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Pegloticase (Krystexxa) Clinical Guideline for Home Intravenous Therapy

Section: Clinical Guideline
Compliance: ACHC Infusion Pharmacy
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I. BACKGROUND

Pegloticase (Krystexxa) is a PEGylated uric acid specific enzyme co-administered with weekly oral methotrexate and folic acid supplementation for the treatment of chronic gout in adult patients who are refractory to conventional therapy. Pegloticase is not recommended for the treatment of asymptomatic hyperuricemia. Pegloticase is a uric acid specific enzyme which is a recombinant uricase and achieves its therapeutic effect by catalyzing the oxidation of uric acid to allantoin, thereby lowering serum uric acid. Allantoin is an inert and water-soluble purine metabolite. It is readily eliminated by renal excretion. The following outlines the procedures for servicing patients in need of outpatient pegloticase home infusions.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon admission criteria.

B. The decision to administer a first dose in the home by a field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:

1. Prescriber preference
2. Allergy profile
3. Age
4. Other relevant social and/or medical history
5. Pre-treatment with methotrexate: Confirmation and documentation that patient has been taking once weekly methotrexate and folic acid supplementation for at least four weeks prior to the start of pegloticase.
6. Baseline serum uric acid (sUA) level < 6mg/dL

C. Physician orders for pegloticase must include:

1. Drug
2. Dose
3. Route of administration
4. Frequency of administration
5. Emergency medications per protocol
6. Orders for pre-medications

7. Line care protocol
8. Routine lab monitoring. Confirmation and/or documentation that patient was provided a standing lab script and counseled to obtain outpatient sUA prior to each treatment. Results must be available to report to nursing and pharmacy prior to delivery and infusion, ideally 48-72 hours prior to visit. **Inability of patient to obtain a pre-infusion sUA level will result in delay of treatment.**

D. Baseline labs or tests prior to starting therapy

1. Patients at high risk for a Glucose 6 phosphate dehydrogenase (G6PD) deficiency. Patients with a G6PD deficiency are not candidates for pegloticase due to risk of life-threatening hemolytic reactions. G6PD deficiency is an inherited X-linked recessive mutation usually occurring in males, more common in those of African, Mediterranean, or Asian descent. The prevalence in the Middle East, Africa, and parts of the Mediterranean and Asia range from 5-30% of the population. In the United States, G6PD deficiency is present in 10-14% of African American males.
2. Serum uric acid level (sUA)

E. Confirmation that patient is not taking concomitant urate lowering drugs with pegloticase. Administration of pegloticase with urate lowering drugs such as probenecid or allopurinol should be avoided as this may blunt the rise in serum uric acid levels and thereby increase the risk of anaphylaxis and infusion reactions. Discontinue treatment with oral urate-lowering drugs before initiating pegloticase therapy, and do not initiate therapy with urate-lowering agents while patients are on pegloticase therapy.

F. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless a more comprehensive patient-specific orders are provided by physician. See Appendix A (Nursing CarepathRx policy on *Management of Allergic/Anaphylactic Reactions*).

III. PHARMACOLOGY OVERVIEW

Refer to manufacturer's full Prescribing Information for most up to date information

A. Indications: treatment of chronic gout in adult patients refractory to conventional therapy. Pegloticase is not recommended for the treatment of asymptomatic hyperuricemia.

B. Dosage: 8 mg IV given as an intravenous infusion every two weeks.

1. Co-administered with methotrexate 15mg once weekly with daily folic acid or folinic acid supplementation.

C. Dose adjustment: No dose adjustments for renal or hepatic impairment.

D. Duration: Duration of therapy is dependent on patient response and adverse reactions.

E. Contraindications:

1. Glucose-6-phosphate dehydrogenase (G6PD) Deficiency. Before starting therapy, patients at higher risk for G6PD deficiency (e.g., those of African and Mediterranean ancestry) should be screened due to the risk of hemolysis and methemoglobinemia.
2. Patients with a serious hypersensitivity reaction to pegloticase

F. Warnings and Precautions:

1. Anaphylaxis: During pre-marketing controlled clinical trials, anaphylaxis was reported with a frequency of 6.5% of patients treated with pegloticase every 2 weeks, compared to none with placebo. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimation. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including the first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration. The risk of anaphylaxis is higher in patients whose 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. Because of the possibility that concomitant use of oral urate-lowering therapy and pegloticase may potentially blunt the rise of serum uric acid levels, it is recommended that before starting pegloticase patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking pegloticase.

