Pegloticase (Krystexxa®)
Criteria for Use
September 2012
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive pegloticase.*

- ☐ **Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.** *(Patients at high risk for G6PD deficiency should be screened prior to initiating therapy with pegloticase. Higher risk patients include those of African or Mediterranean descent)*
- ☐ **Patients receiving other urate lowering therapies including allopurinol, febuxostat, probenecid, etc.** *(Combined use of pegloticase and other urate lowering drugs may mask a rise in uric acid concentrations attributable to loss of effectiveness of pegloticse, due to antibody development. Development of anti-pegloticase antibodies can lead to loss of efficacy and a higher risk for infusion reactions and anaphylaxis)*

Inclusion Criteria *The answers to the following must be fulfilled in order to meet criteria.*

PRIOR TO PRESCRIBING PEGLOTICASE, REFER TO "MONITORING" AND "ISSUES FOR CONSIDERATION" SECTIONS OF THESE CRITERIA FOR BOXED WARNINGS ASSOCIATED WITH PEGLOTICASE ADMINISTRATION.

I. New Patients:

Treatment Indication:

☐ Three or more gout flares in the past 18 months and baseline serum uric acid concentration (SUAc) ≥8 mg/dl

AND

☐ One or more tophi (affecting physical function and/or quality of life)

OR

☐ Chronic gouty arthritis (documented clinically or radiographically as joint damage due to gout)

AND

Therapeutic Trial of Conventional Agents for Gout:

☐ Failure to reduce serum uric acid concentration (SUAc) to <6 ml/dl despite an adequate therapeutic trial of maximally tolerated doses of allopurinol (up to 800 mg/day*) and then of febuxostat (up to 80 mg/day*) for at least 3 months (at the highest tolerated dose). **And**, patient confirms ≥80% adherence with xanthine oxidase inhibitors. To be clear, allopurinol and febuxostat should not used in combination with each other or with pegloticase. *Probenecid should also be considered in appropriate patients (CrCl >50ml/min, absence of urolithiasis, etc.) prior to use of pegloticase.*

OR

☐ Documented contraindication or inability to tolerate allopurinol and febuxostat

AND

☐ Reversible causes of gout have been considered and treated as indicated (e.g., alcohol use, excessive intake of purine rich foods such as meat and seafood, obesity, medications [diuretics, niacin, low dose salicylates, tacrolimus, cyclosporine, etc.).

AND

☐ Prescribed by VA Rheumatologist or other locally designated physician with appropriate training on infusion reactions and issues specific to use of pegloticase.

II. Continued Treatment with Pegloticase *(Patients currently receiving pegloticase who have already met above listed criteria): (Criterion must be met before prior to infusion)*

☐ Uric acid level <6 mg/dl prior to scheduled infusion. **Patients with documented serum uric acid concentrations (prior to their next infusion) of >6 mg/dl on more than one occasion during treatment must discontinue treatment with pegloticase.** *(Elevated uric acid concentrations in patients receiving pegloticase may reflect development of anti-pegloticase antibodies resulting in loss of efficacy and a higher risk for infusion reactions, particularly when 2 consecutive levels >6 mg/dl are observed) Caution should be observed If uric acid levels increase significantly between infusions (e.g., 2.0 mg/dl to 5.5 mg/dl prior to the next infusion) since this may also reflect development of antibodies.*

III. Individual Treatment Goals Met with Pegloticase *(Consider switching back to maintenance therapy with allopurinol or febuxostat if no contraindications exist):*

☐ For patients who have met individual patient treatment goals (e.g., improved quality of life, reduced gout flares, improved mobility, reduced tophi, improved gouty arthritis pain, no longer need for surgery to remove tophi, etc.), consider switch back to maintenance therapy with allopurinol or febuxostat (if meets criteria for use) if no contraindications exist.

*See Issues for consideration for allopurinol dose titration and febuxostat dosing.

Dosage and Administration

Dosage: The recommended dose of pegloticase is 8 mg given as an intravenous infusion every 2 weeks.

It is recommended that gout flare prophylaxis (e.g., colchicine or nonsteroidal anti-inflammatory drugs) be initiated at least one week prior to the first infusion of pegloticase and continued for at least the first 6 months of pegloticase therapy unless contraindicated or unable to tolerate.

Administration:

- Using aseptic technique, withdraw 1 ml of pegloticase from the vial into a sterile syringe. Inject the contents of the syringe into a 250 ml bag of 0.9% sodium chloride injection, USP or 0.45% sodium chloride injection, USP for intravenous infusion. The manufacturer recommends against mixing or diluting the pegloticase infusion with other drugs. The infusion bag should be inverted several times to ensure thorough mixing, but should not be shaken.
- Once mixed, the pegloticase infusion is stable for four hours when refrigerated or kept at room temperature. However, it is recommended that the solution be stored in the refrigerator (not frozen) and protected from light and used with four hours of mixing.
- Prior to infusion, the pegloticase solution should be allowed to reach room temperature. ***Diluted and undiluted pegloticase should never be exposed to artificial heating such as microwaves or hot water to bring them to room temperature.***
- ***DO NOT ADMINISTER PEGLOTICASE AS AN IV PUSH OR BOLUS.***
- Infuse the pegloticase solution over no less than 120 minutes via gravity feed, syringe-type pump or infusion pump.
- **Patients should be pre-treated prior to the infusion with an antihistamine and a corticosteroid to minimize the risk of anaphylaxis and infusion-related reactions.** *In the phase III clinical trials, all patients received an oral dose of an antihistamine the evening prior to and just before the infusion and IV hydrocortisone 200 mg and acetaminophen 1000 mg immediately prior to the infusion.*
- **Administration of pegloticase should be done in a healthcare setting and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be observed for an appropriate period of time following completion of the infusion.**

