CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

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

REVIEW DATE: 05/13/2026

OVERVIEW

Krystexxa, a PEGylated uric acid specific enzyme, is indicated for the treatment of **chronic gout refractory to conventional therapy** in adults.[1] Gout that is refractory to conventional therapy refers to patients who have not achieved adequate serum uric acid reduction and continue to have uncontrolled signs and symptoms despite treatment with a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat) at maximally tolerated doses, or have a contraindication to such therapy.

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

Concomitant use with methotrexate is recommended to increase effectiveness, reduce immunogenicity, and decrease infusion reactions; however, data also support use with azathioprine, leflunomide, or mycophenolate mofetil.[1,4-6] Oral urate-lowering therapy should be discontinued during Krystexxa treatment, as concomitant use may mask loss of therapeutic response as reflected by rising serum uric acid levels.[1] Krystexxa reduces serum uric acid by catalyzing the conversion of uric acid to allantoin, which is more readily eliminated, primarily via renal excretion.

Disease Overview

Gout is a form of inflammatory arthritis resulting from hyperuricemia, a metabolic disorder caused by the overproduction or underexcretion of uric acid.[2,3] Asymptomatic hyperuricemia does not constitute gout and does not require treatment. Elevated serum uric acid can lead to deposition of monosodium urate crystals in joints and connective tissues, resulting in acute pain and inflammation. Patients may also develop tophi in soft tissues (e.g., elbow, ear, or distal finger joints). Some patients are unable to achieve adequate serum uric acid reduction or symptom control despite maximally appropriate oral urate-lowering therapy (e.g., allopurinol, febuxostat, probenecid) or have contraindications to these agents. It is important to distinguish true treatment-refractory disease from suboptimal management or nonadherence. Patients with uncontrolled gout often have a high burden of disease, including frequent flares, tophi, progressive joint damage, decreased quality of life, and functional impairment.

Guidelines

The American College of Rheumatology (ACR) published guidelines (2020) for the management of gout.[3] The ACR guidelines recognize frequent gout flares (e.g., ≥ 2 per year) and the presence of tophi as indicators of increased disease burden and support escalation of urate-lowering therapy in these patients. Allopurinol is recommended as the preferred first-line urate-lowering therapy, including in patients with moderate to severe disease. Febuxostat and probenecid are conditionally recommended as alternative first-line therapies for select patients. Urate-lowering therapy should be titrated to achieve a target serum uric acid level (e.g., < 6 mg/dL). For patients with persistent disease despite appropriate therapy, combination treatment with a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat) and a uricosuric agent (e.g., probenecid, fenofibrate, losartan) is recommended. Krystexxa is reserved for patients with severe disease burden who are refractory to, or intolerant of, appropriately dosed oral urate-lowering therapies.

Safety

Krystexxa has a Boxed Warning for anaphylaxis and infusion reactions, and for hemolysis and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[1] Administration should occur in a healthcare setting by providers prepared to manage anaphylaxis and infusion reactions. Krystexxa is contraindicated in patients with G6PD deficiency due to the risk of hemolysis and methemoglobinemia. Warnings and precautions also include the potential for exacerbation of congestive heart failure.

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 at least 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 therapy for the treatment of gout; AND
Note: Examples of oral urate-lowering therapies 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 therapy for the treatment of gout; AND
Note: Examples of oral urate-lowering therapies 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 no more frequently than 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 2026.
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 8, 2026.
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	**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
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
Annual Revision	**Gout, Chronic**: The requirement that a patient has had two previous gout flares was clarified to add "at least" two previous flares. The term "drug" was updated to "therapy" throughout. Also, the dosing was clarified to add "no more frequently than".	05/13/2026