BlueCross BlueShield of Alabama

Name of Policy:
Pegloticase (Krystexxa™)

Policy #: 456
Category: Pharmacy

Latest Review Date: November 2010
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:
Pegloticase (Krystexxa™) is a Pegylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients that are refractory to conventional therapy.

Chronic gout that is refractory to conventional therapy occurs in patients whose serum uric acid levels have failed to normalize 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. Xanthine oxidase inhibitors that are often prescribed for the treatment of gout include Zyloprim (allopurinol) and Uloric (febuxostat). Krystexxa is not recommended for the treatment of asymptomatic hyperuricemia.

Use of Krystexxa is contraindicated in patients with G6PD deficiency due to the risk of hemolysis and methemoglobinemia. It is recommended that patients at higher risk for G6PD deficiency (e.g. patients of African or Mediterranean ancestry) be screened for G6PD deficiency prior to starting Krystexxa.

Serum uric acid levels prior to infusions should be monitored. Consideration should be given to discontinuing treatment if levels increase to above 6mg/dL, particularly when 2 consecutive values above 6 mgldL are observed. The risk of anaphylaxis and infusion reactions is higher in patients whose uric acid level increases to above 6 mg/dL.

Krystexxa is a clear, colorless, sterile 8 mg/mL solution of pegloticase in a 2 mL single-use vial, expressed as amounts of uricase protein. Krystexxa must be diluted prior to use. The recommended dose and regimen of Krystexxa is 8 mg given as an IV infusion every two weeks. Krystexxa should not be administered by IV push or bolus. The drug should only be administered in a health care setting and by health care providers prepared to manage anaphylaxis.

The Krystexxa admixture should only be administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump. Patients should receive pre-infusion medications (e.g. antihistamines, corticosteroids), to minimize the risk of anaphylaxis and infusion reactions.

If an infusion reaction occurs during the administration of Krystexxa, the infusion may be slowed, or stopped and restarted at a slower rate, at the discretion of the physician. Since infusion reactions can occur after completion of infusion, observation of patients for approximately an hour post-infusion should be considered.

Policy:

Effective for dates of service on or after September 10, 2011:

Pegloticase (Krystexxa™) for the treatment of chronic gout in adult patients that are refractory to conventional therapy **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and

his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Gout is an acute inflammatory and chronically destructive disorder resulting from the formation and deposition in tissues of urate crystals from extracellular fluid saturated for urate, the end product of human purine metabolism. These patients have severe and progressive crystal deposition disease due to failure of or intolerance to currently available urate-lowering therapy (ULT). The severity of TFG is manifested by frequent acute attacks of disabling arthritis, chronic deforming joint disease, destructive masses of urate crystal (tophi), progressive physical disability, and poor health-related quality of life. TFG affects approximately 50,000 patients or about 1% of the overall population of patients with gout in the US. It is anticipated that only Rheumatologists and a subset of Nephrologists who have experience infusing biologics will administer pegloticase in patients with treatment failure gout.

Gout is the most prevalent form of arthritis in men and is increasing in incidence and prevalence among older persons of both genders. Treatment failure gout (TFG) is an uncommon but severe outcome of progressive gout resulting from demonstrated intolerance of or refractoriness to available therapy to prevent urate crystal deposition by reducing and maintaining serum urate levels in a subsaturating range. TFG is characterized clinically by: painful arthritis and chronic arthropathy; destructive tophi; impaired quality of life; and chronic disability. Hyperuricemia and gout are often accompanied by significant medical co-morbidities including cardiovascular disease, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, and obesity. These associated disorders are especially frequent among patients with TFG. The combination of severe gout and a high burden of cardiovascular and metabolic co-morbidities, often requiring polypharmacy, make TFG exceptionally difficult to manage. The severe and advanced nature of TFG manifestations, require modification in the pursuit of the historical goals of medical management of gout: prompt termination of acute flares of gouty arthritis; prophylaxis to reduce recurrent flares; and urate-lowering to prevent and reverse urate crystal deposition, eventually abolishing gouty signs and symptoms. The high prevalence of severe tophaceous gout among TFG patients makes rapidity in the resolution of tophi an important aim, as do measures to achieve prompt relief of chronic pain and improve physical function and quality of life by accelerated reduction of the total body urate burden.

