Effective Date **1/1/2025**
Coverage Policy Number **IP0336**

Hereditary Angioedema - Ecallantide

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for ecallantide (**Kalbitor®**) subcutaneous injection.

Medical Necessity Criteria

Ecallantide (Kalbitor) is considered medically necessary when the following are met:

Hereditary Angioedema (HAE) - Treatment of Acute Attacks. Individual meets **ALL** of the following criteria:

A. Diagnosis of HAE confirmed by documentation of **ONE** of the following:
   i. Confirmed pathogenic variant in the *SERPING1, F12, ANGPT1*, *PLG* or *KNG1* gene
   ii. One C4 level below the lower limit of normal as defined by the laboratory performing the test and **ONE** of the following:

a. Has low levels of functional C1-INH protein (less than 50% of normal) at baseline, as documented by laboratory reference values
b. Has low C1-INH antigenic levels (less than 50% of normal) at baseline, as documented by laboratory reference values

B. Kalbitor will not be concomitantly administered with other FDA-approved treatments for acute HAE attacks (for example, Berinert®, Cinryze®, icatibant, or Ruconest®)
C. Medication is prescribed by, or in consultation with, an allergist/immunologist
D. Preferred product criteria is met for the product as listed in the below table(s)

Dosing. Up to a maximum dose of 30 mg per injection, administered subcutaneously no more frequently than twice daily.

Employer Group:

Product	Criteria
Kalbitor (ecallantide subcutaneous injection)	**ONE** of the following**:** 1. Individual less than age 18 years 2. Individual is currently receiving Kalbitor 3. Documentation of failure, contraindication, or intolerance to generic icatibant (for example, Sajazir)

Individual and Family Plan:

Product	Criteria
Kalbitor (ecallantide subcutaneous injection)	**ONE** of the following**:** 1. Individual less than age 18 years 2. Individual is currently receiving Kalbitor 3. Documentation of failure, contraindication, or intolerance to generic icatibant (for example, Sajazir)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of ecallantide (Kalbitor) is considered medically necessary for treatment of acute hereditary angioedema (HAE) attacks when **ALL** of the following are met:

1. The above medical necessity criteria have been met prior to the start of Kalbitor therapy
2. There is documentation of beneficial response since initiating Kalbitor therapy (for example, decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity)
3. Medication continues to be prescribed by, or in consultation with, an allergist/immunologist

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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

2. **C1-Inhibitor normal (levels and function) episodes of angioedema not related to a documented pathogenic variant in the *F12*, *ANGPT1*, *PLG*, or *KNG1* gene.**

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1290	Injection, ecallantide, 1 mg

Background

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.[1] Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE.

Guidelines
According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest® (C1-INH [recombinant] intravenous [IV] infusion), Kalbitor, and icatibant.

In guidelines from the World Allergy Organization/European Academy of Allergy and Clinical Immunology (2021), it is recommended that all attacks be treated with either IV C1-INH, Kalbitor, or icatibant (evidence level A for all).[3] Regarding IV C1-INH, it is noted that Berinert® (C1 esterase inhibitor [human] IV infusion) and Cinryze® (C1 esterase inhibitor [human] IV infusion) are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

References

1. Kalbitor® [prescribing information]. Lexington, MA: Takeda; December 2023.
2. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	1/1/2025

The policy effective date is in force until updated or retired.