Drug Coverage Policy

Effective Date.....8/1/2025
Coverage Policy Number IP0269
Policy Title.....Krystexxa

Gout - Krystexxa

- Krystexxa® (pegloticase intravenous infusion – Horizon)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Krystexxa, a PEGylated uric acid specific enzyme, is indicated for treatment of **chronic gout refractory to conventional therapy** in adult patients.[1] Gout that is refractory to conventional therapy refers to patients who have failed to normalize serum uric acid levels and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors (allopurinol, febuxostat) at the maximum tolerated dose or have a contraindication to use.

Limitations of Use: Krystexxa is not recommended for the treatment of asymptomatic hyperuricermia.[1]

Krystexxa is recommended for co-administration with methotrexate to increase effectiveness, prevent the formation of antibodies, and reduce infusion reactions; however, data are also available to support concomitant use with azathioprine, leflunomide, or mycophenolate mofetil.[1,4-6] It is recommended that patients discontinue oral urate-lowering medications while on Krystexxa therapy due to the potential blunting of the rise of serum uric acid levels with concomitant use. Krystexxa has Boxed Warnings due to concerns for anaphylaxis and infusion reactions and glucose-6-phosphate dehydrogenase (G6PD) deficiency associated hemolysis and methemoglobinemia.

Disease Overview
Gout is a form of inflammatory arthritis and results from a metabolic disorder called hyperuricemia which is caused by an overproduction or underexcretion of uric acid; however, asymptomatic patients with elevated uric acid levels do not have gout and do not require treatment.[2,3] Excessive amounts of uric acid in the blood lead to deposits of crystals in the joints and connective tissues and may cause excruciating pain. Lumps of urate crystals (tophi) may develop in soft tissues such as the elbow, ear, or distal finger joints. Some patients fail to normalize serum uric acid and have inadequate control of the signs and symptoms of gout with maximum medically appropriate doses or have a contraindication to urate-lowering therapies. Treatment-failure should be differentiated as those who are under-treated for gout or are non-compliant with gout therapy. Those with treatment-failure gout generally have a high prevalence of tophi, frequent and disabling gout flares, deforming arthropathy, diminished quality of life, and disability. Krystexxa achieves a therapeutic effect by catalyzing the oxidation of uric acid to allantoin.[1] Allantoin is then eliminated, mainly by renal excretion, thus lowering serum uric acid.

Guidelines
The American College of Rheumatology provides guidelines (2020) for the management of gout. Allopurinol is the preferred first-line urate-lowering therapy, including patients with moderate to severe gout.[3] Febuxostat and probenecid are conditionally recommended as alternative first-line therapies for specific patient populations. Titration of urate-lowering therapy should be guided by serum uric acid concentrations, with a target of < 6 mg/dL. In patients with refractory disease, effective therapeutic options include combination therapy with a xanthine oxidase inhibitor (e.g., allopurinol or febuxostat) and a uricosuric agent (e.g., probenecid, fenofibrate, or losartan). Krystexxa is not recommended as first-line therapy; however, it is appropriate in patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral urate-lowering therapies.

Coverage Policy

POLICY STATEMENT
Prior Authorization is recommended for benefit coverage of Krystexxa. Approval is recommended for those who meet the Criteria and Dosing for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist).

