

POLICY: Gout – Krystexxa® (pegloticase injection for intravenous infusion – Savient Pharmaceuticals)

REVIEW DATE: 04/29/2020

OVERVIEW

Krystexxa is a PEGylated uric acid specific enzyme indicated for treatment of chronic gout in adult patients refractory to conventional therapy.¹⁻² It is made up of a recombinant modified mammalian uricase produced by a genetically modified strain of *Escherichia coli* which is covalently bonded to monomethoxypoly (ethylene glycol) [mPEG].¹ The recommended dose of Krystexxa is 8 mg administered every 2 weeks over no less than 120 minutes as an intravenous (IV) infusion. Before beginning therapy with Krystexxa, it is recommended that all oral urate-lowering therapies (ULTs) are discontinued and not restarted while on Krystexxa because concomitant use may blunt any increase in serum uric acid (SUA) levels. It is recommended to monitor SUA prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL.¹

Disease Overview

Gout results from a metabolic disorder called hyperuricemia caused by an overproduction or underexcretion of uric acid. Hyperuricemia is typically defined as a serum uric acid level greater than 6.8 mg/dL; however, asymptomatic patients with elevated uric acid levels do not have gout and do not require treatment.³⁻⁴ 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. Treatment-failure gout (TFG) exists in a small population of patients with severe gout.⁵ These patients have failed to normalize SUA and have inadequate control of the signs and symptoms of gout with maximum medically appropriate doses of ULT (e.g., allopurinol, Uloric) or have a contraindication to ULT. TFG should be differentiated from gout in patients who are under-treated for gout or are non-compliant with gout therapy. Those with TFG generally have a high prevalence of tophi, frequent and disabling gout flares, deforming arthropathy, diminished quality of life, and disability.² TFG 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.⁶ Of the estimated 5 million patients in the US with gout, it is believed that TFG affects approximately 50,000 patients,² although some reports indicate that as many as 300,000 patients may be afflicted.⁵ 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 (SUA).

Guidelines

The American College of Rheumatology (ACR) guidelines (2012) for the management of gout have not been updated since the FDA required the labeling of Uloric to have a new Boxed Warning and updated indication due to increased risk of death compared with allopurinol.⁷⁻⁸ Although Uloric was previously approved for use in the first-line setting of gout, it is now labeled for use only following maximal titration of allopurinol, or an intolerance or inability to use allopurinol.⁸⁻⁹ ACR guidelines for gout (developed when Uloric was indicated for hyperuricemia in patients with gout) recommend xanthine oxidase inhibitors, either allopurinol or Uloric® (febuxostat tablets), as first-line pharmacologic ULT.⁷ Serum urate level should be lowered sufficiently to improve the signs and symptoms of gout and may require therapeutic serum urate level lowering to below 5 mg/dL. Probenacid is recommended as an alternative first-line pharmacologic therapy if the patient had intolerance or contraindications to at least one first-line agent but is not recommended as first-line monotherapy in patients with estimated creatinine clearance (CrCl) < 50 mL/min.

In patients with refractory disease, effective therapeutic options include combination therapy with a xanthine oxidase inhibitor and a uricosuric agent (e.g., probenacid, fenofibrate, or losartan). While Krystexxa is never recommended as first-line therapy, it is appropriate in patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULTs.

The European League Against Rheumatism (EULAR) has recommendations for gout (2016).¹⁰ In patients with normal renal function, allopurinol is recommended as first-line ULT. The allopurinol dose should be adapted to the patient's renal function and slowly titrated to the maximum allowed dosage. If the target SUA is not achieved, the guidelines recommend switching to a uricosuric ± allopurinol or Uloric. In patients who do not achieve target SUA, combined therapy with a uricosuric + XOI is recommended. Krystexxa is recommended only in patients with crystal-proven severe, debilitating gout, in patients with poor quality of life, when the target SUA cannot be reached with any other available drug (including combinations) at the maximal dose.

Other Uses with Supportive Evidence

Nephrolithiasis and/or Gouty Nephropathy

Approximately 10% to 20% of patients with primary gout will develop kidney stones, with factors such as diet and genetic aspects playing a role in their development.¹¹ However, the most common reason for the development of uric acid nephrolithiasis has no identifiable secondary cause for the development of uric acid stones. Even though clinical gout is not present, the condition resembles primary gout in many aspects, including a persistently low urine pH, a reduced fractional excretion of uric acid, and varying degrees of hyperuricemia.

