09-J3000-29

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Reviewed: 03/11/26

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Subject: Pegloticase (Krystexxa®) Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Pegloticase (Krystexxa) is a PEGylated, recombinant, mammalian urate oxidase enzyme that was first approved by the Food and Drug Administration (FDA) in September 2010 for the treatment of chronic gout in adult patients refractory to conventional therapy. In July 2022, the labeling was updated to recommend that Krystexxa be co-administered with weekly methotrexate 15 mg orally. This was based on the results of the MIRROR randomized controlled trial that demonstrated improved efficacy and a reduction in infusion reactions compared to Krystexxa alone. Although urate oxidase is present in most mammals, it is not found naturally in humans. Pegloticase 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, primarily by renal excretion

Gout is a disorder with various clinical and pathologic features due to an excess body burden of uric acid, manifested in part by hyperuricemia. Tissue deposition of monosodium urate monohydrate crystals in the joints and certain other sites is responsible for most of the symptoms and features. Gout is one of the most common rheumatic diseases of adulthood, with a 2016 prevalence in the US estimated at 3.9% of adults. The most current American College of Rheumatology (ACR) guidelines for the management of gout (2020) include pegloticase as last-line therapy for the management of gout. The guidelines strongly recommend urate lowering therapy (ULT) in gout patients with ≥1 subcutaneous tophi; evidence of radiographic damage (any modality) attributable to gout; or frequent gout flares, with frequent being defined as ≥2 annually. Initiating ULT is conditionally recommended against in patients with gout experiencing their first gout flare, unless the patient has comorbid moderate-to-severe CKD (stage ≥3), a serum uric acid concentration >9 mg/dL, or urolithiasis. Initiating ULT is also conditionally recommended against in all patients with asymptomatic hyperuricemia (defined as serum uric acid concentration >6.8 mg/dL with no prior gout flair or subcutaneous tophi). Treatment with allopurinol as the preferred first-line agent, over all other ULTs, is strongly recommended for all patients, including those with moderate-to-severe CKD (stage ≥3). Achieving and maintaining a serum uric acid target of <6 mg/dL (vs. the use of no target) is strongly recommended for all patients receiving ULT. Switching to pegloticase (vs. continuing current ULT) is strongly recommended for gout patients for when xanthine oxidase inhibitor treatment, uricosurics, and other interventions have failed to achieve the serum uric acid target, AND who continue to have frequent gout flares (≥2 flares/year) or who have non-resolving subcutaneous tophi. As for management of lifestyle factors, limiting alcohol intake, limiting purine intake, limiting high-fructose corn syrup intake, and using a weight loss program for those who are overweight/obese (no specific program endorsed) is conditionally recommended regardless of disease activity.

The safety and efficacy of pegloticase leading to initial FDA approval was evaluated in two identical, randomized, placebo-controlled trials in patients with symptomatic gout unresponsive to allopurinol. Patient inclusion criteria included a serum urate level ≥8 mg/dL with established and symptomatic gout, a failure to achieve serum urate <6 mg/dL despite ≥3 months of appropriately dosed allopurinol, and ≥1 tophus, ≥3 gout flares within previous 18 months, or gouty arthritis. In both studies, patients were randomized 2:2:1 to pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks, or placebo for 6 months. Patients who completed the randomized clinical trials were eligible to enroll in a 2-year open label extension study. The primary endpoint was defined as maintaining plasma uric acid concentrations <6 mg/dL for 80% of the time during the third and sixth months of treatment. The mean age of study subjects was 55 years (23-89); 82% were male, mean body mass index (BMI) was 33 kg/m^2, mean duration of gout was 15 years, and mean baseline serum uric acid level was 10 mg/dL. The primary endpoint was achieved for the labeled pegloticase dose (8 mg every 2 weeks) in 47% at after 3 months of therapy (Trial 1) and 38% (Trial 2) of patients after 6 months, compared to no patients in the placebo groups ($p<0.001$ in each trial). The secondary endpoint characterized the response of tophi to pegloticase treatment. In a combined analysis of both trials, 45% of patients treated with pegloticase every 2 weeks demonstrated a complete response of tophi, compared to 8% of patients in the placebo group ($p<0.05$). A complete response of tophi was defined as full resolution of at least one target tophus, no formation of new tophi, and no progression of any tophus.

