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
Crealta Pharmaceuticals LLC (Crealta) will implement a communication plan to healthcare providers to support implementation of this REMS.

Crealta Pharmaceuticals LLC (Crealta) will implement a communication plan for healthcare providers who are expected to be the predominant clinicians 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 Crealta 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, Crealta 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. Crealta 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. Crealta 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 Society
   These 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

Crealta 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. Crealta will submit each assessment so that it will be received by the FDA by the due date (14 September).
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

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.
ATTACHMENT A: DHCP/DISMP LETTER

Key Aspects of Recommended Management

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

- Infusion reactions
  - Patients should receive pre-treatment medication prior to each infusion to minimize the risk of infusion reactions, including anaphylaxis.
  - Administer KRYSXEXXA 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

KRYSXEXXA 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 KRYSXEXXA to your patients as the information contained within may change over time.

Reporting Patient Adverse Events

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

- Crealta at 1-888-KRYSXEXXA (1-888-579-7839)
- 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/).

Read the accompanying FDA-approved Prescribing Information for KRYSXEXXA.

If you have any questions, please contact Crealta Pharmaceuticals LLC Medical Information at 1-888-KRYSXEXXA (1-888-579-7839).

Please find enclosed the KRYSXEXXA Prescribing Information and Medication Guide.

Sincerely,
Medical Affairs
Crealta Pharmaceuticals LLC
500 W. Silver Spring Drive
Suite K-200
Glendale, WI 53217
ATTACHMENT B: WWW.KRYSTEXXA.COM WEBPAGES

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 Crealta Pharmaceuticals LLC (Crealta) to communicate certain risks about Krystexxa® (pegloticase), Crealta 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
- Concurrent 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 buttons below to access important REMS documents:

- Prescribing Information
- Medication Guide
- Dear Healthcare Professional Letter
- Medical Journal Information Piece

IMPORTANT SAFETY INFORMATION

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.
Important Information on the Safe Use of 
KRYSXEEXXA® (pegloticase)

Cesalia Pharmaceuticals LLC is providing this Important Information on the Safe Use of KRYSXEEXXA® (pegloticase) as part of our commitment to the safe and appropriate use of KRYSXEEXXA.

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

Decision to use KRYSXEEXXA 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 KRYSXEEXXA 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 KRYSXEEXXA 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 KRYSXEEXXA.
- 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.
- KRYSXEEXXA 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 KRYSXEEXXA.
- 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

Intavenous administration of KRYSXEEXXA may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. Anaphylaxis was reported in 6.5% of patients administered KRYSXEEXXA during premarketing clinical trials. All patients received pre-treatment medication.

Infusion Reactions

Infusion reactions were reported in 2.6% of patients administered KRYSXEEXXA 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 (1%), 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 KRYSXEEXXA with oral urate-lowering therapies, including allopurinol and febuxostat, may prevent the detection of patients who have lost therapeutic response to KRYSXEEXXA and increase the risk of infusion reactions and/or anaphylaxis. It is therefore recommended that before starting KRYSXEEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSXEEXXA.

Key Aspects of Recommended Management:

- Discontinue oral urate-lowering therapies before instituting KRYSXEEXXA and do not institute oral urate-lowering therapy while the patient is on KRYSXEEXXA therapy.
- Infusion reactions
  - Patients should receive pre-treatment medication prior to each infusion to minimize the risk of infusion reactions, including anaphylaxis.
  - Administer KRYSXEEXXA 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 6 mg/dL, particularly when 2 consecutive values above 6 mg/dL are observed.

Contraindication in Patients with G6PD Deficiency

Use of KRYSXEEXXA 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 KRYSXEEXXA.

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. KRYSXEEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

If you have any questions regarding KRYSXEEXXA please contact Cesalia Pharmaceuticals LLC Medical Information at 1-888-KRYSXEEXXA (1-888-597-7639).

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/s/

SALLY M SEYMOUR
07/30/2015