Initial REMS approved: 09/2010
Most Recent Modification: 04/2012

BLA 125293
KRYSTEXXA® (pegloticase)
PEGylated uric acid specific enzyme

Savient Pharmaceuticals, Inc.

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

The goal of the KRYSTEXXA Risk Evaluation and Mitigation Strategy (REMS) is:

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

II. REMS ELEMENTS:

A. Communication Plan

Savient Pharmaceuticals, Inc. will implement a communication plan to healthcare providers to support implementation of this REMS.

Savient Pharmaceuticals, Inc. will institute a communication plan for healthcare providers who are expected to be the predominant healthcare providers who prescribe, administer and dispense KRYSTEXXA.

Savient will providenew prescribers and new infusion centers the Dear Healthcare Provider (DHCP) or Dear Infusion Site Medical Personnel (DISMP) Letter, as appropriate, at the time the product is purchased or shipped to ensure those who prescribe, administer and dispense KRYSTEXXA receive these materials.

The communication plan will disseminate risk information about anaphylaxis and infusion reactions, including increased risk of anaphylaxis and infusion reactions with concomitant use of KRYSTEXXA and oral urate-lowering therapy, and the contraindication of use of KRYSTEXXA in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency.

Elements of the communication plan are:

1. A Dear Healthcare Provider Letter (see Attachment A) will be distributed to rheumatologists, nephrologists, and internists and family practice physicians, associated with infusion centers where KRYSTEXXA may be prescribed, administered and dispensed. This letter will be distributed by mail and electronically at product launch or within 60 days of KRYSTEXXA approval, whichever is sooner. The Dear Healthcare Provider Letter will be mailed and distributed electronically via e-mail again to these audiences once per year for an additional 2 years. In addition, for 2 years after launch, any known new prescribers of KRYSTEXXA not previously targeted will also be sent the Dear Healthcare Provider Letter. Savient will initially target approximately 5,000 rheumatologists, 7,500 nephrologists, and those internists and family practice physicians who purchase infused biologics from the Distributors or Pharmacies that Savient contracts with for product distribution. New prescribers purchasing KRYSTEXXA from these Distributors or Pharmacies will also receive the most recent Dear Healthcare Provider Letter and will be receiving letters annually as per the timeline in the communication plan. The targeted healthcare providers will be identified as follows: rheumatologists – American College of Rheumatology membership cross-referenced to the AMA database, nephrologists - American Society of Nephrology membership cross-referenced to the AMA database and Distributor databases. New prescribers will be identified using the Distributor and Pharmacy databases.

   The approved Full Prescribing Information, which includes the Medication Guide, will also be distributed with this letter.

   The DHCP Letter will also be available through a REMS-dedicated link from the www.KRYSTEXXA.com website and distributed by Savient professionals when calling on healthcare providers. (See attached web page in Attachment B). Only FDA approved materials will be included on the REMS dedicated website.

2. A Dear Infusion Site Medical Personnel (DISMP) Letter (see Attachment C) will be distributed to directors or responsible heads of infusion sites engaged in the administration of rheumatologic infusions. This will be distributed by mail and electronically at product launch or within 60 days of KRYSTEXXA approval, whichever is sooner. The Dear Infusion Site Medical Personnel letter will be mailed and distributed electronically via e-mail again to this audience once per year for an additional 2 years. Savient will initially target all infusion sites (approximately 1,500 infusion sites) which will be identified using the customer lists of infusion centers from the databases of Distributors and Pharmacies. In addition, for 2 years after launch, any known new infusion sites for administration of KRYSTEXXA not previously targeted will also be sent the Dear Infusion Site Medical Personnel Letter.

   The approved prescribing information, which includes the Medication Guide, will also be distributed with this letter.

   The DISMP Letter will also be available through a REMS-dedicated link from the www.KRYSTEXXA.com website and distributed by Savient professionals when calling on infusion sites. (See attached web page in Attachment B). Only FDA approved materials will be included on the REMS dedicated website.

3. Savient will distribute Dear Healthcare Provider Letter with Prescribing Information, which includes the Medication Guide, at the American College of Rheumatology, American College of Physicians, and the American Society of Nephrology annual meetings. The Dear

Infusion Site Medical Personnel Letter, Prescribing Information, which includes the Medication Guide, will be distributed at the Infusion Nurses Society Annual Meeting. This effort will start at the first annual meeting post-approval of the REMS, provided the deadlines for processing requests through the respective organizations have not passed (in which case the non-promotional materials will be distributed at the next annual meeting).

