Subject: Kalbitor (ecallantide)	**Original Effective Date:** 3/11/10
Policy Number: MCP-232	**Revision Date(s):** 1/13/15; 10/17

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of **Kalbitor (ecallantide)** for the **treatment of acute attacks of hereditary angioedema in patients 12 years and older** when appropriate criteria are met.

This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

- **Hereditary Angioedema (HAE)**
  - A rare genetic disorder of recurrent attacks of localized subcutaneous or mucosal swelling that affects 1 in 10,000 to 1 in 50,000 individuals in the United States
  - Attacks/episodes range from benign to fatal with swelling episode often lasting between 2 and 5 days. Swelling can occur at any location and can be unilateral or bilateral; however, common sites include the face (periorbital area, lips, tongue), extremities, and gastrointestinal tract or bowel wall. Laryngeal edema, the most serious presentation, is associated with mortality due to potentially causing asphyxiation.[Bork K, Longhurst]
  - Symptoms of the disease can occur annually or several times weekly and are typically self-limiting, generally resolving within 72 hours but potentially lasting up to 5 days until complement C4 is depleted.[Zuraw 2012]
  - The two most common forms of HAE (Types I and II) may be managed with prophylaxis or acute treatment depending on attack frequency, severity, and drug tolerability.
    **Refer to the 'Summary of Evidence' section at the end of document for 'Types of HAE.'*
  - The etiology and management of Acquired C1 inhibitor deficiency (AAE) differ from Type I and II HAE and treatment of AAE is not an FDA-approved indication for Haegarda, Berinert, Firazyr, Kalbitor, Cinryze, or Ruconest; **therefore, AAE is <u>not</u> addressed in this document.**

PHARMACOLOGIC THERAPY

There is no cure for HAE at this time. The goals of pharmacotherapy for HAE are to reduce morbidity and to prevent complications. Pharmacologic agents are used to decrease the attack rate, hasten symptom relief, decrease symptom severity, and improve morbidity and mortality. Normalizing biomarkers of the complement pathways (C4 and C1-INH) should not be goals of therapy.

- Treatment strategies are focused on three main areas: prophylaxis, management of acute attacks, and prophylactic therapy in situations where attacks may occur.
  - Long-term prevention for patients with frequent attacks, attacks involving the face or throat, or incapacitating gastrointestinal attacks
  - Short-term prevention of attacks when dental work or invasive medical or surgical procedures are planned
  - Treatment of acute attacks when attacks are moderate-to-severe or involve the airway

- The following are FDA-approved products for preventing and treating HAE attacks at the time of this writing:
  - ACUTE Treatment
    - **Berinert** is an FDA-approved C1-inhibitor concentrate for treating acute HAE attacks in adults and pediatric patients. Berinert is delivered intravenously and is approved for on-demand treatment through self-administration. The medicine is usually administered when a patient feels an attack coming on.
    - **Kalbitor** is an FDA-approved kallikrein inhibitor for treating acute HAE attacks in patients 12 years of age and older. Kalbitor is delivered by subcutaneous injection and must be administered by a healthcare professional.
    - **Firazyr** is an FDA-approved B2 bradykinin receptor antagonist for treating acute HAE attacks in patients 18 years and older. Firazyr is delivered by subcutaneous injection and is approved for self-administration. The medicine is usually administered when a patient feels an attack coming on.
    - **Ruconest** is an FDA-approved plasma free recombinant C1-inhibitor concentrate for treating acute HAE attacks in adults and adolescents. Ruconest is delivered intravenously and is approved for self-administration. The medicine is usually administered when a patient feels an attack coming on.
  - PROPHYLACTIC Treatment
    - **Danazol: First-line**†

      †*Danazol is FDA-approved for the prevention of attacks of angioedema of all types (cutaneous, abdominal, and laryngeal) in males and females. Danazol increases C1 esterase inhibitor levels as well as levels of C4. Danazol is also used for short-term prophylaxis prior to an event or procedure.*
    - **Cinryze** is an FDA-approved C1-inhibitor concentrate for preventing HAE attacks in teenagers and adults. Cinryze is delivered intravenously and is approved for home infusion to prevent HAE attacks.
    - **Haegarda** is a self-administered, plasma-derived concentrate of C1-esterase inhibitor and the only subcutaneous therapy approved in the United States for routine prophylaxis to prevent HAE attacks in adolescent and adult patients.

- Summary of Prophylactic Treatment Recommendations:
  - Treatment with low-to-moderate doses of anabolic androgens provides effective and relatively safe long-term HAE prophylaxis for many patients (AAAI/ACAAI/AAI, Zuraw, 2013b)
  - Treatment with antifibrinolytic agents provides somewhat effective and relatively safe long-term HAE prophylaxis but is generally less effective than androgens (AAAI/ACAAI/AAI, Zuraw, 2013b)
  - Treatment with replacement plasma-derived C1INH provides effective and safe long-term HAE prophylaxis (AAAI/ACAAI/AAI, Zuraw, 2013b)
  - C1 inhibitor will provide an alternative for long-term prophylaxis for patients in whom long-term use of androgens is ineffective, poorly tolerated, or inappropriate (e.g., pregnant women, children).