2. Infusion reactions: During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with pegloticase 8 mg every 2 weeks, and 41% of patients treated with pegloticase 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimation. Patients should be pre-treated with antihistamines and corticosteroids. pegloticase should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate. The risk of an infusion reaction is higher in patients whose 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. Because of the possibility that concomitant use of oral urate-lowering therapy and pegloticase may potentially blunt the rise of serum uric acid levels, it is recommended that before starting pegloticase patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking pegloticase

3. Glucose-6-phosphate dehydrogenase (G6PD) Deficiency Associated Hemolysis and Methemoglobinemia: Life threatening hemolytic reactions and methemoglobinemia have been reported in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency receiving pegloticase. Because of the risk of hemolysis and methemoglobinemia, do not administer pegloticase to patients with G6PD deficiency. Screen patients at risk for G6PD deficiency prior to starting pegloticase therapy.

4. Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of pegloticase therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. Pegloticase does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient.

5. Congestive heart failure: Pegloticase has not been formally studied in patients with congestive heart failure, but two patients in the clinical trials experienced exacerbation of congestive heart failure. Exercise caution when using pegloticase in patients who have congestive heart failure and monitor patients closely following infusion.

6. Re-treatment with pegloticase: No controlled trial data are available on the safety and efficacy of re-treatment with pegloticase after stopping treatment for longer than 4 weeks. Due to the immunogenicity, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully.

7. Pregnancy and Lactation: There are no adequate and well-controlled studies of pegloticase in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively. It is not known whether pegloticase is excreted in human milk. Pegloticase should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

G. Pharmacokinetics: Pegloticase levels were determined in serum based on measurements of uricase enzyme activity. Following single intravenous infusions of 0.5 mg to 12 mg pegloticase in 23 patients with symptomatic gout, maximum serum concentrations of pegloticase increased in proportion to the dose administered. The population pharmacokinetic analysis showed that age, sex, weight, and creatinine clearance did not influence the pharmacokinetics of pegloticase. Significant covariates included in the model for determining clearance and volume of distribution were found to be body surface area and anti-pegloticase antibodies.

1. Onset: Mean plasma uric acid levels approximately 24 hours after a single 8mg dose of pegloticase was 0.7 mg/dL
2. Duration: Plasma uric acid levels, IV: below 6 mg/dL for greater than 300 hours
3. Peak concentration: Co-administration with methotrexate: The median pegloticase Cmax was 3.01 mcg/mL in a randomized study of adult patients with uncontrolled gout also receiving pegloticase plus oral methotrexate 15 mg/week (n=100) compared with 2.66 mcg/mL in patients receiving placebo plus pegloticase (n=52); higher pegloticase concentration was associated with improved response rates.
4. Excretion: Pegloticase is an enzyme that catalyzes the oxidation of uric acid to allantoin, an inert and water-soluble purine metabolite that is readily eliminated, primarily by renal excretion.

H. Adverse reactions:

1. Cardiovascular: Chest pain (6%)
2. Gastrointestinal: Constipation (6%), Nausea (5% to 12%), Vomiting (5% to 8%)
3. Immunologic: Antibody development (92%); Anaphylaxis (Up to 6.5%)
4. Musculoskeletal: Arthralgia (10% to 14%), Gout, Flare (67% to 77%)
5. Respiratory: Nasopharyngitis (7%)
6. Other: Infusion reaction (Monotherapy, 26% to 31%; combination therapy, 4%), Fatigue (4% to 5%)

I. Drug Interactions:

1. No studies of interactions of pegloticase with other drugs have been conducted. Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.
2. Concomitant administration of pegloticase with urate lowering drugs such as probenecid or allopurinol should be avoided as this may blunt the rise in serum uric acid levels, and thereby increase the risk of anaphylaxis and infusion reactions. Discontinue treatment with oral urate-lowering drugs before initiating pegloticase therapy, and do not initiate therapy with urate-lowering agents while patients are on pegloticase therapy.
3. Drug-drug interactions may exist. Consult interaction database for patient specific assessment.

