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Policy Number: 027.006

Title: Coverage Determination Policy for Krystexxa (Pegloticase)

Regions: ☒ **Texas** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:
WellMed Coverage Determination Policies are developed as needed, are regularly reviewed and updated, and are subject to change. They represent a portion of the resources used to support WellMed coverage decision making. WellMed may modify these Policy Guidelines at any time. Medicare source materials used to develop these guidelines include, but are not limited to, CMS National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Medicare Benefit Policy Manual, Medicare Claims Processing Manual, Medicare Program Integrity Manual, Medicare Managed Care Manual, etc. The information presented in the WellMed Coverage Determination Policies is believed to be accurate and current as of the date of publication, and is provided on an "AS IS" basis. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

WELLMED
Doctors helping patients for more than 25 years

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Coverage Policy Number: 027.006

Line of Business: Medicare Part B

Policy Type: Prior Authorization

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Coverage Determination:

Step Therapy Criteria

****Step Therapy is applicable to members who have MAPD plans only****

This policy supplements the Medicare guidelines such as NCDs, LCDs, and other Medicare manuals for the purposes of determining coverage under the Part B medical benefits. This Step Therapy Policy is implemented to enforce a step therapy requirement for new starts only. This policy is not applicable to members continuing therapy within the past 365 days. Coverage is granted if Medicare Coverage requirements PLUS these step criteria are met.

Non-preferred drug(s): Krystexxa (pegloticase)

Preferred drug(s): Allopurinol, Febuxostat

Non-Preferred Product Step Therapy Criteria

Coverage of **Krystexxa (pegloticase)** may be covered when **ONE** of the following is met:

I. BOTH of the following:
   A. Trial of at least 3 months of therapy (at the maximally medically appropriate dose) of Allopurinol resulting in minimal clinical response to therapy
   B. Trial of at least 3 months of therapy (at the maximally medically appropriate dose) of Febuxostat resulting in minimal clinical response to therapy

II. History of contraindication, intolerance or adverse event(s) to Allopurinol **and** Febuxostat

III. Continuation of prior therapy within the past 365 days

Initial/New Requests

Note: Patients at risk of G6PD deficiency (e.g. African, Mediterranean, and Southern Asian ancestry) should be screened for G6PD deficiency prior to initiation of therapy due to potential life-threatening hemolytic reactions and methemogloginemia.

Krystexxa (pegloticase) is **proven and medically necessary** for the treatment of **Chronic Gout** when **ALL** of the following criteria are met:

I. **ONE** of the following:
   A. History of at least 2 gout flares in the previous 12 months
   B. At least 1 gouty tophus
   C. Chronic Gouty Arthropathy

II. History of contraindication, intolerance, or treatment failure after 3 months of therapy at maximally tolerated dose with BOTH of the following:
   A. Allopurinol
   B. Febuxostat

III. NOT being given concomitantly with oral urate-lowering therapy (ULT)*. Oral ULT should be discontinued during pegloticase therapy

IV. Krystexxa is initiated and titrated according to US FDA labeled dosing for chronic gout

Renewal/Continuation of Therapy Requests

For renewal and continuation of therapy requests **ALL** of the following must be met:

A. Patient has previously received treatment with Krystexxa
B. Patient has experienced a positive clinical response to Krystexxa (e.g., serum uric acid levels < 6mg/dL, tophus reduction, etc)
C. Krystexxa is initiated and titrated according to US FDA labeled dosing for chronic gout
D. NOT being given concomitantly with oral urate-lowering therapy (ULT)*. Oral ULT should be discontinued during pegloticase therapy

Note: If uric acid level is > 6 mg/dL on two consecutive labs, discontinuation of pegloticase should be considered as risk of anaphylaxis is increased in patients who lose therapeutic response to pegloticase

Krystexxa is ***not medically necessary*** and will **NOT** be covered for the treatment of:

- Asymptomatic hyperuricemia

FDA Approved Dose and Indication

Product	FDA Approved Dosing
Krystexxa (Pegloticase)	**Chronic gout, refractory to conventional therapy** • 8 mg IV infusion every 2 weeks • *Off-label dosage:* 8 mg IV every 3-4 weeks

General Background

Pegloticase (Krystexxa®) is a PEGylated uric acid specific enzyme that lowers serum uric acid levels by catalyzing the oxidation of uric acid to allantoin, an inert and water soluble purine metabolite that is readily eliminated, primarily by renal excretion. Pegloticase is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy and is not recommended by ACR as first-line urate-lowering therapy (ULT).

Gout is one of the most common causes of inflammatory arthritis, affecting approximately 8 million people in the United States. It is characterized by intense pain and inflammation resulting from the buildup of monosodium urate (MSU) monohydrate crystals in the synovial joints. MSU crystals materialize after prolonged periods of hyperuricemia (serum uric acid levels >6.8 mg/dL). A variety of risk factors are associated with gout including age, hypertension, overweight or obesity, diuretics, and diet. Conditions such as hypertension, metabolic syndrome, type 2 diabetes mellitus, heart failure, organ transplant, obesity, and chronic kidney disease (CKD) promote an increased incidence of hyperuricemia and gout.

