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Pegloticase

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Pegloticase (Krystexxa®) **is considered medically necessary** for the treatment of chronic gout in adults 18 years of age or older who are refractory to conventional therapies as documented in the medical record by:

- Baseline serum uric acid (SUA) of at least 6 mg/dL; and
- Symptomatic gout with at least two gout flares in the previous year or at least one episode of gout tophus or gouty arthritis; and
- History of contraindication, intolerance, or failure to normalize uric acid (to less than 6 mg/dL) while receiving conventional therapy [e.g. Xanthine oxidase inhibitor (i.e., allopurinol or febuxostat); or Uricosuric agent (e.g., probenecid)].

Pegloticase (Krystexxa®) **is considered experimental, investigational, and/or unproven** for all other non-food and drug administration (FDA) indications including but not limited to treatment of asymptomatic hyperuricemia.

Policy Guidelines

None.

Description

Gout is a painful and potentially disabling form of arthritis that occurs when excess uric acid collects in the body leading to the deposit of needlelike urate crystals in and around the joints. Gout is characterized by sudden, severe attacks of pain, swelling, redness and tenderness in the joints. Although gout most commonly affects the large joint at the base of the big toe, it can occur in any joint, including the ankles, knees, elbows, wrists and fingers. (2)

Treatment

Patients who have repeated gout flares should consider medicines to lower blood uric acid levels. Xanthine oxidase inhibitors (XOIs) (e.g., allopurinol and febuxostat) are most commonly used to return blood levels of uric acid to normal. Uricosuric agents such as probenecid may be used as well, particularly in the setting of contraindication or intolerance to XOIs. For those patients who are intolerant or refractory to these therapies, treatment with pegloticase may be considered. Gout flares are typically followed by periods of no symptoms. (3)

<u>Pegloticase (Krystexxa®)</u>

Krystexxa is a uric acid specific enzyme which achieves its therapeutic effect by catalyzing the oxidation of uric acid to allantoin, thereby lowering serum uric acid (SUA). The recommended dose and regimen of Krystexxa for adult patients is 8 mg (uricase protein) given as an intravenous infusion every two weeks, co-administered with weekly oral methotrexate 15 mg and folic acid or folinic acid supplementation. Krystexxa alone may be used in patients for whom methotrexate is contraindicated or not clinically appropriate. The optimal treatment duration has not been established. However, once SUA levels drop below 6 mg/dL (normal), crystals tend to dissolve, and new deposits of crystals can be prevented. (1)

Krystexxa treatment should be discontinued if there is loss of urate-lowering effectiveness as indicated by serum urate values >6 mg/dL at 2 consecutive visits. (1) Patients were pre-treated with standardized infusion reaction prophylaxis and the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion.

Regulatory Status
The U.S. Food and Drug Administration (FDA) approved Krystexxa on September 15, 2010, for the treatment of chronic gout in adult patients who are refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize SUA and whose signs and symptoms are inadequately controlled with "…xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated." (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for Pegloticase (Krystexxa®) and professional society guidelines.

Pegloticase (1)
Co-administration with Methotrexate
The efficacy of peloticase with methotrexate was studied in a randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy, to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of methotrexate 15 mg, compared to KRYSTEXXA alone: Trial 1 (NCT03994731). In this trial, patients were naïve to KRYSTEXXA therapy. Patients who were able to tolerate two weeks on oral methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy in a 2:1 ratio. Patients were pre-treated with a standardized infusion reaction prophylaxis regimen consisting of an oral fexofenadine, acetaminophen and intravenous methylprednisolone prior to each KRYSTEXXA infusion. Methotrexate or placebo was continued weekly throughout the KRYSTEXXA treatment period with daily oral folic acid in order to evaluate the immunomodulatory effect of methotrexate to attenuate development of anti-drug antibodies.

Entry criteria for patients to be eligible for this trial were: baseline serum uric acid ≥7 mg/dL and inability to maintain serum uric acid <6 mg/dL on other urate-lowering therapy, intolerable

side effects associated with current urate-lowering therapy, and/or presence of clinically evident tophaceous deposits.

The primary endpoint was the proportion of Month 6 responders, where a responder was defined as achieving and maintaining serum uric acid less than 6 mg/dL for at least 80% of the time during Month 6. The proportion of Month 12 responders was a key secondary endpoint. A significantly greater proportion of patients receiving KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone achieved both the primary and secondary endpoints (see Table 1).

Table 1. Serum Uric Acid < 6 mg/dL for at Least 80% of the Time During Month 6 and During Month 12 in Patients Administered KRYSTEXXA Co-administered with Methotrexate

	Treatment group	
Trial 1	**KRYSTEXXA with Methotrexate (N=100)**	**KRYSTEXXA Alone (N=52)**
Number, % of Patients Who Met Response Criteria During Month 6	71 (71%)	20 (39%)
Difference[1] (95% Confidence Interval)	32% (16%, 48%)	
P-Value	<0.0001	
Number, % of Patients Who Met Response Criteria During Month 12	60 (60%)	16 (31%)
Difference[1] (95% Confidence Interval)	29% (13%, 45%)	
P-Value	0.0003	

[1]Difference and its corresponding 95% confidence interval (CI) based on a weighted average of the difference within each randomization stratum (tophi presence, no tophi presence) using Cochran-Mantel-Haenszel (CMH) weights.