R*eference: AAAI/ACAAI/AAI (Zuraw, 2013b; Hereditary Angioedema International Working Group (Cicardi, 2012); International Consensus Algorithm (Bowen, 2010)*

- **ACUTE** Treatment: Berinert, Kalbitor, Firazyr, Ruconest
  - All patients with HAE due to C1-INH deficiency should have access to at least two standard doses of one "on-demand" treatment for acute HAE attacks (Firazyr, Berinert, Kalbitor, Ruconest). Patients should also have access to a management plan with easy access to their health care provider during an acute attack.
  - On-demand treatment most effective early in the attack when swelling is mild; if self-administering treatment, patients should seek medical attention if ineffective in treating the attack; all attack should be considered for treatment as soon as they are clearly recognized; patients who experience symptoms of laryngeal, tongue or throat swelling should seek immediate medical attention even after initial self-treatment.
  - **Insufficient evidence to support use of combination therapy with multiple agents**

- **PROPHYLACTIC** Treatment: Danazol, Cinryze, Haegarda
  - Goal is to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis); or to decrease the number and severity of angioedema attacks (long-term prophylaxis)
  - **Short-term prophylaxis** is used mainly in pre-procedural scenarios and is favored for invasive or major surgeries, higher-risk procedures, surgical sites in close proximity to the respiratory tract, and procedures involving airway manipulation, or before situations that previously provoked an attack. However, minor procedures can also trigger attacks (WAO Guideline).
  - There are three classes of medication used to prevent HAE episodes, including attenuated androgens, antifibrinolytics (tranexamic acid), and plasma-derived C1 esterase inhibitors (C1-INHs).
    - **No comparative trials compare androgens against plasma-derived C1 esterase inhibitors in short-term prophylaxis, but some prescribers may opt for Cinryze for its quick onset and robust half-life (Cicardi M, et al. Hereditary Angioedema International Working Group 2014)**
    - Androgens should not be used for long-term prophylaxis if patient does not tolerate (children under 16, pregnant, breast-feeding)

- **Kalbitor (ecallantide)** is a human plasma kallikrein inhibitor. Ecallantide binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of high molecular weight (HMW) kininogen to bradykinin. By directly inhibiting plasma kallikrein, it reduces the conversion of HMW kininogen to bradykinin. Because excessive bradykinin is thought to be responsible for the characteristic HAE symptoms (localized swelling, inflammation, and pain), ecallantide treats symptoms of acute episodic attacks of HAE by reducing excessive bradykinin generation
  - Kalbitor (ecallantide) is not indicated to prevent HAE attacks nor for any types of angioedema other than HAE (such as allergic and drug-induced angioedema). The safety and efficacy of ecallantide for prophylactic therapy have not been established.
  - The safety and efficacy of Kalbitor (ecallantide) has not been adequately studied in children younger than 12 years of age.

- The safety and efficacy of Kalbitor was assessed in two randomized, double-blind, placebo-controlled trials (EDEMA 4 and EDEMA 3).
  - EDEMA3 and EDEMA4 trials included 168 patients with HAE. Patients having an attack of HAE, at any anatomic location, with at least 1 moderate or severe symptom, were treated with Kalbitor 30 mg subcutaneously or placebo. Because patients could participate in both trials, a total of 143 unique patients participated (94 female, 123 Caucasian). The mean patient age was 36 years and there were 64 patients with abdominal attacks, 55 with peripheral attacks, and 24 with laryngeal attacks.
  - Ecallantide 30 mg, administered as three subcutaneous injections, was found to be effective in the treatment of acute HAE attacks as evaluated by a greater improvement from baseline in two patient-reported outcome measures (e.g., mean symptom complex severity score and treatment outcome score) compared to placebo.
  - Due to the concerns of hypersensitivity reactions, ecallantide should be administered by a healthcare professional with medical support available for the management of anaphylaxis and HAE and would therefore not be appropriate for self-administration until additional safety data are available.

- **Since ecallantide is not derived from human plasma as is C1 esterase inhibitor, there is no concern for viral transmission.** However, ecallantide is a recombinant protein and seroconversion to anti-ecallantide antibodies has been reported, which may occur more frequently with increased exposure to the drug.

⌘ Adverse Events

- Treatment with ecallantide is reported to be well-tolerated, with a similar percentage of patients experiencing a treatment related adverse event as placebo.
- The product information for ecallantide includes a Boxed Warning for anaphylaxis; occurring in 2.7% of 187 patients treated with ecallantide subcutaneously. It has been reported that 7.4% of patients developed anti-ecallantide antibodies, which may increase the risk for hypersensitivity reactions.
- Common Adverse Events: The most frequently occurring adverse events in patients receiving ecallantide included headache, nausea, fatigue, diarrhea, upper respiratory tract infection, injection site reactions, nasopharyngitis, vomiting, pruritus, upper abdominal pain, and pyrexia.
- Deaths and Other Serious Adverse Events: According to the product information, 3.9% (10 of 255 patients who received ecallantide SC or IV during clinical trials) experienced anaphylaxis, with 2.7% of the 187 patients who were treated with ecallantide SC. Symptoms of anaphylaxis were reported to include: chest discomfort, flushing, pharyngeal edema, pruritus, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing, and hypotension; occurring within one hour after receiving the dose.

⌘ No head-to-head direct comparative studies have been conducted on currently FDA-approved six HAE drugs: Berinert (Human C1 Esterase Inhibitor), Cinryze (Human C1 Esterase Inhibitor), Kalbitor (Ecallantide), Firazyr (icatibant), Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) and Ruconest (C1 esterase inhibitor [recombinant]). Therefore, no comparatives studies are available to differentiate efficacy between the agents indicated for acute HAE attacks. Thus selection of therapy for acute HAE attacks should take into consideration previous response, adverse effects, route of administration, and cost-effectiveness.

FDA INDICATIONS

⌘ **Hereditary angioedema**
Treatment of acute attacks of hereditary angioedema in patients 12 years and older

Available as: 10 mg/mL solution single-use vial (3 per carton)

FDA Approved: November 27, 2009

Black Box Warnings: Anaphylaxis has been reported after administration of ecallantide. Because of this risk, ecallantide should only be administered by a healthcare professional who is aware of the similarity of symptoms between anaphylaxis and hereditary angioedema and who has the appropriate medical support to manage both conditions. Patients should be monitored closely.

