Policy Number	**RX501.120**
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Pegloticase

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. 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 acceptable standards of medical practice. 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 adult patients 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) after at least 3 months of therapy with BOTH of the following at the maximum medically appropriate doses:
    - Xanthine oxidase inhibitor (i.e., allopurinol or febuxostat); and
    - Uricosuric agent (e.g., probenecid).

Pegloticase (Krystexxa™) **is considered experimental, investigational, and/or unproven** for all other 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. (1)

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. (2)

Pegloticase (Krystexxa®)

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. (3)

The risk of infusion reactions, including anaphylaxis, is higher in patients who have lost therapeutic response. Krystexxa treatment should be discontinued if there is loss of urate-lowering effectiveness as indicated by serum urate values >6 mg/dL on one occasion, particularly if accompanied by an infusion reaction, or on two successive occasions. (3) Other urate-lowering therapies should not be given to patients receiving Krystexxa because they may mask recognition of the increasing serum urate levels associated with an increased risk for infusion-related reactions and loss of effectiveness resulting from the effects of high titer Krystexxa antibodies. (5)

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". (3)

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The most recent review of the literature was performed through April 27, 2023.

Literature Review

Pegloticase (Krystexxa®) was evaluated in two replicate, multicenter, randomized, double-blind, placebo-controlled clinical trials. Each study lasted six months. Patients were randomized to receive Krystexxa every two or four weeks or placebo in a ratio of 2:2:1. For both trials, the primary end point was the proportion of patients in whom plasma uric acid was reduced to less than 6 mg/dL for at least 80% of the time during months three and six. In both trials, more patients receiving Krystexxa every two weeks reached this end point than patients receiving placebo: 47% ($p<0.001$) and 38% ($p<0.001$), compared with 0% in the placebo arms. Two patients receiving Krystexxa every four weeks also achieved the primary end point; however, this regimen was associated with an increased frequency of infusion reactions and a decreased efficacy with the secondary end point. (3)

The secondary end point was the effect of Krystexxa on tophi, which are deposits of monosodium urate crystals in patients who have sustained long-term high levels of serum uric acid (SUA). Seventy-one percent of patients had baseline tophi. At six months, the combined data from both trials showed that 45% ($p<0.02$) of patients receiving Krystexxa every two weeks had a complete response (CR), which was considered 100% resolution of at least one target tophus, no new tophus developing, and no single tophus showing progression. In comparison, 8% of patients in the combined placebo arms achieved a CR. (3)

In 2013, Baraf et al. reported on the results of an open-label treatment extension (OLE) of the two replicate RCTs outlined above, specifically the temporal course of tophus resolution, total tophus burden in patients with multiple tophi, tophus size at baseline, and the relationship between tophus response and urate-lowering efficacy. Baseline subcutaneous tophi were analyzed quantitatively using computer-assisted digital images in patients receiving pegloticase (8 mg biweekly or monthly) or placebo in the RCTs, and pegloticase in the OLE. Among 212 patients randomized in the RCTs, 155 (73%) had ≥ 1 tophus and 547 visible tophi were recorded at baseline. Overall tophus CR was recorded in 45% of patients in the biweekly group ($P = 0.002$ versus placebo), 26% in the monthly group, and 8% in the placebo group after six months of RCT therapy. Target tophus complete response rates at six months were 28%, 19%, and 2% of tophi, respectively. Patients meeting the primary end point of sustained urate-lowering response to therapy (responders) were more likely than nonresponders to have an overall tophus CR at six months (54% vs 20%, respectively and 8% with placebo). Authors concluded that pegloticase reduced tophus burden in patients with refractory tophaceous gout, especially those achieving sustained urate-lowering. Complete resolution of tophi occurred in some patients by 13 weeks and in others with longer-term therapy. (4)

UpToDate

In a 2022 article, Perez-Ruiz et al. stated, "For patients with advanced gout refractory to conventional treatment or with tophaceous disease significantly affecting physical function or health-related quality of life, use of pegloticase is a therapeutic consideration." (5)

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."

European League Against Rheumatism (EULAR)

In 2016, EULAR conducted a systematic review and update of their 2006 recommendations for the management of gout. (6) 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, urate-lowering therapy (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."

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®) ©2023 American Medical Association: Chicago, IL.

References

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2. 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
3. Krystexxa® Highlights of Prescribing Information (Jul 2022). Available at: <https://www.accessdata.fda.gov> (accessed April 25, 2023).
4. Baraf HS, Becker MA, Gutierrez-Urena, SR, et al. Tophus burden reduction with pegloticase: Results from phase 3 randomized trials and open-label extension in patients with chronic gout refractory to conventional therapy. Arthritis Res Ther. Sep 26 2013; 15(5):R137. PMID 24286509

5. Perez-Ruiz F. Pharmacologic urate-lowering therapy and treatment of tophi in patients with gout. In: UpToDate, Dalbeth N (Ed), UpToDate, Waltham, MA. Available at: <http://www.uptodate.com> (accessed April 24, 2023).
6. 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 <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
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.
10/01/2020	New medical document originating from RX501.051. Pegloticase (Krystexxa®) is considered medically necessary for the treatment of chronic gout in adult patients 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 three gout flares in the previous 18 months 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) after at least 3 months of therapy with BOTH of the following at the maximum medically appropriate doses: xanthine oxidase inhibitor (i.e., allopurinol or febuxostat); and uricosuric agent (e.g., probenecid). Pegloticase (Krystexxa™) is considered experimental, investigational, and/or unproven for all other indications

	including but not limited to treatment of asymptomatic hyperuricemia. The following change was made to Coverage language: Modified conditional criteria specific to contraindication/failure of conventional therapy.