# MEDICAL POLICY

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| POLICY TITLE | PEGLOTICASE (KRYSTEXXA™) |
|---|---|
| POLICY NUMBER | MP- 2.154 |

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| Original Issue Date (Created): | **January 1, 2011** |
| Most Recent Review Date (Revised): | **September 24, 2013** |
| **Effective Date:** | **November 1, 2013** |

## I. POLICY

### PREAUTHORIZATION REQUIRED

**Note:** Requests for pegloticase (Krystexxa™) to treat patients with treatment failure gout must be accompanied by a completed preauthorization form prior to treatment. The maximum initial authorization will be for one year. Maintenance therapy will be authorized on a yearly basis.

**Initial Therapy**

Pegloticase (Krystexxa™) may be considered **medically necessary** for the treatment of chronic gout in adult patients when ALL of the following conditions are met:

- Consulting rheumatologist recommends treatment with pegloticase (Krystexxa™)
- Baseline serum uric acid (SUA) level equal to or greater than 8 mg/dL
- Pharmacologic treatment history includes ANY ONE of the following:
    - Medical contraindication to xanthine oxidase inhibitors (e.g. allopurinol [Aloprim®, Zyloprim®], febuxostat [Uloric®]); OR
    - Failure to normalize the serum uric acid (to between 6-8 mg/dL) after at least 3 months of treatment at the maximum medically appropriate dose of xanthine oxidase inhibitors or a documented lack of clinical response in regard to ongoing gout-related symptoms such as arthritis, tophi or uric acid renal stones.
- Symptomatic gout flare when ALL of the following criteria are met:
    - Diagnosis established by ONE of the following criteria:
        - Crystal identification in the joint fluid; OR
        - Classic presentation of podagra involving the first metatarsophalangeal (MTP) joint
    - ANY ONE of the following criteria:
        - At least 3 gout flares in the previous 18 months; OR
        - At least 1 gout tophus; OR

- Gouty arthritis

Pegloticase (Krystexxa™) for the treatment of asymptomatic hyperuricemia is considered **not medically necessary**.

The use of pegloticase (Krystexxa™) for all other indications than those listed in the policy statement is considered **investigational.** There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with treatment of this drug for other indications.

**Maintenance Therapy**

Pegloticase (Krystexxa™) maintenance therapy may be considered medically necessary when therapy has demonstrated efficacy as evidenced by an improvement in serum uric acid levels (to less than 6 mg/dL).

Treatment with pegloticase (Krystexxa™) is considered not medically necessary when 2 consecutive pre-infusion serum uric acid levels above 6 mg/dL are observed.

## II. PRODUCT VARIATIONS

*[N] = No product variation, policy applies as stated*
*[Y] = Standard product coverage varies from application of this policy, see below*

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO (see note)
[N] SeniorBlue PPO (see note)
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO**

Note: "FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if determined that the use is medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice." Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2- Unlabeled Use of Drug)." *http://www.cms.gov/manuals/Downloads/bp102c15.pdf*

** Refer to FEP Medical Policy Manual MP-5.02.14 Krystexxa. The FEP Medical Policy manual can be found at: http://bluewebportal.bcbs.com/landingpagelevel3/504100?docId=23980



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## III. DESCRIPTION/BACKGROUND

Gout is a painful condition that occurs when uric acid is deposited as needle-like crystals in the joints and/or soft tissues. In the joints, these uric acid crystals cause inflammatory arthritis, which in turn leads to intermittent swelling, redness, heat, pain, and stiffness in the joints. Joints that may be affected include the toes (especially the great toe), insteps, ankles, heels, knees, wrists, fingers, and elbows. One manifestation of gout is gouty arthritis, a chronic arthropathy, characterized by uric acid crystal deposits in the joint which, over time, result in joint erosion. Chalky deposits of uric acid, also known as tophi, may also appear as lumps under the skin that surrounds the joints and covers the rim of the ear. Uric acid crystals can also collect in the kidneys and cause kidney stones.

The most common treatments for an acute attack of gout are nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (oral or injectable). NSAIDs reduce the inflammation caused by deposits of uric acid crystals, but have no effect on the amount of uric acid in the body. Colchicine, an antigout agent that inhibits deposition of ureate crystals in soft tissues, may be used when NSAIDs or corticosteroids do not control symptoms.