CLASSIFICATION: Plasma kallikrein inhibitor

RECOMMENDATIONS/COVERAGE CRITERIA

Kalbitor (ecallantide) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ALL]

- ❒ Prescribed by, or in consultation with, a board-certified immunologist, allergist, hematologist, or physician experienced in the treatment of C1-esterase inhibitor deficiency. Submit consultation notes if applicable.
  - *Due to the complexity and variability of HAE and treatment, it is strongly recommended that every patient with HAE be followed up by a physician who is (1) knowledgeable about the condition, (2) experienced in managing patients with HAE, and (3) familiar with all HAE treatment options.* US HAE Association Medical Advisory Board 2013

- ❒ If primary care provider is the prescribing physician, clinical documentation of appropriate specialist visits must be included in supporting documentation.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]

- ❒ Diagnosis of Type I or Type II HAE confirmed by ONE (1) of the following: [ONE]

  - ❍ Genetic testing: Presence of a mutation in the C1INH gene altering protein synthesis and/or function

  - ❍ BOTH of the following (documentation of TWO (2) separate low measurements for each test defined as below the testing laboratory's lower limit of the normal range): [BOTH]

    1) Low serum complement factor 4 (C4) level (< 14 mg/dL)
       AND
    2) Low C1 inhibitor (C1INH) level (C1INH < 19.9 mg/dL), **OR**
       Low C1INH functional level (functional C1INH < 72%)

  Refer to Appendix 1 for additional information regarding 'Laboratory Findings in HAE'

  NOTE: Diagnosis of Type III HAE does not meet criteria and will not be authorized.
  **There are no randomized controlled trials evaluating the efficacy of ecallantide (Kalbitor) in patients with Type III HAE.*

- ❒ Prescribed for **ACUTE treatment** of acute abdominal, facial, or laryngeal HAE attacks associated with HAE (not for routine prophylaxis)
  - *The safety and efficacy of ecallantide (Kalbitor) for prophylactic therapy have not been established.*

- ❒ Recurrent history of acute episodes of moderate to severe facial, cutaneous or abdominal attacks and/or airway swelling, tongue swelling, laryngeal edema or pharyngeal edema

3. Age/Gender/Other restrictions [ALL]

- ❒ 12 years of age or older
  - *Safety and effectiveness of ecallantide in patients less than 12 years of age have not been established.*
  - *Ecallantide (Kalbitor) is approved for use in patients 12 years of age and older. The effectiveness of ecallantide in 12 to 15 year old patients was extrapolated data in patients at least 16 years of age which showed similar drug exposure in adult and adolescent patients.*

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ All other causes and potentially treatable triggers of HAE attacks (i.e. stress, trauma, infection, etc.) have been identified and optimally managed

- ❒ Concurrent therapies that may exacerbate HAE, have been evaluated and has been discontinued as appropriate, including: [ALL]
  - ❍ Estrogen-containing medications [e.g. hormone replacement therapy, contraceptives]
  - ❍ ACE-inhibitor (ACEI)
  - ❍ Angiotensin II receptor blockers

  MOLINA REVIEWER: Verify pharmacy claims data for the above drugs within the past 30 days, OR for members new to Molina Healthcare, review member's current medical records or chart notes to confirm.

  Informational Note: Other types of angioedema must be ruled out (e.g., ACEI/ARB-associated or other drug-induced angioedema, allergic angioedema, non-histaminergic angioedema)

- ❒ Member is NOT concurrently on, or using in combination with, other approved treatments for **ACUTE** HAE attacks (e.g. Firazyr®, Ruconest®, and Kalbitor®)
  - *Insufficient evidence to support use of combination therapy with multiple agents*

  NOTE: Members will only be authorized for one (1) acute HAE medication* at a time.
  **Berinert®, Kalbitor®, Ruconest® and Firazyr® are indicated for treatment of acute HAE attacks.*

  MOLINA REVIEWER: Verify pharmacy claims data for the above drugs within the past 30 days, OR for members new to Molina Healthcare, review member's current medical records or chart notes to confirm.

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply: [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to ecallantide or any component of the formulation
- ❒ History of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations
- ❒ Less than 12 years of age

Exclusions [ANY]

- ❒ Concomitant therapy, or concurrently prescribed with drugs which may exacerbate HAE: [ANY]
  - ❍ Angiotensin-converting enzyme (ACE) inhibitors
  - ❍ Angiotensin II receptor blockers
  - ❍ Estrogen-containing medications [i.e. hormone replacement therapy and contraceptives]
- ❒ Prescribed for treatment of the following: [ANY]
  - ❍ ROUTINE PROPHYLAXIS against HAE attacks
    - ◆ *Kalbitor is not indicated for the prophylaxis of HAE attacks. The safety and efficacy of Kalbitor for prophylactic therapy have not been established.*
  - ❍ Acquired angioedema (AAE)

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Kalbitor (ecallantide) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Member currently meets ALL initial coverage criteria

- ❒ Subsequent authorizations require re-assessment treatment regimen/plan, an evaluation of the frequency of HAE attacks and complete clinical review of member's condition to determine if continuation of treatment with requested treatment is medically necessary. Submit all relevant clinical notes, chart notes, and consultation notes (if applicable) for review at least once every 6 months.
  - *Because disease severity may change over time, the need to start or continue therapy should be periodically reviewed and discussed with the patient (US HAE, Zuraw, 2013a)*