4. Savient will publish, within 90 days of product approval, journal information pieces about risks of anaphylaxis, infusion reactions, including increased risk of anaphylaxis and infusion reactions with concomitant use of KRYSTEXXA and oral urate-lowering therapy, and the contraindicated use of KRYSTEXXA in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency, with key aspects of management. These announcements will appear in the following professional societies' journals: American College of Rheumatology, American College of Physicians, the American Society of Nephrology and the Infusion Nurses Society.

   - Arthritis and Rheumatism – Official monthly journal of the American College of Rheumatology.
   - Annals of Internal Medicine – Official monthly journal of the American College of Physicians
   - Journal of the American Society of Nephrology – Official monthly journal of American Society of Nephrology.
   - Journal of Infusion Nursing – Official bi-monthly journal of the Infusion Nurses Society

   These announcements will be published on a twice-yearly basis for the first 3 years after product approval. (See Attachment D)

B. Timetable for Submission of Assessments

Savient 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 (September 14, 2010).
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. Savient will submit each assessment so that it will be received by the FDA on or before the due date.

ATTACHMENT A: DEAR HEALTHCARE PROVIDER LETTER

IMPORTANT DRUG WARNING
KRYSTEXXA®
(pegloticase)

Subject: **- Risk of anaphylaxis and infusion reactions**
- Concomitant use of KRYSTEXXA and oral urate-lowering therapies
- Contraindication of use of KRYSTEXXA in patients with G6PD deficiency

<Insert date>

Dear Healthcare Provider:

The purpose of this letter is to inform you of important safety information about KRYSTEXXA® (pegloticase), which has been approved by the US Food and Drug Administration (FDA). KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated. KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

Important Information about the Risks of KRYSTEXXA

1. The FDA has approved KRYSTEXXA with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of:

   - **Anaphylaxis*,**
   - **Infusion reactions***

   *** New post-marketing safety information suggests that concomitant use of KRYSTEXXA with oral urate-lowering therapies may increase the risk of infusion reactions and anaphylaxis (see Section below: Concomitant Use with Urate-Lowering Agents).**

2. **Contraindication of use of KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency**

The KRYSTEXXA labeling includes the following Boxed Warning:

WARNING: ANAPHYLAXIS and INFUSION REACTIONS
See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed**.

Anaphylaxis

Intravenous administration of KRYSTEXXA may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions.

Anaphylaxis was reported in 6.5% of patients administered KRYSTEXXA every 2 weeks compared to none with placebo during pre-marketing controlled clinical trials. **All patients received pre-treatment medication**.

Infusion Reactions

Infusion Reactions were reported in 26% of patients administered KRYSTEXXA 8mg every 2 weeks and 41% administered 8 mg every 4 weeks compared to 5% of patients with placebo during pre-marketing controlled clinical trials. **All patients received pre-treatment medication**. The most commonly reported signs and symptoms included urticaria (11%), dyspnea (7%), erythema (6%, and flushing (6%). The risk of infusion reaction is higher in patients who have lost therapeutic response.

Concomitant Use with Urate-Lowering Agents

Post-marketing safety information suggests that the concomitant use of KRYSTEXXA with oral urate-lowering therapies, including allopurinol and febuxostat, may prevent the detection of patients who have lost therapeutic response to KRYSTEXXA, and increase the risk of infusion reactions and/or anaphylaxis. It is therefore recommended that before starting KRYSTEXXA patients **discontinue** oral urate-lowering medications and **not institute therapy with oral urate-lowering agents** while taking KRYSTEXXA.

Contraindication of KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency

Use of KRYSTEXXA is **contraindicated** in patients with G6PD deficiency due to the risk of hemolysis and methemoglobinemia. It is recommended that patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) be screened for G6PD deficiency prior to starting KRYSTEXXA.

Key Aspects of Recommended Management

- Discontinue oral urate-lowering therapies before instituting KRYSTEXXA and do not institute oral urate-lowering therapy while the patient is on KRYSTEXXA therapy

- Infusion reactions
  - Patients should receive pre-treatment medication prior to each infusion to minimize the risk of infusion reactions, including anaphylaxis.
  - Administer KRYSTEXXA in a healthcare setting prepared to manage anaphylaxis.
  - Observe patients for an appropriate period of time after administration.
- Serum uric acid
  - Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6mg/dL, particularly when 2 consecutive values above 6 mg/dL are observed. The risk of anaphylaxis and infusion reactions is higher in patients whose uric acid level increases to above 6 mg/dL.