The effect of KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone on tophi was assessed using standardized digital photography, image analysis and Central Readers blinded to treatment assignment. Approximately 53.3% (81/152) of randomized patients had tophi at baseline (Week -6) that were confirmed by digital photography. Of those, 54% (28/52) in the KRYSTEXXA co-administered with methotrexate group and 31% (9/29) in the KRYSTEXXA alone group achieved a complete response at Month 12 (defined as 100% resolution of at least one target tophus, no new tophi appear and no single tophus showing progression). The difference between the two treatment groups was statistically significant (22.8%, 95% CI: 1.2%, 44.4%).

KRYSTEXXA Alone

The efficacy of KRYSTEXXA was studied in adult patients with chronic gout refractory to conventional therapy in two replicate, multicenter, randomized, double-blind, placebo-controlled studies of six months duration: Trial 2 and Trial 3. 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. Seventy-one percent (71%) of patients had baseline tophi. All patients were prophylaxed with an oral antihistamine, intravenous corticosteroid and acetaminophen. Patients also received prophylaxis for gout flares with non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine, or both, beginning at least one week before KRYSTEXXA treatment unless medically contraindicated or not tolerated. Patients who completed the randomized clinical trials were eligible to enroll in a 2-year open label extension study.

Entry criteria for patients to be eligible for the trials were: baseline serum uric acid of at least 8 mg/dL; had symptomatic gout with at least 3 gout flares in the previous 18 months or at least 1 gout tophus or gouty arthritis; and had a self-reported medical contraindication to allopurinol or medical history of failure to normalize uric acid (to less than 6 mg/dL) with at least 3 months of allopurinol treatment at the maximum medically appropriate dose.

The mean age of study subjects was 55 years (23-89); 82% were male, mean body mass index (BMI) was 33 kg/m2, mean duration of gout was 15 years, and mean baseline serum uric acid was 10 mg/dL.

To assess the efficacy of KRYSTEXXA in lowering uric acid, the primary endpoint in both trials was the proportion of patients who achieved plasma uric acid (PUA) less than 6 mg/dL for at least 80% of the time during Month 3 and Month 6. As shown in Table 4, a greater proportion of patients treated with KRYSTEXXA every 2 weeks achieved urate lowering to below 6 mg/dL than patients 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.

Table 2. Plasma Uric Acid < 6 mg/dL for at Least 80% of the Time During Months 3 and 6

Treatment Group	**N**	**Number (%) of Subjects Who Met Response Criteria**	**95% Confidence Interval[1]**	**P-Value[2]**
Trial 2				
KRYSTEXXA 8 mg every 2 weeks	43			
KRYSTEXXA 8 mg every 4 weeks	41			
Placebo	20			
Trial 3				

KRYSTEXXA 8 mg every 2 weeks	42			
KRYSTEXXA 8 mg every 4 weeks	43			
Placebo	23			

[1]95% confidence interval for differences in responder rate between pegloticase group vs. placebo
[2]P-value using Fisher's exact test to compare pegloticase group vs. placebo Note: Based on post-hoc analyses of the clinical trial data, if KRYSTEXXA had been stopped when a patient's uric acid level rose to greater than 6 mg/dL on a single occasion, the incidence of infusion reactions would have been reduced by approximately 67%, but the success rates for the primary efficacy endpoint would have been reduced by approximately 20%. If KRYSTEXXA had been stopped after 2 consecutive uric acid levels greater than 6 mg/dL, the incidence of infusion reactions would have been half, and there would have been little change in the efficacy outcome.

The effect of treatment on tophi was a secondary efficacy endpoint and was assessed using standardized digital photography, image analysis, and a Central Reader blinded to treatment assignment. Approximately 70% of patients had tophi at baseline. A pooled analysis of data from Trial 2 and Trial 3 (NCT00325195) was performed as pre-specified in the protocols. At Month 6, the percentage of patients who achieved a complete response (defined as 100% resolution of at least one target tophus, no new tophi appear and no single tophus showing progression) was 45%, 26%, and 8%, with KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The difference between KRYSTEXXA and placebo was statistically significant for the every 2 week dosing regimen, but not for the every 4 week dosing regimen.