The labeling change in July 2022 (i.e., recommendation to use pegloticase in combination with methotrexate) was based on the results of a 52-week, randomized, double-blind trial (MIRROR; NCT03994731) conducted in adult patients with chronic gout refractory to conventional therapy. The trial compared pegloticase 8 mg every 2 weeks co-administered with weekly methotrexate (MTX) 15 mg, vs. pegloticase alone. Patients were naïve to pegloticase therapy. Patients who were able to tolerate two weeks on oral MTX 15 mg were randomized to receive four additional weeks on either MTX 15 mg or matching placebo prior to initiating pegloticase therapy in a 2:1 ratio. Patients were pretreated with a standardized infusion reaction prophylaxis regimen of oral fexofenadine, acetaminophen and IV methylprednisolone prior to each pegloticase infusion. Methotrexate or placebo was continued weekly throughout the pegloticase treatment period with daily oral folic acid in order to evaluate the immunomodulatory effect of MTX to attenuate development of anti-drug antibodies. Inclusion criteria were baseline serum uric acid ≥7 mg/dL and inability to maintain serum uric acid <6 mg/dL on other urate-lowering therapy, intolerable side effects associated with current urate-lowering therapy, and/or presence of clinically evident tophaceous deposits. The primary endpoint was the proportion of Month 6 responders, where a responder was defined as achieving and maintaining serum uric acid <6 mg/dL for at least 80% of the time during Month 6. The proportion of Month 12 responders was the key secondary endpoint. A significantly greater proportion of patients receiving pegloticase co-administered with MTX vs. pegloticase alone achieved both the primary [71/100 (71%) vs. 20/52 (39%), $p<0.0001$] and secondary [60/100 (60%) vs. 16/52 (31%), $p=0.0003$] endpoints. The effect on tophi was assessed using standardized digital photography, image analysis and Central Readers blinded to treatment assignment. Approximately 53.3% (81/152) of randomized patients had tophi at baseline. Of those, 54% (28/52) in the pegloticase co-administered with MTX group and 31% (9/29) in the pegloticase alone group achieved a complete response at Month 12 (defined as 100% resolution of at least one target tophus, no new tophi appear and no single tophus showing progression). The difference between the two treatment groups was statistically significant (22.8%, 95% CI: 1.2%, 44.4%).

POSITION STATEMENT:

Initiation of pegloticase (Krystexxa) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “8”):

1. Member has a diagnosis of chronic, treatment-refractory gout, and meets at least **ONE** of the following criteria (“a”, “b”, or “c”) - medical record documentation supporting the diagnosis must be submitted:
    a. Two or more gout flares in the previous 12 months that required systemic treatment [such as with colchicine, corticosteroids, and/or nonsteroidal anti-inflammatory drugs (NSAIDs)]

b. One or more gouty tophus

c. History of chronic gouty arthropathy, defined clinically or radiographically as joint damage due to gout

2. Member has a baseline serum uric acid level greater than 6 mg/dL prior to initiation of treatment with pegloticase - laboratory documentation of a serum uric acid level within the past 90 days must be submitted