Medication Guide

KRYSTEXXA has a **Medication Guide** that accompanies the Full Prescribing Information. You should review the information in the Medication Guide with your patients. Provide each patient with a Medication Guide every time you administer KRYSTEXXA to your patients as the information contained within may change over time.

Reporting Patient Adverse Events

Healthcare professionals should report all adverse events suspected to be associated with the use of KRYSTEXXA by calling 1-888-KRYSTEXXA (1-888-579-7839). Alternatively, report this information to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/) or by mail, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Read the accompanying FDA-approved Full Prescribing Information for KRYSTEXXA.

If you have any questions, please contact Savient Pharmaceuticals, Inc. Medical Information at 1-888-KRYSTEXXA (1-888-579-7839).

Please find enclosed the KRYSTEXXA Full Prescribing Information and Medication Guide.

Sincerely,

Medical Affairs
Savient Pharmaceuticals, Inc.

This letter has been reviewed and approved by the FDA as part of the KRYSTEXXA REMS.

ATTACHMENT B: WWW.KRYSTEXXA.COM WEBPAGES

IMPORTANT DRUG WARNING
KRYSTEXXA® (pegloticase)

Subject: **- Risk of anaphylaxis and infusion reactions**
- Concomitant use of KRYSTEXXA and oral urate-lowering therapies
- Contraindication of use of KRYSTEXXA in patients with G6PD deficiency

<Insert date>

Dear Infusion Site Medical Personnel:

The purpose of this letter is to inform you of important safety information about KRYSTEXXA® (pegloticase), which has been approved by the US Food and Drug Administration (FDA). KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated. KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

Important Information about the Risks of KRYSTEXXA

1. The FDA has approved KRYSTEXXA with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of:

   - **Anaphylaxis***
   - **Infusion reactions***

   ***New post-marketing safety information suggests that concomitant use of KRYSTEXXA with oral urate-lowering therapies may increase the risk of infusion reactions and anaphylaxis (see Section below: Concomitant Use with Urate-Lowering Agents).**

2. **Contraindication of use of KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency**

The KRYSTEXXA labeling includes the following Boxed Warning:

WARNING: ANAPHYLAXIS and INFUSION REACTIONS
See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed**.

Anaphylaxis
Intravenous administration of KRYSTEXXA may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions.

Anaphylaxis was reported in 6.5% of patients administered KRYSTEXXA every 2 weeks compared to none with placebo during pre-marketing controlled clinical trials. **All patients received pre-treatment medication**.**Infusion Reactions**

Infusion Reactions were reported in 26% of patients administered KRYSTEXXA 8 mg every 2 weeks and 41% administered 8 mg every 4 weeks compared to 5% of patients with placebo during pre-marketing controlled clinical trials. **All patients received pre-treatment medication**. The most commonly reported signs and symptoms included urticaria (11%), dyspnea (7%), erythema (6%, and flushing (6%). The risk of infusion reaction is higher in patients who have lost therapeutic response.

Concomitant Use with Urate-Lowering Agents

Post-marketing safety information suggests that the concomitant use of KRYSTEXXA with oral urate-lowering therapies, including allopurinol and febuxostat, may prevent the detection of patients who have lost therapeutic response to KRYSTEXXA, and increase the risk of infusion reactions and/or anaphylaxis. It is therefore recommended that before starting KRYSTEXXA patients **discontinue** oral urate-lowering medications and **not institute therapy with oral urate-lowering agents** while taking KRYSTEXXA.

Contraindication of KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency

Use of KRYSTEXXA is contraindicated in patients with G6PD deficiency due to the risk of hemolysis and methemoglobinemia. It is recommended that patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) be screened for G6PD deficiency prior to starting KRYSTEXXA.

Key Aspects of Recommended Management

- Discontinue oral urate-lowering therapies before instituting KRYSTEXXA and do not institute oral urate-lowering therapy while the patient is on KRYSTEXXA therapy
- Infusion reactions

- Patients should receive pre-treatment medication prior to each infusion to minimize the risk of infusion reactions, including anaphylaxis.
- Administer KRYSTEXXA in a healthcare setting prepared to manage anaphylaxis.
- Observe patients for an appropriate period of time after administration.