The pegloticase development program has demonstrated the clinical efficacy of this agent in achieving these aims in the TFG population, representing the first evidence for any urate-lowering regimen in achieving clinical endpoints in gout patients in the course of randomized controlled trials. In this sense, pegloticase is demonstrably a disease modifying agent for what is currently a patient group with an unmet medical need.

The safety and efficacy of pegloticase were evaluated in six clinical studies (not yet published), including two replicate 6-month randomized double-blind, placebo-controlled phase three studies (C0405 and C0406) in which 8 mg of pegloticase was administered

intravenously every 2 (pegloticase q 2 weeks) or every 4 weeks (pegloticase q 4 weeks). A total of 225 subjects were randomized in phase 3; 212 were dosed, and 157 subjects completed protocol treatment. In the ITT population, all subjects who discontinued were considered "treatment failures" in the primary analysis.

Both randomized controlled trials (RCTs) (Studies C0405 and C0406) were replicates and designed in collaboration with FDA. The Phase 3 protocol C0405 was approved by FDA under a Special Protocol Assessment (SPA).

Subjects who completed either phase 3 pivotal study (C0405 or C0406) were eligible to be enrolled in a long-term Open Label Extension (OLE) Study (C0407). Of 74% of subjects (157 of 212) who completed phase 3 RCTs, 151 of 157 (96%) enrolled in the open label extension (representing 71% [151 of 212] of the ITT population), choosing either pegloticase 8 mg every 2 weeks (82 of 151), pegloticase 8 mg every 4 weeks (67 of 151), or observation (2 of 151). Overall safety exposure of pegloticase-treated subjects was:

- 121 subjects: study duration of approximately 12 months or more,
- 115 subjects: study duration of approximately 15 months or more, and
- 95 subjects: study duration of approximately 18 months or more.

Pegloticase was demonstrated effective in both RCTs using the primary outcome measure of normalization of PUA ≥ 80% of the time during Months 3 and 6. In both phase 3 RCTs, treatment with pegloticase 8 mg q 2 weeks resulted in statistically significant decreases in PUA compared with placebo, also evident with pegloticase 8 mg dosed every 4 weeks. In the pooled studies, all subjects had rapid normalization of uric acid; in 42 % of subjects receiving pegloticase 8 mg every 2 weeks, normalization of uric acid levels was sustained throughout the 6-month treatment period, compared with 35% with pegloticase q 4 weeks, although results differed between studies. In most subjects with transient responses to pegloticase, uric acid levels rose to > 6 mg/dL within 3 months after initiation of treatment.

The full prescribing information for Krystexxa contains a boxed warning regarding anaphylaxis and infusion reactions. In clinical trials, 1 of 4 patients experienced severe allergic reactions during Krystexxa infusions. A corticosteroid and an antihistamine should be administered to all patients before an infusion is initiated to minimize the risk of such a reaction.

Other adverse reactions that occurred during the clinical trials include gout flare, nausea, injection-site bruising, irritation of the nasal passages, constipation, chest pain, and vomiting.

Physicians are also being warned to use caution about administering Krystexxa to patients with congestive heart failure because the drug was not studied in this patient population.

Savient plans to conduct a post-approval observational safety study of 500 patients treated for 1 year to further evaluate the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events, and to identify serious adverse events associated with Krystexxa therapy.

Key Words:
Krystexxa, Pegloticase

Approved by Governing Bodies:
FDA approved September 10, 2010

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member's benefit plan.
Pre-determination requirements: Pre-determinations will be performed as a courtesy review at the request of the physician and/or subscriber.

Coding:
CPT Codes:
Effective for dates of service on or after January 1, 2012:

J2507 Injection, pegloticase, 1 mg

Effective for dates of service through December 31, 2011:

J3490 Unclassified drug

References:

1. www.fda.gov
2. www.kreytexxa.com

Policy History:
Medical Policy Group, October 2010
Medical Policy Administration Committee, December 2010
Available for comment December 2, 2010 through January 16, 2011
Medical Policy Group, December 2011 **(1)** Update to Coding related to new code J2507