3. **ANY** of the following ("a", "b", "c", or "d"):

   a. Member has had an inadequate response (i.e., failure to normalize serum uric acid to less than 6 mg/dL) to at least 3 months of continuous treatment with a **combination** of the maximally tolerated dose of a xanthine oxidase inhibitor **AND** maximally tolerated dose of a uricosuric agent (e.g., probenecid) – reason for using a lower dosage (such a renal impairment) must be provided for members unable to take at least 300 mg twice daily (600 mg/daily) of allopurinol or 80 mg once daily of febuxostat

   b. Member has had an inadequate response (i.e., failure to normalize serum uric acid to less than 6 mg/dL) to at least 3 months of continuous treatment the maximally tolerated dose of a xanthine oxidase inhibitor, **AND** has had intolerable adverse effects with or has a contraindication to probenecid or the member is not a candidate for probenecid due to creatinine clearance (CrCl) less than 30 mL/min - the specific adverse effects and/or contraindications to probenecid or CrCl in the past 90 days must be provided, and the reason for using a lower dosage (such a renal impairment) must be provided for members unable to take at least 300 mg twice daily (600 mg/daily) of allopurinol or 80 mg once daily of febuxostat

   c. Member has had an inadequate response (i.e., failure to normalize serum uric acid to less than 6 mg/dL) to at least 3 months of continuous treatment the maximally tolerated dose of a uricosuric agent (e.g., probenecid), **AND** has had intolerable adverse effects with, is not a candidate for, and/or has contraindications to **BOTH** allopurinol and febuxostat - the specific adverse effects, acceptable reasons for non-candidacy*, and/or contraindications must be provided

   d. Member has had intolerable adverse effects with, has contraindications to, and/or is otherwise not a candidate for **ALL** of the following - the specific adverse effects, acceptable reasons for non-candidacy*, and/or contraindications must be provided

      i. Allopurinol

      ii. Febuxostat

      iii. Probenecid

   *Acceptable reasons for non-candidacy include the following:

      - Allopurinol - member is positive for the HLA-B*5801 allele
      - Febuxostat - member has a CrCl less than 15 mL/min **OR** history of cardiovascular disease
      - Probenecid - member has a CrCl less than 30 mL/min

4. Pegloticase is prescribed by either a rheumatologist or nephrologist

5. Member has undertaken appropriate lifestyle modifications (e.g., weight loss for obese individuals, avoidance of or limiting alcohol consumption, avoidance of or limiting dietary intake of meats and fish high in purine content, and other medications known to precipitate gout attacks have been discontinued or changed when possible) – medical record documentation supporting the lifestyle modifications attempted by the member must be submitted

6. Member is 18 years of age or older

7. Pegloticase will be co-administered with methotrexate 15 mg weekly and folic acid or folinic acid supplementation, **UNLESS** methotrexate is contraindicated or not clinically appropriate – medical

record documentation of the specific contraindication or reason not clinically appropriate must be submitted

8. Dosage of pegloticase does not exceed 8 mg IV every 2 weeks

Approval duration: 6 months

Continuation of pegloticase (Krystexxa **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. An authorization or reauthorization for pegloticase has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of chronic, refractory gout (if another health plan, documentation of a health plan-paid claim for pegloticase during the 90 days immediately before the authorization request must be submitted), **OR** the member has previously met **ALL** indication-specific criteria.
2. The member has had a beneficial response to pegloticase treatment defined as **EITHER** of the following ("a" or "b"):
    a. Serum uric acid level less than 6 mg/dL - laboratory documentation of a serum uric acid level within the past 90 days must be submitted
    b. Resolution or regression of one or more tophi - medical record documentation must be submitted
3. Pegloticase is prescribed by either a rheumatologist or nephrologist
4. Member continues to engage in appropriate lifestyle modifications (e.g., weight loss for obese individuals, avoidance of or limiting alcohol consumption, avoidance of or limiting dietary intake of meats and fish high in purine content, and other medications known to precipitate gout attacks have been discontinued or changed when possible)
5. Member is 18 years of age or older
6. Pegloticase will be co-administered with methotrexate 15 mg weekly and folic acid or folinic acid supplementation, **UNLESS** methotrexate is contraindicated or not clinically appropriate – medical record documentation of the specific contraindication or reason not clinically appropriate must be submitted
7. Dosage of pegloticase does not exceed 8 mg IV every 2 weeks