It should be noted that hyperuricemia alone is not a sufficient for the diagnosis of gout. According to the American Academy of Rheumatology, a combination of clinical signs and laboratory values are needed for appropriate diagnosis.

Oral Urate Lowering Therapies (ULT)*
Probenecid (Benemid, Probalan)
Allopurinol (Aloprim, Zyloprim)
Febuxostat (Uloric)
Lesinurad (Zurampic)
Colchicine (Colcyrs)

American College of Rheumatology Diagnostic Criteria for Gout
Presence of urate crystals in the joint fluid or;
Presence of tophus or tophi or
Six of more of the following: • Asymmetric swelling within a joint on radiography • Attack of monoarticular arthritis • Culture of joint fluid negative for microorganisms during attack of joint inflammation • Development of maximal inflammation within one day • Hyperuricemia • Joint redness • More than one attack of acute arthritis • Pain or redness in the first metatarsophalangeal joint • Subcortical cyst without erosions on radiography • Suspected tophus • Unilateral attack involving first metatarsophalangeal joint • Unilateral attack involving tarsal joint

American College of Rheumatology (ACR) 2020: Recommendations for choice of initial ULT for patients with gout

- Treatment with allopurinol as the preferred first-line agent, over all other ULTs, is strongly recommended for all patients, including those with moderate-to-severe CKD (stage ≥3).
- The choice of either allopurinol or febuxostat over probenecid is strongly recommended for patients with moderate-tosevere CKD (stage ≥3).
- The choice of pegloticase as a first-line therapy is strongly recommended against.
- Starting treatment with low-dose allopurinol (≤100 mg/day and lower in patients with CKD [stage ≥3]) and febuxostat (≤40 mg/day) with subsequent dose titration over starting at a higher dose is strongly recommended.
- Starting treatment with low-dose probenecid (500 mg once to twice daily) with subsequent dose titration over starting at a higher dose is conditionally recommended.
- Administering concomitant antiinflammatory prophylaxis therapy (e.g., colchicine, nonsteroidal antiinflammatory drugs [NSAIDs], prednisone/ prednisolone) over no antiinflammatory prophylaxis therapy is strongly recommended.

When to consider changing ULT strategy:

- Switching to pegloticase over continuing current ULT is strongly recommended for patients with gout for whom XOI treatment, uricosurics, and other interventions have failed to achieve the SU 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 XOI treatment, uricosurics, and other interventions have failed to achieve the SU target, but who have infrequent gout flares (<2 flares/year) AND no tophi.

Clinical Evidence

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.

American College of Rheumatology (ACR) Guidelines for Management of Gout

In patients with a diagnosis of gout, administer pharmacologic treatment of hyperuricemia (serum urate level greater than 6.8 mg/dL) after addressing baseline recommendations: patient education with initiation of diet and lifestyle recommendations, consideration of secondary causes of hyperuricemia, elimination of non-essential prescription medications that induce hyperuricemia (eg, thiazide and loop diuretics, niacin, calcineurin inhibitors), and clinical evaluation of disease burden (evidence C). Patients with an established diagnosis of gout and signs of arthritis such as tophi or synovitis (evidence A), frequent gout attacks (at least 2 per year; evidence A), chronic kidney disease stage 2 or worse (evidence C), or past urolithiasis (evidence C) indicate the need for pharmacologic urate-lowering therapy.

- Initiate first line urate-lowering therapy with a xanthine oxidase inhibitor (either allopurinol or febuxostat; evidence A) and alternatively with probenecid, if contraindicated or intolerant to at least one xanthine oxidase inhibitors (evidence B), to a serum urate target of less than 6 mg/dL (evidence A), or below 5 mg/dL if needed to improve gout signs and symptoms (evidence B).

• Concomitant acute anti-inflammatory gout prophylaxis is recommended (evidence A). Urate lowering therapy can be instituted during an acute gout attack with concurrent anti-inflammatory therapy (evidence C).
• Treat to target serum urate level, increasing the urate-lowering therapy and re-evaluate serum urate levels. Regular monitoring of serum urate is recommended every 2 to 5 weeks during urate-therapy titration and every 6 months once serum urate target is achieved (evidence C).
• If serum urate target not achieved and with continuing disease activity, add an uricosuric agents to a xanthine oxidase inhibitor and titrate to maximum appropriate dose (evidence B) or vice versa (evidence C).
• If serum urate target still not achieved and with continuing disease activity, consider pegloticase therapy (evidence A).

Evidence Grades for Gout Recommendations:
Level A - supported by multiple randomized clinical trials (RCTs) or meta-analyses
Level B - derived from single RCT or nonrandomized trials
Level C - consensus opinion of experts, case studies, or standard of care

HCPCS Code

HCPCS Code	J2507: Injection, Pegloticase (Krystexxa)
Available Dosage Form (s)	8 mg/mL of uricase protein in single dose vials
Route of Administration	Administer by IV infusion

Acronyms

G6PD = glucose 6-phosphate dehydrogenase

NCD = National Coverage Determination

LCD = Local Coverage Determination

FDA = Food and Drug Administration

PBO = Placebo

AE = Adverse events

SAE = Serious adverse events

ACR = American College of Rheumatology

ULT = Urate-lowering therapy

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