



Drug and Biologic Coverage Policy

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Pegloticase

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Related Coverage Resources

[Canakinumab \(Ilaris®\)](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Pegloticase (Krystexxa®) is considered medically necessary when ALL of the following criteria are met:

- Age 18 years of age and older
- Treatment of chronic gout
- At least ONE of the following:
 - History of at least 3 gout flares in the previous 18 months
 - At least 1 gouty tophus
 - Chronic gouty arthritis
- EITHER of the following:
 - Failure to normalize serum uric acid to less than 6 mg/dL after BOTH of the following:
 - Use of the maximum medically appropriate dose of ONE xanthine oxidase inhibitor [maximum recommended dosage - allopurinol (Zyloprim) is 800 mg/day / febuxostat (Uloric) is 80 mg/day]
 - Combination of ONE xanthine oxidase inhibitor and ONE uricosuric agent (for example, probenecid)
 - Contraindication per FDA label to the following:
 - Xanthine oxidase inhibitors [allopurinol (Zyloprim) and febuxostat (Uloric)] (for example, hypersensitivity, concomitant use of azathioprine, mercaptopurine, or theophylline) and/or

- Uricosuric agents [probenecid (for example, hypersensitivity)]

Initial authorization is up to 12 months.

Pegloticase (Krystexxa) is considered medically necessary for continued use when the initial criteria are met.

Reauthorization for up to 12 months

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Pegloticase (Krystexxa) is considered experimental, investigational or unproven for ANY other use including the following:

- Chronic Kidney Disease

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

FDA Approved Indications

FDA Approved Indication

Krystexxa (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid 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.

Limitations of Use:

Krystexxa is not recommended for the treatment of asymptomatic hyperuricemia.

Recommended Dosing

FDA Recommended Dosing

The recommended dose and regimen of Krystexxa for adult patients is 8 mg (uricase protein) given as an intravenous infusion every two weeks. The optimal treatment duration with Krystexxa has not been established.

Drug Availability

Krystexxa for intravenous infusion is supplied as 8 mg of uricase protein in 1 mL volume.

General Background

Pharmacology

Pegloticase oxidizes uric acid forming allantoin, thereby decreasing serum uric acid levels. Allantoin is an inactive metabolite that is readily excreted by the kidneys.

Professional Societies/Organizations

American College of Rheumatology

The ACR guidelines for the management of gout (2012) recommend Krystexxa as third-line therapy for the management of severe disease. Serum urate levels should be lowered sufficiently to durably improve signs and symptoms of gout, with a target serum urate level of < 6 mg/dl. Core therapeutic measures include education on diet, lifestyle, treatment objectives, and management of co-morbidities. The following are the recommended first, second, and third line treatment options for gout to achieve target serum urate levels:

- First-line therapy - xanthine oxidase inhibitor (XOI) (allopurinol or febuxostat)
- Second-line therapy – if maximum tolerated doses of either XOI recommended therapy do not achieve serum urate target then a combination oral urate-lowering therapy (ULT) with 1 XOI agent and 1 uricosuric agent (probenecid or off-label use of losartan or fenofibrate) is appropriate
- Third-line therapy - pegloticase (Krystexxa) is appropriate for patients with severe gout disease who are refractory to or intolerant of oral ULT options

Krystexxa is not recommended as first-line therapy for any case scenario treatment of gout. Recommendations also noted that there was no consensus achieved on the duration of Krystexxa therapy once decreased symptoms and signs of gout had been reached. (Khanna, 2012)

EULAR

2016 Updated EULAR Evidence-Based Recommendations for the Management of Gout

The 2016 EULAR recommendations represent a systematic review and update of the 2006 recommendations. For flare treatment, recommendations include: colchicine, NSAIDs, oral or intra-articular steroids or a combination. Next, for patients that have frequent flare and contraindications to colchicine, corticosteroids, or NSAIDs, EULAR recommends an interleukin-1 blocker should be considered. Urate-lowering therapy should be considered from at the the first presentation, and serum uric acid levels should be maintained at less than 6 mg/dL and less than 5 mg/dL in severe gout. Allopurinol is recommended as first-line urate-lowering therapy. EULAR recommends that if the serum urate acid target cannot be achieved with allopurinol, then febuxostat, a uricosuric or a combination of xanthine oxidase inhibitor with a uricosuric should be considered. Pegloticase is recommended in cases of crystal-proven, severe debilitating chronic tophaceous gout with reduced quality of life when serum uric acid levels cannot be attained using maximum doses of other drug therapies. (Richette, 2017)

American College of Physicians (ACP)

Guidelines published in 2016 address the management of acute and recurrent gout. Recommended therapies for treatment of acute gout include corticosteroids, NSAIDs, and low dose colchicine. Pegloticase is not addressed in the recommendations. (Qaseem, 2017)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for gout agents.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for pegloticase (Krystexxa).