- Serum uric acid
  - Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6mg/dL, particularly when 2 consecutive values above 6 mg/dL are observed. The risk of anaphylaxis and infusion reactions is higher in patients whose uric acid level increases to above 6 mg/dL.

Medication Guide

KRYSTEXXA has a **Medication Guide** that accompanies the Full Prescribing Information. You should review the information in the Medication Guide with your patients. Provide each patient with a Medication Guide every time you administer KRYSTEXXA to your patients as the information contained within may change over time.

Reporting Patient Adverse Events

Healthcare professionals should report all adverse events suspected to be associated with the use of KRYSTEXXA by calling 1-888-KRYSTEXXA (1-888-579-7839). Alternatively, report this information to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/) or by mail, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Read the accompanying FDA-approved Full Prescribing Information for KRYSTEXXA.

If you have any questions, please contact Savient Pharmaceuticals, Inc. Medical Information at 1-888-KRYSTEXXA (1-888-579-7839).

Please find enclosed the KRYSTEXXA Full Prescribing Information and Medication Guide.

Sincerely,

Medical Affairs
Savient Pharmaceuticals, Inc.

This letter has been reviewed and approved by the FDA as part of the KRYSTEXXA REMS.

ATTACHMENT D: JOURNAL INFORMATION PIECE

Important Information on the Safe Use of KRYSTEXXA® (pegloticase)

Savient Pharmaceuticals, Inc. is providing this Important Information on the Safe Use of KRYSTEXXA® (pegloticase) as part of our commitment to the safe and appropriate use of KRYSTEXXA.

KRYSTEXXA is a PEGylated uric acid specific enzyme for administration by intravenous infusion for the treatment of chronic gout in adult patients refractory to conventional therapy.

Decisions to use KRYSTEXXA must balance the potential benefits with the potential risks of therapy based upon your patients' individual needs. Please review the key safety information below and the product labeling carefully before initiating therapy.

The US Food and Drug Administration (FDA) has approved KRYSTEXXA with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of anaphylaxis and infusion reactions and contraindication of use of KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be premedicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**

Anaphylaxis

Intravenous administration of KRYSTEXXA may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions.

Anaphylaxis was reported in 6.5% of patients administered KRYSTEXXA during premarketing clinical trials. All patients received pre-treatment medication.

Infusion Reactions

Infusion reactions were reported in 26% of patients administered KRYSTEXXA every 2 weeks during premarketing clinical trials compared to 5% of patients treated with placebo. All patients received pre-medication. The most commonly reported signs and symptoms included urticaria (11%), dyspnea (7%), erythema (6%), and flushing (6%). The risk of infusion reaction is higher in patients who have lost therapeutic response.

Concomitant Use with Urate-lowering Agents

Concomitant use of KRYSTEXXA with oral urate-lowering therapies, including allopurinol and febuxostat, may prevent the detection of patients who have lost therapeutic response to KRYSTEXXA, and increase the risk of infusion reactions and/or anaphylaxis. It is therefore recommended that before starting KRYSTEXXA patients **discontinue** oral urate-lowering medications and **not institute therapy with oral urate-lowering agents** while taking KRYSTEXXA.

Key Aspects of Recommended Management

- Discontinue oral urate-lowering therapies before instituting KRYSTEXXA and do not institute oral urate-lowering therapy while the patient is on KRYSTEXXA therapy.
- Infusion reactions
  - Patients should receive pre-treatment medication prior to each infusion to minimize the risk of infusion reactions, including anaphylaxis.
  - Administer KRYSTEXXA in a healthcare setting prepared to manage anaphylaxis.
  - Observe patients for an appropriate period of time after administration.
- Serum uric acid
  - Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6mg/dL, particularly when 2 consecutive values above 6 mg/dL are observed.

Contraindication in Patients with G6PD Deficiency

Use of KRYSTEXXA is contraindicated in patients with G6PD deficiency due to the risk of hemolysis and methemoglobinemia. It is recommended that patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) be screened for G6PD deficiency prior to starting KRYSTEXXA.

Additional Information: Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated. KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

If you have any questions regarding KRYSTEXXA, please contact Savient Pharmaceuticals, Inc. Medical Information at 1-888-KRYSTEXXA (1-888-579-7839).

KRYSTEXXA® (pegloticase)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
04/16/2012