POLICY: Hereditary Angioedema – Kalbitor® (ecallantide injection for subcutaneous use – Dyax)

APPROVAL DATE: 08/07/2019

OVERVIEW

Kalbitor, a plasma kallikrein inhibitor, is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients ≥ 12 years of age.[1] Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with Kalbitor. Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE.

Disease Overview

HAE due to C1 esterase inhibitor (C1-INH) deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.[2,3] Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE, currently called HAE with normal C1-INH (previously referred to as HAE type III), have normal C4 and C1-INH antigenic protein levels.[2] The exact cause of HAE with normal C1-INH has not been determined. There are no randomized or controlled clinical trial data available with any therapy for use in HAE with normal C1-INH.[4,5] The consensus panel notes that until data from randomized controlled studies become available, no firm recommendations regarding the treatment of HAE with normal C1-INH can be made.[4]

Guidelines

Per the World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2017), all attacks should be considered for acute treatment; treatment is mandatory for any attack potentially affecting the upper airway.[3] Attacks should be treated as early as possible. Self-administration at home facilitates earlier response. The guidelines recommend C1-INH products (Cinryze, Berinert, or Ruconest), Kalbitor, or icatibant (Firazyr, generics) as first-line treatment options. Androgens and antifibrinolytics are not effective as acute treatment. Patients should carry acute treatment with them at all times and should have enough supply on hand for treatment of two attacks. Other guidelines from the US Hereditary Angioedema Association Medical Advisory Board (2013) and a practice parameter update from a Joint Task Force (2013) have similar recommendations.[6,7]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Kalbitor. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as [documentation required]. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks**. Approve Kalbitor for the duration noted if the patient meets one of the following criteria (A or B):
   - **A)** Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):
     - **i.** The patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       - **a)** The patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values [documentation required]; AND
       - **b)** The patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values [documentation required]; AND
     - **ii.** The medication is prescribed by, or in consultation with, an allergist/immunologist or a physician that specializes in the treatment of HAE or related disorders.
   - **B)** Patients who have treated previous acute HAE attacks with Kalbitor. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):
     - **i.** The patient has treated previous acute HAE type I or type II attacks with Kalbitor [documentation required to confirm HAE type I or type II diagnosis]; AND
     - **ii.** According to the prescriber, the patient has had a favorable clinical response (e.g., decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, decrease in HAE acute attack frequency or severity) with Kalbitor treatment; AND
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician that specializes in the treatment of HAE or related disorders.

Dosing.[1] Approve up to a maximum dose of 30 mg by subcutaneous injection, no more frequently than twice daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kalbitor has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Hereditary Angioedema (HAE) Prophylaxis**. Data are not available and Kalbitor is not indicated for prophylaxis of HAE attacks.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Kalbitor® [prescribing information]. Burlington, MA: Dyax Corporation; March 2015.
2. Bowen T, Cicardi M, Farkas H, et al. 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;6:24.
3. Mauer 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. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1111/all.13384. Accessed on August 1, 2019.
4. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc.* 2012;33:S145-S156.
5. Magerl M, Germenis AE, Maas C, et al. Hereditary angioedema with normal C1 inhibitor. Update on evaluation and treatment. *Immunol Allergy Clin N Am.* 2017;37:571-584.
6. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol: In Practice*. 2013;1:458-467. Available at: https://haei.org/wp-content/uploads/2015/04/Zuraw-B-L-US-HAEA-MAB-2013-Recommendations.pdf. Accessed on August 1, 2019.
7. Zuraw BL, Bernstein JA, Lang DM. 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.e25.

HISTORY

Type of Revision	Summary of Changes	Approval Date
New policy	--	10/03/2018
Annual revision	**All Indications:** "Prescribing information" changed to "prescriber" throughout policy. Dosing clarified to reflect maximum approvable dosing.	08/07/2019