pegloticase (Krystexxa®)

Medicare Advantage Medical Policy # 079
Original Effective Date: 03/01/2025
Current Effective Date: 03/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider the use of pegloticase (Krystexxa®)‡ for the treatment of chronic gout in adult patients refractory to conventional therapy to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of pegloticase (Krystexxa) for the treatment of chronic gout will be considered when all of the following patient selection criteria are met:

- Initial
  - Patient is ≥ 18 years of age; and
  - Patient has a diagnosis of chronic gout; AND
  - Patient has a documented failure of, contraindication to, or intolerance of at least one xanthine oxidase inhibitor agent (e.g. Uloric®, Zyloprim®)‡ after 3 months of use at maximum medically appropriate doses (see background information for discussion of maximum doses) unless there is clinical evidence or patient history that suggests xanthine oxidase inhibitors will be ineffective or cause an adverse reaction to the patient; AND
  - Patient was unable to achieve target serum uric acid levels on a xanthine oxidase inhibitor (e.g. Uloric, Zyloprim) PLUS probenecid unless patient has a documented contraindication to the use of probenecid. Examples of contraindications to probenecid include nephrolithiasis, cystinuria, current use of penicillin, known renal calculi, or moderate-to-severe chronic kidney disease stage ≥3; AND
  - Patient had at least 2 gout flares in the last 12 months OR at least 1 subcutaneous non-resolving tophi; AND
  - Patient has a negative screening of G6PD deficiency; AND
  - Krystexxa will be coadministered with an immunomodulator such as methotrexate unless immunomodulators are contraindicated or not clinically appropriate for the patient; AND
  - Dose will not exceed 8 mg every 2 weeks.

- Continuation
    - Patient has received an initial authorization for Krystexxa from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
    - Krystexxa will be coadministered with an immunomodulator such as methotrexate unless immunomodulators are contraindicated or not clinically appropriate for the patient; AND
    - Patient has not lost therapeutic response as evidenced by a serum uric acid level ≤6 mg/dL prior to scheduled infusion.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of pegloticase (Krystexxa) when the patient is able to achieve target serum uric acid levels on a xanthine oxidase inhibitor plus probenecid or in the absence of at least 2 gout flares in the last 12 months or at least 1 subcutaneous non-resolving tophi to be **not medically necessary**.**

Based on review of available data, the Health Plan considers the continued use of pegloticase (Krystexxa) when the patient has lost therapeutic response (as evidenced by a serum uric acid level above 6 mg/dL) to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of pegloticase (Krystexxa) when patient selection criteria are not met (with the exception of the criteria denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Krystexxa is the first PEGylated uric acid specific enzyme approved by the Food and Drug Administration (FDA) for treatment of chronic gout in adult patients refractory to conventional therapy. Krystexxa is not recommended in patients who have asymptomatic hyperuricemia. It is made up of a recombinant modified mammalian uricase produced by a genetically modified strain of *Escherichia coli* which is covalently bonded to monomethoxypolyethylene glycol [mPEG]. It achieves a therapeutic effect by catalyzing the oxidation of uric acid to allantoin. Allantoin is then eliminated, mainly by renal excretion, thus lowering serum uric acid (SUA). The recommended dose of Krystexxa is 8mg administered every 2 weeks over no less than 120 minutes as an intravenous infusion.

Gout refractory to conventional therapy exists in a small population of patients with severe gout. These patients have failed to normalize SUA and have inadequate control of the signs and symptoms

of gout with maximum medically appropriate doses of urate-lowering therapy (ULT) (e.g., allopurinol, febuxostat) or have a contraindication to ULT. Gout refractory to conventional therapy should be differentiated from patients who are under-treated for gout or are non-compliant with gout therapy. Those refractory to conventional therapy generally have a high prevalence of tophi, frequent and disabling gout flares, deforming arthropathy, diminished quality of life, and disability. Gout refractory to conventional therapy commonly co-exists with other conditions, including hypertension, cardiovascular disease (CVD), diabetes mellitus, chronic kidney disease, obesity and hyperlipidemia. Although many patients with gout have concomitant cardiovascular (CV) co-morbidities, it is unknown if elevated SUA is a predictor or causative factor associated with CVD. Of the estimated 5 million patients in the US with gout, it is believed that gout refractory to conventional therapy affects approximately 50,000 patients though some reports indicate that as many as 300,000 patients may be affected.