Clinical Efficacy

A single published dose-finding study examined pegloticase for treating patients with gout unresponsive to at least one other urate lowering therapy. Two pivotal, placebo-controlled trials are reported only in the product labeling.

Sundy et al conducted a phase 2 dose-finding study, randomly assigning 41 patients to receive 1 of 4 pegloticase dosing schedules: 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks, or 12 mg every 4 weeks. The primary outcome was defined as maintaining plasma uric acid levels ≤ 6 mg/dL during 80% of the treatment period. The primary outcome was achieved most frequently in the group receiving pegloticase 8 mg every 2 weeks (87.5%). Mean plasma urate concentration in this group was 1.4 mg/dL over the entire study period. Results were not significantly different between treatment groups, but the study was underpowered to detect a difference. In patients that responded to pegloticase in any treatment group, serum urate concentrations fell to ≤ 6 mg/dL within 6 hours of administration. Gout flare was common in all 4 treatment groups (88%).

Two identical, unpublished, randomized, placebo-controlled trials evaluated the efficacy of pegloticase in patients with symptomatic gout unresponsive to allopurinol. Patient inclusion criteria included a serum urate level ≥ 8 mg/dL with established and symptomatic gout, a failure to achieve serum urate < 6 mg/dL despite ≥ 3 months of appropriately dosed allopurinol, and ≥ 1 tophus, ≥ 3 gout flares within previous 18 months, or gouty arthritis. In both studies, patients received pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks, or placebo for 6 months. The primary endpoint was defined as maintaining plasma uric acid concentrations < 6 mg/dL for 80% of the time during the third and sixth months of treatment. The primary endpoint was achieved for the labeled

pegloticase dose (8 mg every 2 weeks) in 47% at after 3 months of therapy (trial 1) and 38% (trial 2) of patients after 6 months, compared to no patients in the placebo groups ($p < 0.001$ in each trial). The secondary endpoint characterized the response of tophi to pegloticase treatment. In a combined analysis of both trials, 45% of patients treated with pegloticase every 2 weeks demonstrated a complete response of tophi, compared to 8% of patients in the placebo group ($p < 0.05$). A complete response of tophi was defined as full resolution of at least one target tophus, no formation of new tophi, and no progression of any tophus.

Pegloticase was not studied in pediatric patients. Patients up to 89 years of age were included in the pivotal trials, but subgroup analyses were not presented comparing elderly patients to other patients. Pegloticase efficacy was not studied in patients with renal insufficiency or hepatic impairment.

Experimental, Investigational, Unproven Uses

The use of Krystexxa for chronic kidney disease has not been evaluated prospectively. Data available is limited to post-hoc subgroup analyses, which revealed treatment with pegloticase does not effect estimated glomerular filtration rate. (Yood, 2014)

Coding/ Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

HCPCS Codes	Description
J2507	Injection, pegloticase, 1 mg

References

1. Khanna D, Fitzgerald J, Khanna P, et al. 2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia. *Arthritis Care & Research* Vol. 64, No. 10, October 2012, pp 1431–1446.
2. Horizon Pharma Rheumatology LLC, Krystexxa (pegloticase) intravenous infusion [product information]. Lake Forest, IL: Horizon Pharma Rheumatology. July 2018.
3. Qaseem A, Harris RP, Forclea MA. Management of acute and recurrent gout: A clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2017;166(1):58-68.
4. Richette P et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017 Jan;76(1):29-42. doi: 10.1136/annrheumdis-2016-209707. Epub 2016 Jul 25
5. Sundy JS, Ganson NJ, Kelly SJ, et al. Pharmacokinetics and pharmacodynamics of intravenous PEGylated recombinant mammalian urate oxidase in patients with refractory gout. *Arthritis Rheum*. Mar 2007;56(3):1021-1028.
6. Yood R, Ottery F, Irish W, et al. Effect of pegloticase on renal function in patients with chronic kidney disease: a post hoc subgroup analysis of 2 randomized, placebo-controlled, phase 3 clinical trials. *BMC Research Notes* 214, 7:54.

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