

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.

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/ Dear Infusion Site Medical Personnel Letter (DHCP/DISMP) (see [Attachment A](#)) will be distributed by Savient representatives at least once between September 14, 2013 and September 14, 2014, to rheumatologist offices and infusion sites where KRYSTEXXA may be prescribed, administered and dispensed.

New healthcare prescribers and infusion site customers purchasing KRYSTEXXA from Distributors or Pharmacies will also receive the DHCP/DISMP Letter and the approved Prescribing Information. Between the date of approval of the 2013 REMS modification and September 14, 2014, Savient will mail the DHCP/DISMP letter within one month of each initial shipment of KRYSTEXXA. New prescribers and infusion site customers will be identified using the sales and distributor databases.

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

2. Savient will distribute the DHCP/DISMP Letter with Prescribing Information, which includes the Medication Guide, at the American College of Rheumatology Annual Meeting for an additional year (2014 Annual Meetings).

3. The DHCP/DISMP Letter will also be available through a REMS-dedicated link from the www.KRYSTEXXA.com website (See attached web page in [Attachment B](#)). Only FDA approved materials will be included on the REMS dedicated website. This REMS-dedicated link will exist throughout the 7 year time period. The KRYSTEXXA REMS webpage will also be accessible through a search engine.
4. Savient will publish 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 and the Infusion Nurses Society.
 - Arthritis and Rheumatism – Official monthly journal of the American College of Rheumatology.
 - Journal of Infusion Nursing – Official bi-monthly journal of the Infusion Nurses SocietyThese announcements will be published in the fourth year after product approval (September 14, 2013 to September 14, 2014). (See [Attachment C](#))

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 by the due date (14 September).

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ATTACHMENT A: DHCP/DISMP 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 / Infusion Site Medical Personnel:

The purpose of this letter is to inform you of important safety information about KRYSTEXXA® (pegloticase). 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.

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of KRYSTEXXA outweigh the risks of:

- **Anaphylaxis***
- **Infusion reactions***
- **Concomitant use of KRYSTEXXA with urate lowering therapies**

Important Safety Consideration

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

Contraindications

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.

Important Limitations of Use

KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

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.

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.

Medication Guide

KRYSTEXXA has a **Medication Guide** that accompanies the 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 Adverse Events

To report any adverse events with the use of KRYSTEXXA contact:

- Savient at 1-888-KRYSTEXXA (1-888-579-7839)
- FDA's Med Watch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (<https://www.accessdata.fda.gov/scripts/medwatch/>).

Read the accompanying FDA-approved 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 Prescribing Information and Medication Guide.

Sincerely,

Medical Affairs
Savient Pharmaceuticals, Inc.
400 Crossing Boulevard
Bridgewater, NJ 08807

KRYSTEXXA[®]

(pegloticase)

Prescribing Information

Medication Guide

REMS

Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

In order for Savient Pharmaceuticals, Inc. (Savient) to communicate certain risks about KRYSTEXXA[®] (pegloticase), Savient has worked with the FDA to develop materials to communicate the risks of:

- Anaphylaxis
- Infusion reactions
- Contraindication of use of KRYSTEXXA in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency
- Concomitant use of KRYSTEXXA and urate-lowering therapies

The REMS program is designed to inform healthcare providers and patients about the risks with KRYSTEXXA. To learn more about serious risks, read the important safety information provided in this link, including the Medication Guide, and discuss it with your patients.

The goal of the KRYSTEXXA 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.

Use the links below to access important REMS documents

 [Prescribing Information](#)

 [Dear Healthcare Provider / Infusion Site Medical Personnel Letter](#)

 [Medication Guide](#)

 [Medical Journal Information Piece](#)

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 **SAVIENT[®]**
PHARMACEUTICALS, INC.

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).

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KRYSTEXXA[®]
(pegloticase)

Blind 8.75 x 11.25

Blind 7.75 x 10.75

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