Policy Title:	Kalbitor (ecallantide) (Subcutaneous)		
		Department:	PHA
Effective Date:	01/01/2020		
Review Date:	10/02/19, 12/18/19, 1/22/20, 5/06/21, 2/10/2022, 3/16/2023, 12/07/2023, 01/10/2024, 07/09/2025		

Purpose: To support safe, effective, and appropriate use of Kalbitor (ecallantide).

Scope: Medicaid, Commercial, Medicare

Policy Statement:

Kalbitor (ecallantide) is covered under the Medical Benefit when used within the following guidelines. Use outside of these guidelines may result in non-payment unless approved under an exception process.

Procedure:

Coverage of Kalbitor (ecallantide) will be reviewed prospectively via the prior authorization process based on criteria below.

Summary of Evidence:
Kalbitor (ecallantide) is a plasma kallikrein inhibitor indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older. HAE is characterized by recurrent episodes of angioedema caused by excess bradykinin due to C1 esterase inhibitor deficiency. Kalbitor acts by selectively inhibiting plasma kallikrein, thereby reducing bradykinin generation and associated edema. Kalbitor's approval is supported by two randomized, double-blind, placebo-controlled clinical trials (EDEMA3 and EDEMA4) in 168 patients with acute HAE attacks. In both trials, patients received a 30 mg subcutaneous dose of Kalbitor. In EDEMA4 (N=96), Kalbitor significantly improved symptoms at 4 hours compared to placebo, with a greater decrease in the Mean Symptom Complex Severity (MSCS) score (−0.8 vs. −0.4; p=0.01) and higher Treatment Outcome Score (TOS) (53 vs. 8; p=0.003). Similar results were observed in EDEMA3 (N=72), with MSCS −1.1 vs. −0.6 (p=0.041) and TOS 63 vs. 36 (p=0.045). The most common adverse events (≥3%) included headache (8%), nausea (5%), diarrhea (4%), pyrexia (4%), injection site reactions (3%), and nasopharyngitis (3%). Anaphylaxis occurred in 4% of treated patients and is a boxed warning.

Initial Criteria:

- Member is 12 years of age or older; AND
- Kalbitor is being used for treatment of acute hereditary angioedema (HAE) attacks
- Medication is prescribed by, or in consultation with allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders; AND
- Member has history of moderate to severe cutaneous attacks (without concomitant hives) OR abdominal attacks OR mild to severe airway swelling attacks of HAE (i.e.,

debilitating cutaneous/gastrointestinal symptoms OR laryngeal/pharyngeal/tongue swelling); AND

- Patient has documented diagnosis of HAE type I or type II and meets one of the following:
    - Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets of the following criteria:
        - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, OR
        - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test); OR
    - Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
        - Member has an F12, angiopoietin-1, plasminogen, or kininogen-1 (KNG1) gene mutation as confirmed by genetic testing, OR
        - Member has a documented family history of angioedema, and the angioedema was refractory to a trial of high-dose antihistamine (e.g., cetirizine) for at least one month.
- Dose does not exceed FDA approved labeling; AND
- The requested medication will not be used in combination with other products indicated for acute treatment of HAE attacks (e.g., Ekterly, Ruconest, Haegarda, or Icatibant)
- Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements.

Continuation of Therapy Criteria:

- Patient continues to meet initial criteria; AND
- Patient has experienced reduction in severity and duration of attacks since starting treatment; AND
- Documentation supporting a positive clinical response to therapy with Kalbitor (e.g., chart notes, medical records)

Coverage durations:

- Initial coverage: 6 months
- Continuation of therapy coverage: 6 months

Per §§ 42 CFR 422.101, this clinical medical policy only applies to Medicare in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD).

Policy Rationale:
Kalbitor was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its

members use Kalbitor according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For Medicare members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.

Dosage/Administration:

Indication	Dose	Maximum dose (1 billable unit = 1 mg)
HAE	30 mg injected subcutaneously by a health care professional in three 10 mg injections. An additional dose of 30 mg may be administered if the attack persists. Not to exceed a total of two 30 mg doses (60 mg) in 24 hours	240 billable units per 28 days

Investigational use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

Applicable Codes:
Below is a list of billing codes applicable for covered treatment options. The below tables are provided for reference purposes and may not be all-inclusive. Requests received with codes from tables below do not guarantee coverage. Requests must meet all criteria provided in the procedure section.

The following HCPCS/CPT codes are:

HCPCS/CPT Code	Description
J1290	Injection, ecallantide, 1 mg

References:

1. Kalbitor [package insert]. Burlington, MA: Dyax Corp.; December 2023. Accessed June 2025.
2. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6(1):24.
3. Cicardi M, Bork K, Caballero T, et al. Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy. 2012;67:147-157.
4. 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(5): 458-467.
5. 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(6):S145-S156.
6. 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;00:1-22.
7. Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. Ann Allergy Asthma Immunol. 2012; 109:395-202.
8. 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: 602-616.
9. Bowen T. Hereditary angioedema: beyond international consensus – circa December 2010 – The Canadian Society of Allergy and Clinical Immunology Dr. David McCourtie Lecture. Allergy Asthma Clin Immunol. 2011;7(1):1.
10. Bernstein J. Update on angioedema: Evaluation, diagnosis, and treatment. Allergy and Asthma Proceedings. 2011;32(6):408-412.
11. Longhurst H, Cicardi M. Hereditary angio-edema. Lancet. 2012;379:474-481. 12. Clinical Consult: Caremark Clinical Programs Review: Focus on Hereditary Angioedema Clinical Programs. June 2015.
12. Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy. 2017;72(2):300-313.