2. Compliance

- ❑ N/A

3. Labs/Reports/Documentation required [ALL APPLICABLE]
Reauthorization requires *positive* response or *demonstrated efficacy* to Kalbitor (ecallantide) therapy: [ALL]

- ❒ Significant improvement in the following aspects of HAE attacks have been achieved and sustained. Documentation required. [ALL]

  - ❍ **Frequency:** At least a 50% reduction in frequency of HAE attacks has been achieved or sustained
    NOTE: More than one severe HAE event per month should prompt a discussion with the Prescriber regarding the potential need for chronic prophylaxis with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy (to be used in addition to Firazyr (icatibant) for acute treatment)

  - ❍ **Severity**

  - ❍ **Duration**

- ❒ Clinical documentation of functional improvement

- ❑ Documentation of ONE (1) of the following: [ONE]

  - ❍ Adherence to prophylactic therapy for HAE (with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy), IF APPLICABLE
    NOTE: Adherence to prescribed prophylactic therapy for HAE must be confirmed by member's prescription claims. For member is new to Molina and does not have a prescription claims history, Prescriber certify that the member has been adherent to the prescribed prophylactic therapy.

    OR
  - ❍ More than one severe HAE event per month should prompt a discussion with the Prescriber regarding the potential need for chronic prophylaxis (with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy) as part of HAE therapy with Kalbitor (ecallantide) for acute treatment)

4. Discontinuation of Treatment [ANY]

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to ecallantide or any component of the formulation
- ❒ History of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations
- ❒ Less than 12 years of age

Exclusions [ANY]

- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms following the initial authorization period
- ❑ Intolerable adverse effects or drug toxicity (i.e. injection site reactions, pyrexia, transaminase increase, dizziness, and rash)
- ❒ Concomitant therapy, or concurrently prescribed with drugs which may exacerbate HAE: [ANY]
  - ❍ Angiotensin-converting enzyme (ACE) inhibitors
  - ❍ Angiotensin II receptor blockers
  - ❍ Estrogen-containing medications [i.e. hormone replacement therapy and contraceptives]
- ❒ Prescribed for treatment of the following: [ANY]
  - ❍ ROUTINE PROPHYLAXIS against HAE attacks
    - ◆ *Kalbitor is not indicated for the prophylaxis of HAE attacks. The safety and efficacy of Kalbitor for prophylactic therapy have not been established.*
  - ❍ Acquired angioedema (AAE)

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

1. Recommended Dosage

- ❑ **12 years of age and older:** 30 mg (3 mL) administered subcutaneously in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24 hour period. Must be administered by a health care provider.
  - *Younger than 12 years of age: Safety and efficacy have not been established.*

2. Authorization Limit [ALL]

- ❑ Quantity limit: May authorize up to a sufficient quantity for member to have a cumulative amount on-hand to treat up to **2 acute attacks per month [4 kits per 30 days]**

- ❒ **Dispensing limit: 1-month supply sufficient for 2 acute attacks** for member to have on-hand

  MOLINA PHARMACY: Prior to dispensing, verify that the member does not have more than a 1-month supply (sufficient for 2 acute attacks) currently on-hand

  EXCEPTIONS: For dosages or regimens exceeding the allowable quantity/dispensing limit of **2 acute attacks per month**: Prescriber submit supporting clinical documentation for Medical Director review (e.g. frequency of attacks within the past 3 months has been more than 2 attacks per month)

  Rationale for Quantity on-hand: All patients with HAE due to C1-INH deficiency should have access to at least two standard doses of one"on-demand" treatment for acute HAE attacks (Firazyr, Berinert, Kalbitor, Ruconest). [*2013 US HAE Association Consensus Guidelines]*

- ❒ Duration of Authorization: [AS APPLICABLE]

  - ❍ Initial authorization: **THREE (3) months**

  - ❍ Re-authorization for continuation of treatment is required **SIX (6) months** to determine continued need based on documented clinical response

- ❑ Authorization for ONE (1) acute HAE medication at a time
  [MOLINA REVIEWER TO VERIFY CLAIMS/AUTHORIZATION PROFILE]

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3. Route of Administration [ALL]

- ❒ Kalbitor (ecallantide) is considered a **provider-administered** medication by a healthcare professional in a facility equipped to provide appropriate medical support to manage anaphylaxis and hereditary angioedema
  - *Boxed warnings advise that ecallantide should only be administered by a health care professional with appropriate medical support to manage anaphylaxis and HEA. Patients should be observed for an appropriate period of time after administration of ecallantide.*

- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

This policy addresses the coverage of **Kalbitor (ecallantide)** for **the treatment of acute attacks of hereditary angioedema in patients 12 years and older** when appropriate criteria are met.

All other uses of Kalbitor (ecallantide)**, including** §**acquired angioedema,** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

§*The etiology and management of Acquired C1 inhibitor deficiency (AAE) differ from Type I and II HAE and treatment of AAE is not an FDA-approved indication for Haegarda, Berinert, Firazyr, Kalbitor, Cinryze, or Ruconest;* ***therefore, AAE is <u>not</u> addressed in this document.***

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY OF EVIDENCE/POSITION STATEMENTS

- **Hereditary Angioedema (HAE)**
  - A rare genetic disorder of recurrent attacks of localized subcutaneous or mucosal swelling that affects 1 in 10,000 to 1 in 50,000 individuals in the United States
  - Attack frequency varies from a few days to decades between attacks and severity ranges from mild to more severe laryngeal edema causing airway obstruction and fatal asphyxiation
  - Formal diagnosis is often significantly delayed following onset of symptoms and misdiagnosis or medical mismanagement is not uncommon. The two most common forms of HAE (Types I and II) may be managed with prophylaxis or acute treatment depending on attack frequency, severity, and drug tolerability.

