Clinical Policy: Ecallantide (Kalbitor)

Reference Number: ERX.SPA.29
Effective Date: 07.01.16
Last Review Date: 11.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Ecallantide (Kalbitor®) is a plasma kallikrein inhibitor.

FDA Approved Indication(s)
Kalbitor is indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Kalbitor is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Hereditary Angioedema (must meet all)**:**

1. Diagnosis of HAE confirmed by one of the following (a or b):
   a. Low C4 level and low C1-INH antigenic or functional level (*see Appendix D*);
   b. Normal C4 level and normal C1-INH levels, and both of the following (i and ii):
      i. History of recurrent angioedema;
      ii. Family history of angioedema;
2. Prescribed by or in consultation with a hematologist, allergist, or immunologist;
3. Age ≥ 12 years;
4. Prescribed for treatment of acute HAE attacks;
5. Member is not using Kalbitor in combination with another FDA-approved product for treatment of acute HAE attacks (e.g., Berinert®, Ruconest®, Firazyr®);
6. Kalbitor will be administered by a healthcare professional with appropriate medical support to manage anaphylaxis at one of the following (a or b):
   a. Infused in physician's office or controlled medical setting;
   b. Home infusion by a Kalbitor-trained registered nurse (RN);
7. Dose does not exceed 30 mg (1 carton [3 vials]) per dose, with up to 2 doses administered in a 24-hour period.

Approval duration: 6 months (up to 4 doses per month)

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Hereditary Angioedema (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;

3. Member is not using Kalbitor in combination with another FDA-approved product for treatment of acute HAE attacks (e.g., Berinert, Ruconest, Firazyr);
4. Documentation or claims history supports that Kalbitor has been administered by a healthcare professional in a physician's office or controlled medical setting or home infusion by a Kalbitor-trained RN;
5. If request is for a dose increase, new dose does not exceed 30 mg (1 carton [3 vials]) per dose, with up to 2 doses administered in a 24-hour period.

Approval duration: 12 months (up to 4 doses per month)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CI-INH: C1 esterase inhibitor
C4: complement component 4
FDA: Food and Drug Administration
HAE: hereditary angioedema
RN: registered nurse

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): known clinical hypersensitivity to Kalbitor
- Boxed warning(s): Due to the risk for anaphylaxis, Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer Kalbitor to patients with known clinical hypersensitivity to Kalbitor.

Appendix D: General Information

- Diagnosis of HAE:
  - There are two classifications of HAE: HAE with C1-INH deficiency (further broken down into Type 1 and Type II) and HAE of unknown origin (also known as Type III).
  - In both Type 1 (~85% of cases) and Type II (~15% of cases), C4 levels are low. C1-INH antigenic levels are low in Type I while C1-INH functional levels are low in Type II. Diagnosis of Type I and II can be confirmed with laboratory tests. Reference ranges for C4 and C1-INH levels can vary across laboratories (see below for examples); low values confirming diagnosis are those which are below the lower end of normal.

Laboratory Test & Reference Range	Mayo Clinic	Quest Diagnostics	LabCorp
C4	14-40 mg/dL	16-47 mg/dL	13-44 mg/dL
C1-INH, antigenic	19-37 mg/dL	21-39 mg/dL	21-39 mg/dL
C1-INH, functional	Normal: > 67% Equivocal: 41-67% Abnormal: < 41%	Normal: ≥ 68% Equivocal: 41-67% Abnormal: ≤ 40%	Normal: > 67% Equivocal: 41-67% Abnormal: < 41%

- Type III, on the other hand, presents with normal C4 and C1-INH levels. Some patients have an associated mutation in the FXII gene, while others have no identified genetic indicators. Type III is very rare (number of cases unknown), and there are no laboratory tests to confirm the diagnosis. Instead, the diagnosis is clinical and supported by recurrent episodes of angioedema with a strong family history of angioedema.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Treatment of acute HAE attacks	30 mg (3 mL) administered SC in three 10 mg (1 mL) injections; if attack persists, an additional dose of 30 mg may be administered within a 24 hour period	60 mg/24 hours

*Kalbitor should only be administered by a healthcare professional

VI. Product Availability

Vial with solution for injection: 10 mg/mL

VII. References

1. Kalbitor Prescribing Information. Burlington, MA: Dyax Corporation; December 2020. Available at: www.kalbitor.com. Accessed August 15, 2021.
2. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy*. 2012; 67(2): 147-157.
3. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014; 69(5): 602-616.
4. Craig T, Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. *WAO Journal*. 2012; 5: 182-199.
5. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2013; 1(5): 458-467.
6. Zuraw BL, Bernstein JA, Lang DM, et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013; 131(6): 1491-1493.
7. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy*. 2018; 73(8):1575-1596.
8. Mayo Clinic Laboratories [internet database]. Rochester, Minnesota: Mayo Foundation for Medical Education and Research. Updated periodically. Accessed November 4, 2019.
9. Quest Diagnostics® [internet database]. Updated periodically. Accessed November 4, 2019.
10. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed November 4, 2019.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: Added specialist requirement Removed "Other types of angioedsema have been ruled out" from part of diagnosis due to its subjective nature, while specialist has been added Added age limit	11.16.17	02.18
1Q 2019 annual review: corrected minimum age requirement to 12 years per package labeling; added quantity limit of 4 doses per month for treatment of acute attacks; added requirement that member is not using requested product in combination with other approved treatments for the treatment of acute HAE attacks; references reviewed and updated.	10.30.18	02.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2020 annual review: HAE lab reference range updated; initial auth duration revised from 12 to 6 months; references reviewed and updated.	11.04.19	02.20
1Q 2021 annual review: no significant changes; references reviewed and updated.	10.08.20	02.21
Per health plan request, added criteria that Kalbitor be administered by a qualified professional equipped to manage possible anaphylaxis as advised in the boxed warning.	08.15.21	11.21

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.