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 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.
    - Limitations of Use: Krystexxa is not recommended for the treatment of asymptomatic hyperuricemia.
- The recommended dosage of Krystexxa is 8 mg given as an IV infusion every two weeks, co-administered with weekly oral methotrexate 15 mg and folic acid or folinic acid supplementation. Krystexxa alone may be used in patients for whom methotrexate is contraindicated or not clinically

appropriate. If co-administering with methotrexate, start weekly methotrexate and folic acid or folinic acid supplementation at least 4 weeks prior to initiating, and throughout treatment with Krystexxa. The optimal treatment duration has not been established.

Dose Adjustments

- Hepatic impairment - Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.
- Renal impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- Supplied as a Ready-to-Use 8 mg/50 mL (0.16 mg/mL) single-dose vial
- Before the preparation for use, 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.

PRECAUTIONS:

Boxed Warning

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

- 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.
- Screen patients at risk for G6PD deficiency prior to starting Krystexxa. Hemolysis and methemoglobinemia have been reported with Krystexxa in patients with G6PD deficiency. Do not administer Krystexxa to patients with G6PD deficiency.

Contraindications

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- History of serious hypersensitivity reactions, including anaphylaxis, to Krystexxa or any of its components

Precautions/Warnings

- **Anaphylaxis**: Anaphylaxis may occur with any Krystexxa infusion. Pre-medicate and monitor patients. 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.

- **Infusion Reactions**: Infusion reactions occurred in patients treated with Krystexxa. Pre-medicate and monitor patients. The risk of 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.
- **G6PD Deficiency Associated Hemolysis and Methemoglobinemia**: Screen patients at risk for G6PD deficiency. Do not administer Krystexxa to patients with G6PD deficiency.
- **Gout Flares**: Gout flare prophylaxis is recommended for at least the first 6 months of Krystexxa therapy.
- **Congestive Heart Failure**: Congestive heart failure exacerbation may occur. Monitor patients closely following infusion.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J2507	Injection, pegloticase, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

M1A.00X0 - M1A.09X1	Idiopathic chronic gout
M1A.10X0 - M1A.19X1	Lead-induced chronic gout
M1A.20X0 - M1A.29X1	Drug-induced chronic gout
M1A.30X0 - M1A.39X1	Chronic gout due to renal impairment
M1A.40X0 - M1A.49X1	Other secondary chronic gout
M1A.9XX0 - M1A.9XX1	Chronic gout, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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12. Troum OM, Botson JK, Obermeyer K, et al. Pegloticase and Methotrexate Cotherapy in Patients With Uncontrolled Gout With Prior Pegloticase Monotherapy Failure: Findings of an Open-Label Trial. ACR Open Rheumatol. 2025 Jan;7(1):e11789.
13. Yood R, Ottery F, Irish W, et al. Effect of pegloticase on renal function in patients with chronic kidney disease: a post hoc subgroup analysis of 2 randomized, placebo-controlled, phase 3 clinical trials. BMC Research Notes 214, 7:54.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/11/26.

GUIDELINE UPDATE INFORMATION:

04/15/19	New Medical Coverage Guideline.
01/01/20	Revision to guideline consisting of updating the position statement.
04/15/20	Review and revision to guideline consisting of updating the description, position statement, billing/coding, and references.
04/15/22	Review and revision to guideline consisting of updating the description, position statement, and references.
09/15/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, and references.
04/15/23	Review and revision to guideline consisting of updating the references.
04/15/24	Review and revision to guideline consisting of updating the position statement and references. Revised diagnostic criteria and added specialist prescriber requirement.
04/15/25	Review and revision to guideline consisting of updating the references.
04/15/26	Review and revision to guideline consisting of updating the dosage/administration section and references. The To-be-Diluted product is being discontinued by the manufacturer. The Ready-to-Use product will remain available.