All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Krystexxa as well as the monitoring required for adverse events and long-term efficacy, approval requires Krystexxa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Krystexxa is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Gout, Chronic.** Approve for the duration noted below if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient meets ONE of the following (a or b):
       - **a)** Patient has at least one tophus; OR
       - **b)** Patient has a history of 2 previous gout flares in the past year (prior to the current flare); AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient had an inadequate response, defined as serum uric acid level that remained > 6 mg/dL following a 3-month trial of a xanthine oxidase inhibitor; OR
         Note: Examples of xanthine oxidase inhibitors include allopurinol, febuxostat.
       - **b)** According to the prescriber, patient has a contraindication or has had an intolerance to a trial of allopurinol; AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient had an inadequate response, defined as serum uric acid level that remained > 6 mg/dL following a 3-month trial of a uricosuric agent; OR
         Note: Examples of uricosuric agents include probenecid, fenofibrate, losartan.
       - **b)** According to the prescriber, the patient has renal insufficiency (e.g., decreased glomerular filtration rate); AND
     - **iv.** Krystexxa will be used in combination with ONE of the following (a, b, c, or d):
       - **a)** Methotrexate; OR
       - **b)** Leflunomide; OR
       - **c)** Mycophenolate mofetil; OR
       - **d)** Azathioprine; AND
     - **v.** Krystexxa will not be used in combination with an oral urate-lowering drug for the treatment of gout; AND
       Note: Examples of oral urate-lowering drugs include allopurinol, febuxostat, probenecid.
     - **vi.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist.
   - **B)** Patient is Currently Receiving Krystexxa. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is continuing therapy with Krystexxa to maintain response/remission; AND
     - **ii.** Patient has responded to therapy with evidence of serum uric acid level < 6 mg/dL with continued Krystexxa treatments; AND
     - **iii.** Krystexxa is being used in combination with ONE of the following (a, b, c, or d):
       - **a)** Methotrexate; OR
       - **b)** Leflunomide; OR
       - **c)** Mycophenolate mofetil; OR
       - **d)** Azathioprine; AND
     - **iv.** Krystexxa is not being used in combination with an oral urate-lowering drug for the treatment of gout.
       Note: Examples of oral urate-lowering drugs include allopurinol, febuxostat, probenecid.

v. Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist.

Dosing. Approve 8 mg as an intravenous infusion every 2 weeks.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Krystexxa for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Known Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency.** Because of risks of hemolysis and methemoglobinemia, Krystexxa is contraindicated in G6PD deficiency.[1] Patients at increased risk of this deficiency (e.g., those of African or Mediterranean ancestry) should be screened prior to initiation of therapy.

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J2507	Injection, pegloticase, 1 mg

References

1. Krystexxa® intravenous infusion [prescribing information]. Lake Forest, IL: Horizon Therapeutics; April 2025.
2. Gout. Centers for Disease Control and Prevention [Website]. Last reviewed January 26, 2024. Available at: https://www.cdc.gov/arthritis/gout/index.html. Accessed on May 5, 2025.
3. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care Res*. 2020 Jun;72(6):744-760.
4. Broadwell A, Albert JA, Padnick-Silver L, LaMoreaux B. Community Practice Experiences with a Variety of Immunomodulatory Agents Co-Administered with Pegloticase for the Treatment of Uncontrolled Gout. *Rheumatol Ther*. 2022;9(6):1549-1558.
5. Khanna PP, Khanna D, Cutter G, et al. Reducing Immunogenicity of Pegloticase With Concomitant Use of Mycophenolate Mofetil in Patients With Refractory Gout: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Rheumatol*. 2021;73(8):1523-1532.

6. Masri KR, Padnick-Silver L, Winterling K, LaMoreaux B. Effect of Leflunomide on Pegloticase Response Rate in Patients with Uncontrolled Gout: A Retrospective Study. *Rheumatol Ther*. 2022;9(2):555-563.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** coverage policy title from *Pegloticase* to *Gout – Krystexxa*. **Gout, chronic.** **Removed** *18 years of age or older* requirement. **Removed** *combination of a xanthine oxidase inhibitor and a uricosuric agent* requirement. **Added** criterion screening for renal insufficiency. **Added** leflunomide, mycophenolate mofetil, and azathioprine as immunosuppressive agent options to be used in combination with Krystexxa (in addition to methotrexate). **Removed** *Asymptomatic Hyperuricemia* from 'Conditions Not Covered' list. **Updated** initial authorization duration from 12 months down to 6 months.	9/1/2024
Annual Revision	**Gout, Chronic**: The previous requirement "Patient has a contraindication or has had an intolerance to a trial of allopurinol, as determined by the prescriber." was updated to "According to the prescriber, patient has a contraindication or has had an intolerance to a trial of allopurinol." Also, the requirement "Krystexxa is not being used in combination with another uric acid lowering drug" was updated to "Krystexxa is not being used in combination with an oral urate-lowering drug for the treatment of gout".	8/1/2025

The policy effective date is in force until updated or retired.