Patients with gout who have recurrent episodes of gouty arthritis or who develop tophi are treated with drugs to reduce uric acid levels. Prophylactic therapy includes uricosurics (e.g., Probenecid) or xanthine oxidase inhibitors (e.g. allopurinol and febuxostat).

Pegloticase is a recombinant PEGylated (polyethylene glycol-ylated) form of the porcine uricase enzyme. Pegloticase works by converting uric acid into allantoin, a substance that is more soluble and better excreted than uric acid.

The Food and Drug Administration (FDA) approved Pegloticase (Krystexxa™) 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. The recommended dose is 8 mg by intravenous infusion every 2 weeks. The optimal treatment duration has not been established.

The FDA label includes a black box warning for anaphylaxis and infusion reactions. As a condition of approval, the FDA required implementation of a Risk Evaluation and Mitigation Strategy (REMS) program as a strategy to manage known or potential serious risks associated with Pegloticase (Krystexxa™).

**Black Box Warning:**

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**WARNING: ANAPHYLAXIS AND INFUSION REACTIONS**

- 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.

Pegloticase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to generation of hydrogen peroxide in conversion of uric acid into allantoin and consequent risk of hemolytic anemia and met-hemoglobinemia G6PD deficient patients. G6PD deficiency is an X-linked recessive hereditary disease.

## IV. RATIONALE

**CLINICAL STUDIES**

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 1 and Trial 2. 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 (SUA) 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 SUA 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 2, 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.13

| **Treatment Group N** | **N** | **Number (%) of Subjects Who Met Response Criteria** | **95% Confidence Interval1** | **P-Value2** |
|---|---|---|---|---|
| **Trial 1** | | | | |
| **Pegloticase 8 mg every 2 weeks** | 43 | 20 (47%) | [32%, 61%] | <0.001 |
| Pegloticase 8 mg every 4 weeks | 41 | 8 (20%) | [7%, 32%] | 0.044 |
| Placebo | 20 | 0 (0%) | | |
| **Trial 2** | | | | |
| **Pegloticase 8 mg every 2 weeks** | 42 | 16 (38%) | [23%, 53%] | <0.001 |
| Pegloticase 8 mg every 4 weeks | 43 | 21 (49%) | [34%, 64%] | <0.001 |
| Placebo | 23 | 0 (0%) | | |

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 1 and Trial 2 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.

## V. DEFINITIONS

**ALLANTOIN** is a crystalline oxidation product of uric acid produced in purine metabolism.

**ARTHROPATHY** is a disease or an abnormality of a joint.

**METATARSOPHALANGEAL JOINTS** are any of the spheroid joints between the heads of the metatarsal bones and the bases of the proximal phalanges of the toes.

**PODAGRA** is gouty pain in the great toe.

## VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

## VII. DISCLAIMER

*Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

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## IX. CODING INFORMATION

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Covered when medically necessary:**

| HCPCS Code | Description |
|---|---|
| J2507 | INJECTION, PEGLOTICASE, 1 MG |

| ICD-9-CM Diagnosis Code* | Description |
|---|---|
| 274.02 | CHRONIC GOUTY ARTHROPATHY WITHOUT MENTION OF TOPHUS (TOPHI) |
| 274.03 | CHRONIC GOUTY ARTHROPATHY WITH TOPHUS (TOPHI) |

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

**The following ICD-10 diagnosis codes will be effective October 1, 2014:**

| ICD-10-CM Diagnosis Code* | Description |
|---|---|
| M1a.00x0 - M1a.0710 | Chronic gouty arthropathy without mention of tophus (tophi) Code range |
| M1a.00x1 - M1a.0711 | Chronic gouty arthropathy with tophus (tophi) Code range |

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

## X. POLICY HISTORY

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|---|---|
| **MP-2.154** | **CAC 11/30/2010** New Policy. |
| | **CAC 11/22/2011** Consensus Review |
| | **7/24/13** Admin coding review complete--rsb |
| | **CAC 9/24/13** Consensus Review. No change to policy statements. References updated. Added Rationale section. |



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