IV. ADMINISTRATIVE GUIDELINES

A. Administration: IV infusions should be given immediately after dilution. Begin infusion within 4 hours of preparation per current USP Immediate-Use Guidelines.

B. Do not co-administer other products in the same infusion line.

C. Review serum uric acid levels prior to each infusion. Patients should be advised to have level drawn within 48-72 hours of treatment with results available prior to delivery and infusion. The pharmacist will contact the prescribing physician for levels greater than 6mg/dL. Consider discontinuing treatment if two consecutive levels are above 6 mg/dL.

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:

1. Alcohol Swabs
2. Gloves
3. Tape
4. IV access supplies, as applicable
    a. Peripheral IV Supplies
        (1) IV start Kit
        (2) Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾")
        (3) Extension set 8" with needless connector
    b. Port access supplies for patients with a port
        (1) Port needle (ex. 22 Gauge x ¾ to 1" safe step)
        (2) Needless connector

(3) Central line dressing change kit

5. IV pole
6. IV administration set (flow regulator or gravity tubing)
7. Supplies if utilizing a pole mounted ambulatory infusion pump for administration:
    a. Ambulatory pump tubing
    b. Pole mounted ambulatory pump
    c. Batteries for ambulatory pump (Ex: 9 Volt Duracell battery or 4 Double A batteries)
    d. Battery change procedure teaching sheet
    e. Continuous delivery mode teaching sheet
    f. Pump return box
8. Syringes (5-10 mL) with needles (20 G x 1")
9. Sharps container
10. Prescription items:
    a. Vial of Pegloticase (8mg/mL)
    b. Bag of sodium chloride 0.9% for dilution (250mL)
    c. Standard flushes per protocol
    d. Anaphylaxis kit per protocol
    e. Methotrexate prescription

B. How supplied: Pegloticase is supplied as a clear, colorless, sterile solution in phosphate buffered saline intended for intravenous infusion after dilution. Pegloticase is supplied in a single-use 2Ml glass vial with a Teflon® coated (latex-free) rubber injection stopper to deliver pegloticase as 8 mg of uricase protein in 1 mL volume.

C. Storage and Handling: Vials must be stored in the carton and maintained at all times under refrigeration between 2° to 8°C (36° to 46°F). Protect from light. Do not shake or freeze.

D. Compatibility: Compatible with 0.45% or 0.9% sodium chloride solutions.

E. Procedures:

1. Explain the reasoning for visit and use of pegloticase.
2. Confirm serum uric acid level was drawn 48-72 hours prior to infusion. Results must be reportable at time of visit. If level was not drawn or is greater than 6mg/dL, confirm plan of care with pharmacy team or contact prescriber.
3. Validate patient compliance with concurrent oral medications, if applicable:
    a. Premedication (ex. corticosteroid, antihistamine, analgesic)
    b. Gout flare prophylaxis (ex. colchicine)
    c. Immunomodulator (ex. Methotrexate and folic acid, mycophenolate)
4. Don gloves.
5. Establish venous access prior to preparation of drug.
6. Counsel patient on warnings, precautions, and potential side effects including but not limited to: anaphylaxis reactions, infusion reactions, gout flare, nausea, confusion, nasopharyngitis, constipation, chest pain, and vomiting
7. Administer ordered pre-infusion medications (e.g. antihistamines, corticosteroids) to minimize the risk of anaphylaxis and infusion reactions.
    a. Pre-medication regimens may be patient or provider-specific.
    b. Separate administration of IV pre-medications and pegloticase by at least five to ten minutes.
8. Prepare product:
    a. Visually inspect pegloticase vial for particulate matter and discoloration before

administration, whenever solution and container permit. Do not use vials if either is present.

b. Withdraw 1 mL of pegloticase from the vial into a sterile syringe. Discard any unused portion of product remaining in the 2 mL vial. Inject pegloticase into a 250 mL bag of 0.9% Sodium Chloride.
c. Gently invert the infusion bag a number of times to ensure thorough mixing. Do not shake.
d. Diluted product should be used immediately or within 4 hours of preparation.