Drug therapy for acute gout is aimed at relieving pain and inflammation. Therapeutic options include NSAIDs, colchicine, and corticosteroids. All fast-acting NSAIDs are equally effective when given in optimum doses. In addition to an increased risk of peptic ulcers, bleeds, or perforations, NSAIDs can worsen renal insufficiency, heart failure, and blood pressure control. Colchicine is effective at reducing the severity of an acute attack but has a slower onset than NSAIDs. Corticosteroids are generally used for acute gout in patients who cannot tolerate NSAIDs or colchicine or who are refractory to these agents. Long-term therapy with a urate-lowering agent is usually initiated if a second attack or further attacks of gout occur within 1 year. Prior to the availability of Krystexxa, agents approved for long-term therapy of gout include xanthine oxidase inhibitors (allopurinol and febuxostat) which inhibit production of urate from hypoxanthine and xanthine; and probenecid, a uricosuric agent that promotes urate excretion. Allopurinol is generally recommended as the first-line drug for lowering SUA because of its efficacy, convenience, and benefit to risk ratio in both over producers and under excretors of urate. The FDA has approved allopurinol up to a maximum dose of 800 mg per day and febuxostat up to a maximum dose of 80 mg per day. These agents should be started at a lower dose to reduce risk of flares and increased gradually to achieve the SUA target.

Patients treated with Krystexxa are at risk of anaphylaxis and must be pre-treated with antihistamines and corticosteroids. Risk of anaphylaxis is further increased in those with serum uric acid (SUA) levels above 6 mg/dL. Uric acid (UA) levels should be monitored prior to infusion with consideration of discontinuing Krystexxa if UA levels increase above 6mg/dL, particularly if 2 consecutive levels >6mg/dL are observed.

Patients treated with Krystexxa are also at increased risk of severe infusion reactions despite pre-treatment with antihistamines and corticosteroids. A clinical trial comparing Krystexxa co-administered with methotrexate to Krystexxa alone found that patients receiving Krystexxa and methotrexate had a significantly lower rate of infusion reactions (4%) compared to those receiving Krystexxa alone (31%).

Krystexxa was approved with a Risk Evaluation and Mitigation Strategy (REMS) program intended to inform healthcare providers about anaphylaxis, infusion reactions, and contraindications of use

with Krystexxa. The REMS program is also intended to inform patients about the serious risks associated with Krystexxa.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Pegloticase (Krystexxa) was FDA approved in 2010 for the treatment of chronic gout in adult patients refractory to conventional therapy. It is not recommended for the treatment of asymptomatic hyperuricemia.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Krystexxa demonstrated efficacy in reducing SUA in two Phase III trials (Trials 1 and 2) in patients with chronic gout refractory to conventional therapy. Safety and efficacy were evaluated for up to 30 months in an open-label extension study and were found comparable to the pivotal trials.

Trials 1 and 2 were duplicate multicenter, randomized, double-blind, placebo-controlled studies of 6 months duration. Patients were randomized to receive Krystexxa 8 mg every 2 weeks or every 4 weeks or placebo in a 2:2:1 ratio. Studies were stratified for the presence of tophi with 71% of patients having baseline tophi. All patients received an oral antihistamine, intravenous corticosteroid, and acetaminophen prior to treatment. Patients also received prophylaxis for gout flares with NSAIDs, colchicine, or both, beginning at least one week before Krystexxa treatment. The primary endpoint in both trials was the proportion of patients who achieved SUA less than 6 mg/dL for at least 80% of the time during Month 3 and Month 6. In both trials, a greater proportion of the patients treated with Krystexxa every 2 weeks achieved this endpoint compared to those receiving placebo. Although the 4 week regimen also demonstrated efficacy for the primary endpoint, this regimen was associated with increased frequency of anaphylaxis and infusion reactions and less efficacy with respect to tophi.

Krystexxa is the first PEGylated uric acid specific enzyme approved by the FDA for treatment of chronic gout in adult patients and is only indicated in patients who are refractory to conventional ULT (e.g., allopurinol, febuxostat). Krystexxa is the only ULT administered intravenously and must therefore be administered in a healthcare facility under the care of a healthcare professional trained to recognize and manage an infusion reaction and/or anaphylaxis (e.g., a rheumatologist or nephrologist). Patients with major cardiac conditions (unstable angina, uncontrolled arrhythmia, non-compensated CHF, uncontrolled HTN) were excluded from the pivotal studies; therefore, the safety of Krystexxa is expected to be utilized in the small percentage of the gout population who have advanced symptomatic gout without other available pharmacologic alternatives, many who

have concomitant CV disease. Further long-term data are needed to determine Krystexxa's safety profile, especially in terms of serious events such as anaphylaxis and infusion reactions. Krystexxa's place in therapy will continue to evolve with more clinical research and experience.

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Policy History

Original Effective Date: 03/01/2025
Current Effective Date: 03/01/2025
12/17/2024 UM Committee review. New policy.
Next Scheduled Review Date: 12/2025

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes

HCPCS	J2507
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.