeling and medical supervision/routine emergent management as per standard of care in the infusion center setting. We strongly recommend that the plan entail the least burden possible consistent with clearly stated safety goals and assessment requirements consistent with those goals. ETASU options are:
 - a. Prescriber enrollment with attestation
 - b. Infusion center enrollment
 - c. Patient enrollment and documentation of safe use conditions
- (3) If approval is planned with observational post-marketing study or registry, The Division of Epidemiology should be consulted as soon as possible.
- (4) If pegloticase is approved, the sponsor should be asked to submit post-marketing cardiovascular events and serious infusion reactions as expedited (15-day) reports even though these events will be labeled adverse reactions.