Monitoring

- Serum uric acid concentrations must be obtained prior to each infusion of pegloticase. (*Patients who develop antibodies to pegloticase may lose their therapeutic response and are at a higher risk for anaphylaxis and infusion reactions.)*
- If serum uric acid levels increase to >6 mg/dl, especially when two consecutive levels >6 mg/dl are observed, treatment with pegloticase should be discontinued. And, i*f uric acid levels increase significantly between infusions (e.g., 2.0 mg/dl to 5.5 mg/dl prior to the next infusion), caution should be observed since this may reflect development of antibodies.*
- If an infusion reaction occurs during the pegloticase administration, the infusion can be slowed or stopped and restarted at a slower rate, at the discretion of the physician. Since infusion reactions can occur after the infusion has completed, it is recommended that patients be observed for at least an hour post-infusion.
- Patients should be observed for an appropriate period of time following completion of each infusion. (*Anaphylaxis generally manifested within 2 hours of the infusion. However, delayed type hypersensitivity reactions have been reported.)*

Issues for Consideration

- Because of the relatively high risk for serious adverse events with pegloticase (including infusion reactions and anaphylaxis), the use of pegloticase should be limited to the FDA indication (Adult patients with symptomatic gout refractory to conventional treatment). *Use of pegloticase to quickly lower uric acid levels for rapid debulking of tophi in patients who are not refractory to conventional gout treatment is not recommended because of the severity of adverse events with pegloticase as well as the lack of evidence. There is no evidence for use of pegloticase in patients receiving anti-cancer treatments expected to result in tumor lysis and increased uric acid levels.*
- Anaphylaxis and infusion reactions can occur with any infusion of pegloticase, including the first infusion. All patients should be pre-treated with an oral antihistamine and IV corticosteroids prior to each infusion. (*In the phase III clinical trials, all patients received an oral dose of an antihistamine the evening prior to and just before the infusion and IV hydrocortisone 200 mg and acetaminophen 1000 mg immediately prior to each infusion).* Patients should be monitored for an appropriate period of time after completion of the infusion.
- It is recommended that pegloticase be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.
- It is recommended that gout flare prophylaxis (e.g., colchicine 0.6 mg once or twice daily or nonsteroidal anti-inflammatory drugs) be initiated at least one week prior to the first infusion of pegloticase and continued for at least the first 6 months of pegloticase therapy unless contraindicated or unable to tolerate.
- In patients with frequent gout attacks who do not have documented tophi or gouty arthritis and are unable to tolerate or have contraindications to allopurinol, febuxostat and probenecid, providers may consider once daily colchicine. However, daily colchicine will not alter uric acid levels or the course of the disease and is used only to prevent acute gout flares. (Refer to PBM website for "Colchicine-Guidance for use in the Management of Gout" for dosing and safety information)
- Allopurinol (Treat to target approach): In patients with normal renal function, the initial dose of allopurinol is 100 mg daily; then increase by 100 mg increments on a weekly basis or every 2-4 weeks until uric acid levels are <6 mg/dL or a maximum dose of 800 mg/day is reached. Lower maximum daily doses are recommended in patients with renal impairment *(Labeled dose: CrCl 10-20 ml/min: 200 mg/d, CrCl 3-10 ml/min: ≤100 mg/d, <3 ml/min: 100 mg dose at extended intervals)*. However, this conservative maximum daily allopurinol dose limit has been disputed, as some evidence supports use of higher maximum daily doses in patients with renal insufficiency *(Unlabeled dose: Initiate therapy with 50-100 mg daily, and gradually increase to a maintenance dose to achieve a serum uric acid level of ≤6 mg/dL [with close monitoring of serum uric acid levels and for hypersensitivity]. Hemodialysis: Initial: 100 mg alternate days given postdialysis, increase cautiously to 300 mg based on response. If dialysis is on a daily basis, an additional 50% of the dose may be required postdialysis).* The manufacturer recommends doses >300 mg daily be given in divided doses.
- Febuxostat: Initial dose is 40 mg daily. If uric acid <6 mg/dl is not reached after 2-4 weeks, increase dose to 80 mg daily.
- Data are lacking for re-treatment/restarting treatment with pegloticase in patients stopping therapy with pegloticase for >4 weeks. Due to the immunogenicity of pegloticase, the risk for anaphylaxis and infusion reactions may be increased and therefore these patients should be more closely monitored. In addition, the risk of anaphylaxis or infusion reactions may be increased if an infusion is missed or skipped.
- It is unknown if pegloticase is excreted in human milk. Because of the risk for serious adverse events to the nursing infant if it is, pegloticase should not be administered to nursing mothers.
- Biweekly pretreatment with corticosteroids may alter glucose control in diabetic patients and therefore these patients should be closely monitored.
- There were a limited number of adverse cardiovascular events reported in the premarketing safety database with more

events reported in the pegloticase vs. placebo groups. Events included ischemic cardiovascular events, heart failure, cardiac arrhythmias and death. Although there are no recommendations against the use of pegloticase in patients with known cardiovascular disease, the FDA advisory committee reviewing pegloticase agreed that cardiovascular safety should be monitored post-marketing.

Renewal Criteria

- Serum uric acid concentration should be ≤ 6 mg/dl prior to each infusion.

Prepared: July 2012; finalized September 2012. Contact: Cathy Kelley (cathy.kelley@va.gov), VA Pharmacy Benefits Management Services