- Types of HAE [HAE International Working Group (2014); Bowen 2010; Zuraw 2013; Grigoriadou 2009]
  There are four types of HAE in the classification system, Both type I and type II HAEs are caused by mutations in the gene that encodes C1INH (SERPING1).[US HAE Association Medical Advisory Board 2013]
  - Type I HAE
    - Hereditary C1 inhibitor deficiency indistinguishable clinically from type II HAE
    - This is the most common form of the disease (accounts for about 85% of patients with HAE
    - Characterized by low quantitative levels of C1-inhibitor (decreased production of C1-INH; low levels of endogenous C1 inhibitor)
    - Associated with low complement C4 levels, low C1 inhibitor antigenic levels, and low C1 functional levels
  - Type II HAE
    - Hereditary C1 inhibitor deficiency indistinguishable clinically from type I HAE
    - Accounts for about 15% of patients with HAE
    - Normal or elevated levels of C1-inhibitor, but the protein does not function properly
    - Associated with low complement C4 levels, normal C1 inhibitor antigenic, and low C1 functional levels
  - Type III HAE
    - Occurs primarily in women
    - Type III HAE is estrogen-dependent form of angioedema
    - Attacks are often associated with increased estrogen levels (pregnancy, oral contraception, hormonal replacement therapy)
    - Also known as HAE with normal C1-INH levels, which is the rarest form of this condition
  - Acquired C1 inhibitor deficiency (C1INH-AAE)
    - Not associated with family history of angioedema
    - Associated with low complement C4 levels, low C1 inhibitor antigenic, and low C1 functional levels
    - May be related to malignancy (mainly lymphoproliferative disorder) or autoantibodies to C1 inhibitor deficiency
- Etiology
  - Types I and II HAE caused by C1 inhibitor deficiency (AAAAI/ACAAI)
  - Genetic mutation leads to disrupted C1 inhibitor protein secretion or function (AAAAI/ACAAI)
    - Type 1 HAE: mutation of serpin peptidase inhibitor, clade G (C1 inhibitor), member 1 (SERPING1) results in truncated or misfolded C1 inhibitor proteins that cannot be secreted
    - Type II HAE, mutation of SERPING1 results in C1 inhibitor proteins that can be secreted but are not functional
    - More than 275 different mutations have been found for HAE (according to the C1 inhibitor gene mutation database)
    - Most patients with HAE have family history of angioedema, which is inherited with autosomal dominance (AAAAI/ACAAI)

- Diagnosis
  - The diagnosis of HAE is based on the patient's family history, clinical presentation, and laboratory results.
  - There are three specific blood tests used to confirm Hereditary Angioedema Type I or II:
    - C1-inhibitor quantitative (antigenic)
    - C1-inhibitor functional
    - C4
  - Laboratory testing can confirm or rule out the diagnosis. Assess all patients suspected of having HAE-I/II for blood levels of C4, C1 esterase inhibitor (C-INH) protein, and C1-INH function. (WAO 2013)
  - Almost all patients with HAE have persistently low antigenic C4 levels with normal antigenic C1 and C3 levels. Measurement of C4 levels is often used as a screening test to rule out HAE; subsequent measurement of antigenic and functional C1 inhibitor levels confirms the diagnosis. (Zuraw 2008)
  - The most reliable and cost-effective screening test for HAE is a serum C4 level. The C4 concentration is almost always decreased during attacks and is usually low between attacks. If the C4 level is in the normal range but suspicion for angioedema is high, the test should be repeated. The concentrations of C3 and C1q are normal in patients with HAE, regardless of the clinical status of their disease (Zuraw 2008)

PIVOTAL TRIALS

Evaluation of DX-88's Effect in Mitigating Angioedema (EDEMA)

*The FDA approval of Kalbitor was based on the results of two placebo-controlled phase 3 clinical studies, known as **EDEMA3 and EDEMA4.** The trials included 168 patients with HAE. Patients having an attack of HAE, at any anatomic location, with at least 1 moderate or severe symptom, were treated with Kalbitor 30 mg subcutaneously or placebo. Because patients could participate in both trials, a total of 143 unique patients participated (94 female, 123 Caucasian). The mean patient age was 36 years and there were 64 patients with abdominal attacks, 55 with peripheral attacks, and 24 with laryngeal attacks.*

- **Efficacy Measures** In both trials, the effects of Kalbitor were evaluated using the Mean Symptom Complex Severity (MSCS) score and the Treatment Outcome Score (TOS). The MSCS is a point-in-time measure of symptom severity and the TOS measures symptom response to treatment.

  Primary Endpoint
  - Treatment outcome score (TOS) at 4 hours after initial treatment [EDEMA3]
  - Change from baseline in mean symptom complex severity (MSCS) score at 4 hours post treatment [EDEMA4]

  Secondary and Other Endpoints
  - Change from baseline in MSCS score at 4 hours post treatment [EDEMA3]
  - TOS at 4 hours after initial treatment [EDEMA4]
  - Change from baseline in MSCS score and TOS at 24 hours after initial treatment [EDEMA3, EDEMA4]
  - Time to significant improvement in overall response [EDEMA3]
  - Time to sustained improvement ($\geq$ 45minutes) within 4 hours after treatment [EDEMA3]
  - Percent of patients with significant response maintained through 24 hours [EDEMA4]
  - Percent of patients with TOS $\geq$ 70 or $\geq$ 50 4 hours after initial treatment [EDEMA4]
  - Need for open-label ecallantide [EDEMA4]

  Results
  - In EDEMA 3 (n = 72), patients given Kalbitor also had statistically superior changes in the MSCS and the TOS at four hours compared with placebo. Also, more patients in the placebo group (36%) required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor -treated group (14%).
  - In the EDEMA 4 trial (n = 96), the changes in MSCS and TOS were statistically superior for Kalbitor compared with placebo at 4 hours and at 24 hours. Also, more patients given placebo (50%) required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor-treated group (33%).

