Utilization Review Policy 123

POLICY: Gout – Krystexxa Utilization Management Medical Policy
- Krystexxa® (pegloticase intravenous infusion – Horizon)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 05/14/2025

COVERAGE CRITERIA FOR: All UCare Plans

OVERVIEW

Krystexxa, a PEGylated uric acid specific enzyme, is indicated for the 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.[3] Allopurinol is the preferred first-line urate-lowering therapy, including patients with moderate to severe

gout. 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, febuxostat) and a uricosuric agent (e.g., probenecid, fenofibrate, 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.

POLICY STATEMENT

Prior Authorization is recommended for medical 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Krystexxa is recommended in those who meet the following criteria:

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 two 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)** Azathioprine; OR
       - **b)** Leflunomide; OR

c) Methotrexate; OR
d) Mycophenolate mofetil; 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; OR

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 has responded to therapy with evidence of serum uric acid level < 6 mg/dL with continued Krystexxa treatments; AND

ii. Patient is continuing therapy with Krystexxa to maintain response/remission; AND

iii. Krystexxa is being used in combination with ONE of the following (a, b, c, or d):
a) Azathioprine; OR
b) Leflunomide; OR
c) Methotrexate; OR
d) Mycophenolate mofetil; AND

iv. Krystexxa is not being 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.

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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Krystexxa is not recommended in the following situations:

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.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/17/2023
Annual Revision	**Gout, Chronic**: Mycophenolate mofetil was added as immunosuppressive agent option to be used in combination with Krystexxa in addition to the existing options of methotrexate, leflunomide, or azathioprine.	05/15/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
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".	05/14/2025
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/15/2025