Practice Guidelines and Position Statements

American College of Rheumatology (ACR)

The ACR guidelines for the management of gout (2020) offered the following recommendations for choice of initial urate-lowering therapy (ULT) (2):

- "For patients starting any ULT, we strongly recommend allopurinol over all other ULT as the preferred first agent for all patients, including in those with CKD [chronic kidney disease] stage ≥3.
- We strongly recommend a xanthine oxidase inhibitor over probenecid for those with CKD stage ≥3.
- For allopurinol and febuxostat, we strongly recommend starting at a low dose with subsequent dose titration to target over starting at a higher dose (e.g., ≤100 mg/day [and lower in patients with CKD] for allopurinol or ≤40 mg/day for febuxostat).
- For probenecid, we conditionally recommend starting at a low dose (500 mg once or twice daily) with dose titration over starting at a higher dose.
- We strongly recommend initiating concomitant anti-inflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) over no anti-inflammatory prophylaxis. The choice of specific anti-inflammatory prophylaxis should be based upon patient factors.

- We strongly recommend continuing prophylaxis for 3–6 months rather than <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience flares.
- When the decision is made that ULT is indicated while the patient is experiencing a gout flare, we conditionally recommend starting ULT during the gout flare over starting ULT after the gout flare has resolved.
- We strongly recommend against pegloticase as first-line therapy."

"Switching to pegloticase over continuing current ULT is strongly recommended for patients with gout for whom xanthine oxidase inhibitor treatment, uricosurics, and other interventions have failed to achieve the serum uric target, and who continue to have frequent gout flares (≥2 flares/year) OR who have nonresolving subcutaneous tophi."

"Switching to pegloticase over continuing current ULT is strongly recommended against for patients with gout for whom xanthine oxidase inhibitor treatment, uricosurics, and other interventions have failed to achieve the serum uric target, but who have infrequent gout flares (≥2 flares/year) AND no tophi."

<u>European League Against Rheumatism (EULAR)</u>
In 2016, EULAR conducted a systematic review and update of their 2006 recommendations for the management of gout. (4) Recommendations included:

- "For the treatment of flare, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intra-articular steroids, or a combination are recommended.
- In patients with frequent flare and contraindications to colchicine, NSAIDs, and corticosteroids, an interleukin-1 blocker should be considered.
- In addition to education and a nonpharmacological management approach, ULT should be considered from the first presentation of the disease, and serum uric acid (SUA) levels should be maintained at <6 mg/dL (360 mmol/L) and <5 mg/dL (300 mmol/L) in those with severe gout.
- Allopurinol is recommended as first-line ULT, and its dosage should be adjusted according to renal function.
- If the SUA target cannot be achieved with allopurinol, then febuxostat, a uricosuric, or combining a xanthine oxidase inhibitor with a uricosuric should be considered.
- For patients with refractory gout, pegloticase is recommended."

Summary of Evidence
Based on the U.S. Food and Drug Administration (FDA) label, Pegloticase (Krystexxa®) is indicated for adults (18 years of age or older) who are refractory to conventional therapies as documented in the medical record by baseline serum uric acid (SUA) of at least 6 mg/dL; symptomatic gout with at least two gout flares in the previous year or at least one episode of gout tophus or gouty arthritis; and history of contraindication, intolerance, or failure to normalize uric acid (to less than 6 mg/dL) while receiving conventional therapy [e.g. Xanthine oxidase inhibitor (i.e., allopurinol or febuxostat); or Uricosuric agent (e.g., probenecid)].

Pegloticase (Krystexxa®) is considered experimental, investigational and/or unproven for all other non-FDA approved indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J2507

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label

1. Krystexxa® Highlights of Prescribing Information (Jul 2022). Available at: <https://www.accessdata.fda.gov> (accessed April 16, 2025).

Other

2. American College of Rheumatology – Gout. (February 2025). Available at: <https://www.rheumatology.org> (accessed April 16, 2025).
3. FitzGerald JD, Dalbeth N, Mikuls T, et al. ACR Guidelines for Management of Gout: 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken). Jun 2020; 72(6):744-760. PMID 32391934
4. Richette P, Doherty M, Pascual E, et al. 2016 Updated EULAR Evidence-Based Recommendations for the Management of Gout. Ann Rheum Dis. Jan 2017; 76(1):29-42. PMID 27457514

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
01/01/2026	Document updated with literature review. The following changes were made to coverage: 1) Modified coverage defining conventional therapy. The new statement states: "History of contraindication, intolerance, or failure to normalize uric acid (to less than 6 mg/dL) while receiving conventional therapy [e.g., Xanthine oxidase inhibitor (i.e., allopurinol or febuxostat); or Uricosuric agent (e.g., probenecid)] and 2) Added “non-FDA approved” to the existing experimental, investigational and/or unproven statement. References 4 and 5 removed.
07/15/2024	Reviewed. No changes.
07/01/2023	Document updated with literature review. Coverage unchanged. No new references added.
01/01/2023	Document updated with literature review. The following modification was made to Coverage: Changed “Symptomatic gout with at least three gout flares in the previous 18 months or at least one episode of gout tophus or gouty arthritis…” TO “Symptomatic gout with at least two gout flares in the previous year or at least one episode of gout tophus or gouty arthritis…”. Added/updated the following references: 1-3 and 5.
07/01/2021	Reviewed. No changes.