



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Pegloticase (Krystexxa®)**

Effective Date	5/15/2011
Next Review Date.....	5/15/2012
Coverage Position Number.....	1107

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), 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 supercedes** 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers pegloticase (Krystexxa®) as medically necessary for the treatment of chronic gout in an adult meeting EITHER of the following criteria:

- history of a beneficial clinical response to current treatment with pegloticase (Krystexxa®) as demonstrated by a serum uric acid level less than 6 mg/dL or an improvement in symptoms
- **BOTH** of the following:
 - at least **ONE** of the following indications:
 - history of at least 3 gout flares in the previous 18 months
 - at least 1 gouty tophus
 - chronic gouty arthritis
 - **EITHER** of the following responses to treatment:
 - failure to normalize serum uric acid to less than 6 mg/dL after 3 months of the maximum medically appropriate dose of **ONE** xanthine oxidase inhibitor (maximum recommended dosage of allopurinol [Zyloprim] is 800 mg/day and febuxostat [Uloric] is 80 mg/day)
 - contraindication to xanthine oxidase inhibitors (allopurinol [Zyloprim] and febuxostat [Uloric])

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to pegloticase (Krystexxa[®]) therapy.

FDA Approved Indications

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. Krystexxa is not recommended for the treatment of asymptomatic hyperuricemia.

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.

Black Box Warning

Anaphylaxis and infusion reactions have been reported to occur during and after administration of Krystexxa. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. Krystexxa should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of Krystexxa. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

Drug Availability

Krystexxa is supplied as a clear, colorless, sterile solution in phosphate buffered saline intended for intravenous infusion after dilution. Krystexxa is supplied in a single-use 2 mL glass vial with a Teflon coated (latex-free) rubber injection stopper to deliver Krystexxa 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. Pegloticase plasma concentrations and area under the curve (AUC) increase proportionate to the administered dose. Pegloticase has a plasma half-life of 12.5 ± 0.9 days at the labeled dose.

Clinical Efficacy

A single published dose-finding study examined pegloticase for treating patients with gout unresponsive to at least one other urate lowering therapy. No published data are available comparing pegloticase to placebo or an active comparator. 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. 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% (trial 1) and 38% (trial 2) of patients, 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.

Adverse Drug Reactions / Drug Interactions

The most common adverse event with pegloticase is gout flare. Gout flare occurred during the first 3 months of therapy in 74% of patients receiving pegloticase, compared to 51% of patients receiving placebo. Infusion reactions and anaphylaxis are also common despite pre-treatment with an antihistamine and a corticosteroid with or without acetaminophen. Pegloticase has a boxed warning for anaphylaxis and infusion reactions. Pegloticase is contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficient patients. No formal drug-drug interaction studies have been conducted.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPSC Codes	Description
C9281	Injection, Pegloticase, 1 mg (Code effective 04/01/2011)
J3490 [†]	Unclassified drug

[†]**Note:** Covered when medically necessary and used to report Pegloticase (Krystexxa®) until 03/31/2011.

ICD-9-CM Diagnosis Codes	Description
274.00	Gout arthropathy, unspecified
274.02	Chronic gouty arthropathy without mention of tophus (tophi)
274.03	Chronic gouty arthropathy with tophus (tophi)

References

1. Brunton LL, ed. 11th ed. New York, NY: McGraw-Hill; 2006. Goodman and Gilman's The Pharmacological Basis of Therapeutics.
2. Chapter 15. Gout. In: JH K, ed. Primer on the Rheumatic Diseases. 12th ed. Atlanta, GA: Arthritis Foundation; 2001:307-324.
3. Cheuk DK, Chiang AK, Chan GC, Ha SY. Urate oxidase for the prevention and treatment of tumor lysis syndrome in children with cancer. Cochrane Database Syst Rev. (6):CD006945.
4. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology (Oxford). Aug 2007;46(8):1372-1374.

5. Keith MP, Gilliland WR. Updates in the management of gout. *Am J Med.* Mar 2007;120(3):221-224.
6. McEvoy GK, Snow ED, Miller J, Kester L, Welsh OH, eds. Bethesda, MD: American Society of Health-System Pharmacists; 2009. AHFS 2009 Drug Information.
7. Rider TG, Jordan KM. The modern management of gout. *Rheumatology (Oxford).* Jan;49(1):5-14.
8. Savient. Krystexxa (pegloticase) intravenous infusion [product information]. East Brunswick, NJ: Savient Pharmaceuticals. Sept 2010.
9. Sherman MR, Saifer MG, Perez-Ruiz F. PEG-uricase in the management of treatment-resistant gout and hyperuricemia. *Adv Drug Deliv Rev.* Jan 3 2008;60(1):59-68.
10. So A. Developments in the scientific and clinical understanding of gout. *Arthritis Res Ther.* 2008;10(5):221.
11. Stamp LK, O'Donnell JL, Chapman PT. Emerging therapies in the long-term management of hyperuricaemia and gout. *Intern Med J.* Apr 2007;37(4):258-266.
12. 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.
13. Taylor WJ, Schumacher HR, Jr., Singh JA, Grainger R, Dalbeth N. Assessment of outcome in clinical trials of gout--a review of current measures. *Rheumatology (Oxford).* Dec 2007;46(12):1751-1756.
14. Terkeltaub RA. Clinical practice. Gout. *N Engl J Med.* Oct 23 2003;349(17):1647-1655.
15. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis.* Oct 2006;65(10):1312-1324.

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