Department:	Utilization Management	**Original Approval:**	10/11/2013
Policy #:	PM106	**Last Approval:**	03/08/2019
Title:	Ecallantide (Kalbitor®)		
Approved By:	UM Pharmacy Subcommittee		

BACKGROUND

Kalbitor, a plasma kallikrein inhibitor, is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients aged ≥ 12 years.[1] Kallikrein is a plasma protease which cleaves high-molecular-weight kininogen to produce bradykinin. Bradykinin is a vasodilator which is likely responsible for the characteristic HAE symptoms of localized swelling, inflammation and pain. By preventing the production of bradykinin, Kalbitor treats the clinical symptoms of an acute HAE attack. 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.

HAE is a rare, autosomal dominant disorder characterized by recurrent episodes of non-pruritic, non-pitting, SC or submucosal edema associated with pain, nausea, vomiting, diarrhea, and laryngeal swelling.[2] Mortality associated with untreated laryngeal attacks is significant. There is a wide variation in the frequency and severity of attacks for all types of HAE. Attack triggers may include stress, infections, minor trauma, or other causes; often a specific trigger cannot be identified. Untreated attacks may last over 48 to 96 hours.

HAE due to C1 esterase inhibitor (C1-INH) deficiency has two subtypes: HAE type I and HAE type II. The World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guidelines (2017) and an international consensus algorithm note that 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]

Per the WAO/EAACI guidelines, 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 Firazyr as first-line treatment options. Solvent detergent-treated plasma (SDP) can be used as a second-line option, and fresh frozen plasma (FFP) can be used if SDP is not available. 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]

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

FDA-Approved Indications

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks, Initial Therapy**

Criteria. ***Patient must meet the following criteria (A AND B):***

- **A)** The patient has HAE type I or type II as confirmed by the following diagnostic criteria (i and ii):
  - **i.** The patient has low levels of functional C1-INH protein (<50% of normal) at baseline, as defined by the laboratory reference values; AND
  - **ii.** The patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values; AND
- **B)** 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. *Dosing must meet the following*: 30 mg by SC injection. Do not administer more than two doses in 24 hours.

Approval duration. *Initial/Extended Approval*. 1 year.

Duration of therapy. Indefinite.

Labs/Diagnostics. Functional C1-INH protein and serum C4 levels must be performed at baseline, as outlined in above criteria.

2. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Patients Who have Treated Previous Acute HAE Attacks with Kalbitor**.

Criteria. ***Patient must meet the following criteria (A, B AND C)***:

- **A)** 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
- **B)** According to the prescribing physician, 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
- **C)** 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. *Dosing must meet the following*: 30 mg by SC injection. Do not administer more than two doses in 24 hours

Approval duration. *Initial/Extended Approval.* 1 year.

Duration of therapy. Indefinite.

Labs/Diagnostics. Must have documentation confirming HAE type I or type II diagnosis, as outlined in above criteria.

Waste Management for All. Kalbitor is supplied as three 10 mg/mL single-use vials packaged in a carton.[1] Each vial contains 10 mg of Kalbitor; three vials are required for one 30-mg dose. Kalbitor should be kept refrigerated. Vials removed from refrigeration should be stored below 86°F (30°C) and should be used within 14 days or returned to refrigeration until use.

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.

SPECIAL CONSIDERATIONS

BOXED WARNING: Anaphylaxis has been reported after administration of KALBITOR. Because of the risk of 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.[1]

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

CFR		
WAC		
RCW		
Contract Citation	☒ WAH	http://chpw.org/our-plans/apple-health/
	☐ IMC	
	☒ MA	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
Other Requirements		
NCQA Elements		
References	1. Kalbitor® [prescribing information]. Cambridge, 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 September 12, 2018 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 September 13, 2018. 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.

Revision History

Revision Date	Revision Description	Revision Made By
09/17/2013	Original Draft	Steven Zona, Pharm.D.
10/11/2013	Approval	P&T Committee
10/29/2014	Review for Revisions	Steven Zona, Pharm.D.
11/07/2014	Approval	P&T Committee
10/23/2015	Review for Revisions	Frances McGaugh, Pharm.D.
03/07/2017	Revised FDA indication age and formatting	Sophia Yun, PharmD
03/07/2017	Approval	MMLT
02/15/2018	Updated revision, age limit	Catherine Vu, PharmD
03/01/2018	Approval	MMLT
02/25/2019	Updated background, indications, waste management and conditions not recommended for approval	Ivan Figueira, PharmD
03/08/2019	Approval	UM Pharmacy Subcommittee