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.
Key Aspects of Recommended Management

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

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

Medication Guide

KRYS
texxa 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 KRYS
texxa 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 KRYS
texxa contact:

- Crealta at 1-888-KRYS
texxa (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 KRYS
texxa.

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

Please find enclosed the KRYS
texxa Prescribing Information and Medication Guide.

Sincerely,

Medical Affairs
Crealta Pharmaceuticals LLC
500 W. Silver Spring Drive
Suite K-200
Glendale, WI 53217