- EDEMA-3

  Efficacy of ecallantide in patients (n=72) with hereditary angioedema presenting with an acute attack was evaluated in a double-blind, placebo-controlled trial (Cicardi M. et al. 2010). This randomized, double-blind, placebo-controlled trial enrolled 72 subjects who were randomized to receive Kalbitor or placebo for acute attacks of HAE. The primary endpoint was the TOS at 4 hours, and the key secondary efficacy endpoint was the change from baseline in MSCS at 4 hours. Kalbitor demonstrated a greater decrease from baseline in the MSCS (p=0.041) than placebo and a greater TOS (p=0.045) than patients treated with placebo; these results were statistically significant. In addition, more patients in the placebo group (36%) required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor-treated group (14%).

  - Subjects: Patients at least 10 years of age with an acute attack were randomly assigned, in a 1:1 ratio, to receive subcutaneous ecallantide 30 mg (n=36) or placebo (n=36) and observed for at least 4 hours after administration. Symptoms were assessed every 15 minutes for the first 2 hours, every 30 minutes for the next 2 hours, and finally at 24 hours.
  - Two measures of patient-reported outcomes were used to assess the response: treatment outcome scores, which range from +100 (designated in the protocol as significant improvement in symptoms) to -100 (significant worsening of symptoms), and the change from baseline in the mean symptom complex severity score, which range from +2 (representing a change from mild symptoms at baseline to severe symptoms after) to -3 (representing a change from severe symptoms at baseline to no symptoms after).
  - The primary trial endpoint was the treatment outcome score 4 hours after study-drug administration and secondary end points included the change from baseline in the mean symptom complex severity score at 4 hours and the time to significant improvement.
    - At 4 hours, the median treatment outcome score was 50.0 in the ecallantide group and 0.0 in the placebo group. The median change in the mean symptom complex severity score at 4 hours reported was -1.00 with ecallantide, versus -0.50 with placebo.
    - Median time to significant improvement was 165 minutes with ecallantide versus more than 240 minutes with placebo. There were no deaths, treatment-related serious adverse events, or withdrawals owing to adverse events.
  - **Conclusion: At four hours after administration of ecallantide or placebo for acute attacks of angioedema in patients with HAE, patient-reported treatment outcome scores and mean symptom complex severity scores were significantly better with ecallantide than with placebo.**
  - In EDEMA3, 11% of patients treated with ecallantide reported at least one treatment-emergent adverse event (TEAE) compared to 14% of patients receiving placebo. Adverse events occurring more frequently with ecallantide and in > 3% of patients in either treatment group included headache, diarrhea, pyrexia, nasopharyngitis, tachycardia, and nasal congestion. Three serious adverse events were reported in patients treated with ecallantide and two in the placebo group; all were reported as acute angioedema attacks. None of the patients who were seronegative for anti-ecallantide antibodies at baseline seroconverted after treatment. Two patients previously treated with ecallantide and seropositive for anti-ecallantide antibodies at baseline experienced clinical response to treatment without reports of adverse events. Eight patients were positive for anti-P pastoris IgE antibodies at baseline and 3 patients seroconverted after treatment (2 ecallantide, 1 placebo), without reports of hypersensitivity or anaphylaxis.

- EDEMA-4

  EDEMA4 evaluated ecallantide 30 mg SC in 96 patients with type I or II HAE, with acute symptoms of HAE of any anatomic location that were of moderate to severe intensity, and who presented within 8 hours of the attack (Levy RJ 2010). If severe upper airway compromise occurred within 4 hours, patients could receive an open-label dose of ecallantide 30 mg SC and standard care; or if symptoms did not improve, resolve completely, or relapsed within 4 to 24 hours after the initial dose, patients could receive a single open-label dose (dose B) of ecallantide 30 mg SC and standard care. Patients could be discharged 4 hours after initial treatment, were contacted by phone at 2 days, and returned for a follow-up visit at 7 days.10