9. Infusion rate: administer by intravenous infusion over at least 2 hours.
10. Post infusion monitoring: Monitor patient and vital signs periodically during the infusion and 1 hour after the infusion is complete.

VI. CLINICAL MONITORING

A. Prior to therapy:

1. Baseline labs including serum uric acid level and G6PD
2. Review serum uric acid levels prior to each infusion.
3. Confirmation and documentation that patient has been taking once weekly methotrexate and folic acid supplementation for at least four weeks prior to the start of pegloticase.

B. During therapy:

1. Patients with a history of congestive heart failure should be screened and monitored for disease progression throughout treatment with pegloticase (ex. new or worsening shortness of breath, edema, weight change, modifications to heart failure medication regimen, etc.)
2. Monitor for an increase in gout flares, disease severity, and number/frequency of self-reported gout flares or any adverse reactions such as nausea, confusion, nasopharyngitis, constipation, chest pain, and vomiting.
3. Monitor for signs/symptoms of anaphylaxis and infusion related reactions during and 1 hour after infusion. Consider slowing infusion rate to mitigate adverse events. Combinations of oral and IV steroids or antihistamines may improve tolerability. Coordinate patient-specific regimens with prescriber.
4. Monitor serum uric acid levels (48-72 hours) prior to each dose of pegloticase. Patients should be advised to have level drawn within 48-72 hours of treatment with results available prior to delivery and infusion. The pharmacist will contact the prescribing physician for levels greater than 6mg/dL. For levels above 6mg/dL, assess patient's symptom response (ex. Flare frequency, tophi resolution, etc). If limited symptom improvement and sUA level remains > 6mg/dL, contact prescriber.
5. Patients being re-started on pegloticase after 4 weeks or more drug free interval should be monitored closely for anaphylaxis and infusion reactions when re-starting therapy due to the potential of immunogenicity.
6. Counsel the patient on appropriate gout flare prophylaxis, immunomodulator compliance, and nonpharmacologic management.

Please refer to the package insert for the most up to date guidance on this medication.

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APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS

Emergency Medication After Your Infusion

Please call your pharmacy if you have any questions or concerns. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.
The epinephrine dose will be noted on the Anaphylaxis Protocol included with your kit.

Start with a clean work surface and clean hands.

Open the supply bag labeled Anaphylaxis Kit Contents.

You will need:

1. **Bag containing Pills** (2 Acetaminophen and 2 Diphenhydramine)
2. **Bag containing Alcohol Prep Pads**
3. **Bag labeled IM Epinephrine**

All other contents will not be needed.

Open the IM Epinephrine Bag

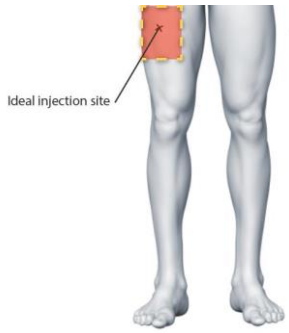
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampule use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

1. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
2. Using an **alcohol swab, wipe the neck of the epinephrine ampule.**
3. Holding the ampule upright, **swirl and flick the ampule until all fluid flows to the bottom chamber** (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. **Quickly snap the top of the ampule off, directing the snap way from you.**
5. **Place the tip of the brown filter needle inside the ampule**. Tilting the ampule, **withdraw dose of medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
6. Remove the needle from the ampule and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
7. **Push the air out of the syringe by gently pushing on the plunger**.

8. Replace the cap on the brown filter needle. Discard remainder in ampule.
9. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



1. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
2. **Push the needle into your leg muscle straight** in at a 90-degree angle.
3. **Inject the medication** by depressing the plunger in a slow and steady motion.
4. **Remove the needle** and wipe the site with the alcohol wipe.
5. May repeat dose every 5 minutes (**maximum 3 doses**) if ordered per protocol.

Take the pills by mouth.

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

Place all trash in the bag the pills came in and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.
Call 911 or have someone drive you to the emergency department.