Kalbitor® (ecallantide) injection for subcutaneous use
Prior Approval Criteria
March 2017

OVERVIEW:
Kalbitor is a recombinant protein that inhibits plasma kallikrein. The binding of Kalbitor to plasma kallikrein blocks the conversion of high molecular weight kininogen to bradykinin. Bradykinin, a vasodilator, is likely responsible for the characteristic symptoms associated with acute attacks of hereditary angioedema (HAE). Kalbitor’s ability to prevent over production of bradykinin helps to reduce the symptoms of acute HAE attacks. Kalbitor is indicated for the treatment of acute attacks of HAE in patients aged ≥ 12 years. The safety and efficacy of Kalbitor for prophylactic therapy has not been established.

Hereditary angioedema is a rare, debilitating, potentially life-threatening genetic disorder caused by a deficiency in C1-INH, a plasma protein involved in the regulation of the complement and intrinsic coagulation pathways. Hereditary angioedema is caused by mutations in the C1-INH gene located on chromosome 11q and inherited as an autosomal dominant trait. Two main types of hereditary angioedema exist: mutations causing Type I hereditary angioedema are associated with decreased production of C1-INH leading to decreased functional levels; Type II hereditary angioedema mutations are associated with a dysfunctional C1 inhibitor but the inhibitor level is normal.

HAE is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema associated with pain syndrome, nausea, vomiting, diarrhea, and/or life-threatening airway swelling. Airway obstruction due to swelling is life-threatening if left untreated. There is a wide variation in the frequency and severity of attacks. Clinical experience suggests that minor trauma and/or stress, among other triggers, may precipitate attacks. Untreated attacks typically last over 48 to 96 hours. Short-term prophylaxis with a C1-INH - is recommended if more than minor manipulation (e.g., mild dental work) is needed, and prior to intubation or major procedures. The dose for short-term prophylaxis with C1-INH varies from 10 U/kg to 20 U/kg or 1,000 units, 1 to 6 hours before procedure. Long-term prophylaxis should be considered in all severely symptomatic patients, taking into consideration the severity of disease, frequency of attacks, patient’s quality of life, availability of resources, and failure to achieve adequate control by on-demand therapy.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Kalbitor is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Hereditary Angioedema (HAE) Treatment of Acute Attacks, Initial Therapy. Approve Kalbitor if the patient meets the following criteria (a, b, c, d, e, f and g):
The patient has HAE as confirmed by following criteria (i and ii):
  i)  Patient has low levels of functional C1-INH protein (< 50% of normal) as defined by the laboratory reference values; AND
  ii) Patient has lower than normal serum C4 levels, as defined by the laboratory reference values; AND

The medication is prescribed by or in consultation with an allergist, immunologist, hematologist or a physician that specializes in the treatment of HAE or related disorders; AND

The patient is 12 years of age or older; AND

All other causes of acquired angioedema (e.g., medications, auto-immune diseases) have been excluded; AND

Patient has at least ONE of the following criteria (i, ii, or iii)
  i) Patient must have history of self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, which is recurrent and lasts >12 hours
  ii) Self-limiting, recurrent abdominal pain without a clear organic cause lasting >6 hours
  iii) A history of laryngeal edema; AND

The patient had an inadequate response, experienced intolerance to, or is unable to receive treatment with human C1 esterase inhibitor (for example, Cinryze or Berinert); AND

Kalbitor is not used in combination with other approved treatments for acute HAE attacks (e.g. Berinert, Firazyr, or Ruconest).

2. Patient has been started on Kalbitor. Approve for, an indication or condition addressed as an approval in the Recommended Authorization Criteria (FDA-Approved Indications), continuation of therapy if ALL of the following are met (a, b, c, d, e, f and g):

The patient has HAE as confirmed by following criteria (i and ii):
  i)  Patient has low levels of functional C1-INH protein (< 50% of normal) as defined by the laboratory reference values; AND
  ii) Patient has lower than normal serum C4 levels, as defined by the laboratory reference values; AND

The medication is prescribed by or in consultation with an allergist, immunologist, hematologist or a physician that specializes in the treatment of HAE or related disorders; AND

The patient is 12 years of age or older; AND

All other causes of acquired angioedema (e.g., medications, auto-immune diseases) have been excluded; AND

Patient has at least ONE of the following criteria (i, ii, or iii)
  i) Patient must have history of self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, which is recurrent and lasts >12 hours
  ii) Self-limiting, recurrent abdominal pain without a clear organic cause lasting >6 hours
  iii) A history of laryngeal edema; AND

The patient had an inadequate response, experienced intolerance to, or is unable to receive treatment with human C1 esterase inhibitor (for example, Cinryze or Berinert); AND
g) Kalbitor is not used in combination with other approved treatments for acute HAE attacks (e.g. Berinert, Firazyr, or Ruconest).

**Approval Duration:** 365 days (1 year)

**References**