  - Subjects: Patients with moderate to severe HAE attacks were randomized 1:1 to receive subcutaneous ecallantide 30mg (n=48) or placebo (n=48). Patients aged 10 years and older with documented evidence of type I or II HAE who presented within 8 hours of a moderate to severe HAE attack affecting any anatomical location were included.
  - The primary efficacy end point was change from baseline in mean symptom complex severity score (MSCS) 4 hours after dosing. Secondary end points included treatment outcome score (TOS) 4 hours after dosing and maintenance of significant overall improvement through 24 hours.
  - Results: Patients treated with Kalbitor demonstrated a greater decrease from baseline in the MSCS (p=0.010) than placebo and a greater TOS (p=0.003) than patients with placebo; these results were statistically significant.
    - Mean (SD) change from baseline in MSCS score 4 hours after dosing was significantly greater with ecallantide use compared with placebo use. Ecallantide therapy was also associated with a significantly larger mean (SD) TOS 4 hours after dosing vs placebo use.
    - The benefit of ecallantide was apparent within 2 hours after dosing and was maintained through 24 hours after dosing as demonstrated by MSCS score and TOS.
    - A significantly greater proportion of ecallantide-treated patients (44%) maintained significant overall improvement through 24 hours compared with placebo users (21%). The safety profile was similar between the treatment groups.
    - At 24 hours, patients treated with Kalbitor also demonstrated a greater decrease from baseline in the MSCS than placebo (-1.5 vs. -1.1; p = 0.04) and a greater TOS (89 vs. 55, p = 0.03). More patients in the placebo group (50%) required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor-treated group (33%).
  - **Conclusion: Ecallantide treatment results in a rapid and significant reduction in symptom severity of acute HAE attacks and that this effect is sustained for up to 24 hours.**
  - According to the safety analysis of EDEMA4, 17% of patients treated with ecallantide reported at least one TEAE compared to 40% of patients receiving placebo. The most frequently reported adverse events with ecallantide were nausea and headache. There were no reports of hypersensitivity reactions in the ecallantide treatment group. Three patients in the placebo group experienced a local injection site reaction after receiving open-label ecallantide (2 mild; 1 severe); one patient had a local injection site reaction after receiving placebo. Three serious adverse events (hospitalizations due to HAE) were reported in patients randomized to the placebo group (two on the day of treatment and one after dose B). No patients seroconverted to anti-ecallantide antibodies through day 7 of follow-up. Three patients (1 ecallantide; 2 placebo) tested positive for anti-ecallantide antibodies at baseline and at 7 day follow-up. The one patient in the ecallantide group tested positive for neutralizing antibodies at the 7 day follow-up and one of the patients in the placebo group tested positive for neutralizing antibodies at baseline. Treatment-emergent adverse events were not reported in these patients.

PRACTICE GUIDELINES/PROFESSIONAL SOCIETIES

WORLD ALLERGY ORGANIZATION (WAO)

The WAO issued the following 2013 recommendations for the management of HAE types I and II (HAE-I/II):

- Assess all patients suspected of having HAE-I/II for blood levels of C4, C1 esterase inhibitor (C-INH) protein, and C1-INH function
- Consider on-demand treatment for all HAE attacks that (1) result in debilitation/dysfunction and/or (2) involve the face, neck, or abdomen; attacks affecting the upper airways must be treated
- Treat all HAE attacks as early as possible with C1-INH, ecallantide, or icatibant; do not use oral antifibrinolytics as on-demand treatment
- Consider intubation or tracheotomy early in progressive upper airway edema
- Administer adjuvant therapy in HAE attacks when indicated, but use specific therapies without delay when indicated
- All HAE-I/II patients should (1) have on-demand treatment for 2 attacks and (2) carry their on-demand treatment at all times
- Plasma-derived (pd) C1-INH is the preferred on-demand therapy for HAE-I/II attacks in children and for pregnant or breastfeeding women
- All patients should have an action plan, product available to treat HAE attacks, and an HAE identification card
- Self-administration of treatment should be taught to all patients given on-demand treatment that is licensed for self-administration
- All patients should have at least 1 annual assessment by an HAE specialist

The WAO's 2013 recommendations regarding prophylaxis and screening in HAE are as follows:

- Consider administering short-term pre-procedural prophylaxis, particularly in cases involving dental/intraoral surgery, bronchoscopy or endoscopy, endotracheal intubation, or manipulation of the upper airway or pharynx
- Before beginning long-term prophylaxis with androgens, assess the patient for cardiac risk factors and obtain a complete blood count (CBC), urine analysis, liver function test results, a lipid profile, and liver ultrasonography
- During the use of androgens for long-term prophylaxis and for 6 months after cessation of therapy, monitor the patient's CBC, urine analysis, lipid profile, liver function test results, and blood pressure every 6 months; perform annual ultrasonography of the liver
- Defer screening children for HAE-I/II until the age of 12 months; test all offspring of an affected parent
- Family members of HAE-I/II patients should be screened so that appropriate therapy can be available for treatment
- Administer hepatitis A and B vaccinations to HAE-I/II patients receiving blood products, including pdC1-INH; administer influenza vaccine to all HAE-I/II patients

HEREDITARY ANGIOEDEMA INTERNATIONAL WORKING GROUP (Cicardi, 2012) and the **INTERNATIONAL CONSENSUS ALGORITHM** (Bowen, 2010)

- ACUTE HAE ATTACKS
  - Interventions for acute HAE attacks include both pharmacological therapy and the possibility of intubation in case of a severe laryngeal attack.
  - **First-line agents for the treatment of an acute attack of HAE include plasma-derived C1-esterase inhibitor (Berinert or Cinryze), ecallantide (Kalbitor) and icatibant (Firazyr).**
  - **In the U.S., Berinert is labeled for acute treatment and Cinryze is only labeled for prophylaxis of HAE attacks, however, international guidelines indicate the C1-esterase inhibitors are interchangeable.**
  - When first-line agents are not available, fresh frozen plasma (FFP) is recommended.

- SHORT-TERM PROPHYLAXIS
  - Recommendations for short-term prophylaxis depend on the availability of C1-esterase inhibitors (Berinert and Cinryze).
  - In minor manipulations (for example, dental work), no prophylaxis is necessary, as long as a C1-esterase inhibitor is immediately available.
  - Major procedures (for example, surgery or intubation) require administration of C1-esterase inhibitor prior to the procedure.
  - **When C1-esterase inhibitor is not available, danazol or stanozolol are recommended for both minor and major procedure prophylaxis.**
  - **C1-esterase inhibitor, androgens, or antifibrinolytic agents are recommended for long-term prophylaxis.**

U.S. HEREDITARY ANGIOEDEMA ASSOCIATION (HAEA) ADVISORY BOARD (2012)
HAEA Consensus Document: An approach to diagnosis and treatment of HAE (2012)
Berinert, Firazyr, Kalbitor and Cinryze listed as approved medications (Danazol was also listed as an "Older drug") with the following recommendations:

- ACUTE HAE attacks
  - All patients with HAE due to C1-INH deficiency should have access to at least one of these specific effective medicines for treatment of acute attacks "on-demand"
  - Patients should have an existing management plan in place with easy access to their health care provider during an acute attack. The management plan should include either home administration (either self-treatment, treatment by a family member, or treatment by a home health care provider) or pre-arranged access to a medical facility or health care provider
  - On-demand treatment of attacks may be most effective when administered early in the attack at a time when the swelling is mild. Patients who self-administer treatment should seek medical care if their response to self-treatment is ineffective
  - All attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized
  - Patients who experience symptoms of laryngeal, tongue or throat swelling should seek emergency medical care as soon as possible, even after initial self-treatment
- PROPHYLACTIC treatment of HAE
  - Short-term prophylaxis is indicated prior to medical, surgical, or dental procedures. Dental surgery is associated with swelling of the oral cavity that can progress and cause airway obstruction;
  - 17-alpha-alkylated androgens should not be used for long-term prophylaxis when the patient does not tolerate them, in patients under the age of 16, or in pregnant or breastfeeding women. Caution should be exercised if the dose exceeds the equivalent of 200 mg danazol/day as side effects are dose-related
  - Patients on a prophylactic treatment regimen must also have access to effective on-demand treatment of acute attacks
  - Prophylactic medications should be used at the lowest effective dose that controls disease activity

U.S. HEREDITARY ANGIOEDEMA ASSOCIATION (US HAE) MEDICAL ADVISORY BOARD (2013)
In 2013, the US HAE Medical Advisory Board issued Recommendations for the Management of HAE due to C1 inhibitor deficiency, which reiterated the 2012 recommendations (listed above) and added the following information:

- ACUTE HAE attacks
  - All patients with HAE due to C1INH deficiency should have access to at least 2 standard doses of U.S. FDA medicine for on-demand treatment of acute HAE attacks
  - There is overwhelming consensus that all abdominal, facial, oral, and upper respiratory attacks should be treated as early as possible; extremity attacks are often disabling, and early treatment can prevent dysfunction
  - Because not all patients respond the same to each medication, it is the responsibility of the coordinating expert physician to work with each patient to define the optimal medication(s) for that particular patient
  - In cases in which more than one on-demand medication is prescribed, the justification for use of more than a single medication should also be both explicit and understood by the patient
  - Once treatment has been initiated, onset of treatment effect may take 30 to 60 minutes; in general, a second dose of the on-demand treatment is not warranted unless the attack begins worsening again
  - There should be ongoing monitoring of frequency and efficacy of on-demand treatments by the physician with regular follow-up visits, the frequency of which will depend on the patient's course of treatment

- PROPHYLACTIC treatment of HAE
  - The extent of the local trauma may influence the decision about whether to treat the patient prophylactically; a large retrospective study found a 19.9% risk of swelling after a tooth extraction; the risk of swelling was 21.5% in patients who did not receive any prophylaxis and fell to 16% and 7.5% in patients who received 500 or 1000 units of C1INH 1 hour before a dental extraction;
  - C1INH given for short-term prophylaxis should be administered 1-12 hours before the stressor
  - Anabolic androgens used for short-term prophylaxis should be started 7-10 days before the stressor
  - It is critically important that effective on-demand treatment be available whether the patient is given short-term prophylaxis or not
  - Decisions regarding which patients should be considered for long-term prophylaxis should take into account attack frequency, attack severity, comorbid conditions, access to emergent treatment, and patient experience and preference
  - **Because disease severity may change over time, the need to start or continue long-term prophylaxis should be periodically reviewed and discussed with the patient (US HAE, Zuraw, 2013a).**

American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (AAI) (2013)
The AAAAI, ACAAI, and the Joint Council of AAI issued a focused parameter update in 2013 for 'Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor–associated angioedema.' This practice parameter update provided the following:

- The treatment recommendations are consistent with those from the 2012 US HAE consensus document
- All patients with HAE should have access to an effective, on-demand HAE-specific agent (Evidence Level: Grade A)
- Short-term prophylaxis can be achieved by using FFP, C1INH replacement, or short-term, high-dose anabolic androgen therapy (Evidence Level: Grade B)
- Treatment with low-to-moderate doses of anabolic androgens provides effective and relatively safe long-term HAE prophylaxis for many patients (Evidence Level: Grade B)
- Treatment with antifibrinolytic agents provides somewhat effective and relatively safe long-term HAE prophylaxis but is generally less effective than androgens (Evidence Level: Grade B)
- Treatment with replacement plasma-derived C1INH provides effective and safe long-term HAE prophylaxis (Evidence Level: Grade A) (AAAI/ACAAI/AAI, Zuraw, 2013b)

§Definition of evidence levels: Grade A = Directly based on Category I (RCT) evidence; Grade B = Directly based on category II (≥1 non-RCT or quasi-experimental study) evidence or extrapolated recommendation from Category I evidence.

DEFINITIONS

N/A

APPENDIX

Appendix 1: Laboratory Findings in Hereditary Angioedema

Laboratory Findings in Hereditary Angioedema		
Type I	**Type II**	**Type III**
Low C1-INH	High or low C1-INH; however, noted as dysfunctional	Normal C1-INH
Low C4 and C2	Low C4 and C2	C1-INH functional assay and C4 level normal
Normal C1q	Normal C1q	
Data from Nzeako UC, et al. Arch Intern Med 2001;161:2417–2429;1 and Gompels MM, et al. J Clin Pathol 2002;55:145–147.9.		

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CPT	Description

HCPCS	Description
J1290	Injection, ecallantide, 1 mg

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