Safety

Krystexxa has Boxed Warnings due to concerns of anaphylaxis and infusion reactions.¹ Krystexxa should be administered in a healthcare setting by a healthcare professional. Patients should be pre-medicated with corticosteroids and antihistamines. Anaphylaxis may occur with any infusion, including the first infusion. Systems of anaphylaxis generally manifest within 2 hours of the infusion; delayed-type hypersensitivity reactions have also been reported. The risk of anaphylaxis and infusion reactions are higher in patients whose uric acid level increases to above 6 mg/dL, particularly when two consecutive levels above 6 mg/dL are observed. Current recommendations are to monitor SUA prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. There is also a Boxed Warning concerning hemolysis and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

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(s). 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.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. Gout, Chronic. Approve for the duration noted below if the patient meets ONE of the following conditions (A or B):

- A) Initial Therapy.** Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- i.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist; AND
 - ii.** The patient meets one of the following conditions (a or b):
 - a)** Patient has had an inadequate response, defined as serum uric acid level that remained > 6 mg/dL following a 3-month trial of at least ONE of the following agents: allopurinol, Uloric, or a uricosuric agent.
Note: Examples of uricosuric agents include probenecid, fenofibrate, and losartan; OR
 - b)** Patient has a contraindication or has had an intolerance to a trial allopurinol, as determined by the prescribing physician; AND
 - iii.** Patient has current symptoms of gout.
Note: Examples of gout symptoms include gout flares, gout tophus, and gouty arthritis.
- B) Patients currently receiving Krystexxa.** Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- i.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist; AND
 - ii.** The patient is continuing therapy with Krystexxa to maintain response/remission; AND
 - iii.** Patient has responded to therapy with evidence of serum uric acid level < 6 mg/dL with continued Krystexxa treatments.

Dosing. Approve the following dosing (A and B):

- A)** 8 mg as an intravenous infusion; AND
- B)** Subsequent doses are administered no sooner than 2 weeks following the previous infusion.

Other Uses with Supportive Evidence

2. Nephrolithiasis and/or Gouty Nephropathy. Approve for the duration noted below if the patient meets ONE of the following conditions (A or B):

- A) Initial Therapy.** Approve for 6 months if the patient meets BOTH of the following conditions (i and ii):
- i.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist; AND
 - ii.** Patient meets one of the following conditions (i or ii):
 - a)** Patient has had an inadequate response, defined as a serum uric acid level that remained > 6 mg/dL following a 3-month trial of allopurinol or Uloric; OR
 - b)** Patient has a contraindication or has had an intolerance to a trial allopurinol, as determined by the prescribing physician.
- B) Patients Currently Receiving Krystexxa.** Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- i.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist; AND
 - ii.** The patient is continuing therapy with Krystexxa to maintain response/remission; AND
 - iii.** Patient has responded to therapy with evidence of serum uric acid level < 6 mg/dL with continued Krystexxa treatments.

Dosing. Approve the following dosing (A and B):

A) 8 mg as an intravenous infusion; AND

B) Subsequent doses are administered no sooner than 2 weeks following the previous infusion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Krystexxa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 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™ injection for intravenous infusion [prescribing information]. East Brunswick, NJ: Savient Pharmaceuticals; July 2018.
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3. Shen Z, Rowlings C, Kerr B, et al. Pharmacokinetics, pharmacodynamics, and safety of lesinurad, a selective uric acid reabsorption inhibitor, in healthy adult males. *Drug Des Devel Ther*. 2015;9:3423-3434
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7. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology Guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res*. 2012;64:1431-1446.
8. Food and Drug Administration. FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat). Updated February 21, 2019. Accessed on April 21, 2020. Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm631182.htm>.
9. Uloric [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals; February 2019.
10. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76(1):29-42.
11. Wiederkehr MR, Moe OW. Uric Acid Nephrolithiasis: a systemic metabolic disorder. *Clin Rev Bone Miner Metab*. 2011;9(3-4):207-217.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/24/2019
Annual revision	Gout, Chronic: Clarify in criteria that an inadequate response to previous therapy is defined by serum uric acid (SUA) level that remains > 6 mg/dL (previously SUA level was listed as an i.e. in the criteria). Examples uricosuric agents were moved to a Note in the criteria section (previously listed within the criteria). Examples of gout symptoms were moved to a note (previously included within the criteria). For patients continuing therapy, remove criterion that	04/29/2020

	<p>generally require that the patient has previously responded to Krystexxa (not needed because criteria also require a specific response, defined as evidence of serum uric acid level < 6 mg/dL with Krystexxa).</p> <p>Nephrolithiasis and/or Gouty Nephropathy: Clarify in criteria that an inadequate response to previous therapy is defined by serum uric acid (SUA) level that remains > 6 mg/dL (previously SUA level was listed as an i.e. in the criteria). For patients continuing therapy, remove criterion that generally require that the patient has previously responded to Krystexxa (not needed because criteria also require a specific response, defined as evidence of serum uric acid level < 6 mg/dL with Krystexxa).</p>	
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