DISCLAIMER

This Molina Clinical Policy (MCP) 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 MCP document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) for the routine prophylaxis against angioedema attacks in adults and adolescents with hereditary angioedema (HAE) 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.
- 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.
- 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 not addressed in this document.
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**: 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**: 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**: 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**: 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**: 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**: 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).

Reference: 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)

Haegarda, the first C1 Esterase Inhibitor (Human) for subcutaneous administration for routine prophylaxis to prevent HAE attacks in adolescent and adult patients, was FDA approved on June 22, 2017. Haegarda is a self-administered, plasma-derived concentrate of C1 esterase inhibitor injected subcutaneously twice weekly.

The FDA approval was based on the Phase III COMPACT (Clinical Studies for Optimal Management in Preventing Angioedema with low-volume subcutaneous C1-inhibitor replacement Therapy) trial, which showed that at the approved dose of 60 IU/kg, Haegarda reduced the median number of HAE attacks by 95 percent relative to placebo. Use of rescue medication was reduced by greater than 99 percent versus placebo.

**PIVOTAL TRIAL**

The FDA approval was based on the Phase III COMPACT (Clinical Studies for Optimal Management in Preventing Angioedema with low-volume subcutaneous C1-inhibitor replacement Therapy) trial, which showed that at the approved dose of 60 IU/kg, Haegarda reduced the median number of HAE attacks by 95 percent relative to placebo. Use of rescue medication was reduced by greater than 99 percent versus placebo.

- Efficacy based on clinical trial in 90 patients aged 12-72 years with symptomatic HAE randomized to receive twice per week subcutaneous doses of either 40 units/kg or 60 units/kg vs. placebo
- During the 16-week trial period patients in both treatment groups experienced a significantly reduced number of HAE attacks vs. placebo
- Adverse events include injection site reactions, hypersensitivity reactions, nasopharyngitis, and dizziness
- Haegarda contraindicated in patients who have experienced life-threatening hypersensitivity reactions including anaphylaxis to a C1-esterase inhibitor (C1-INH) preparation or its inactive ingredients

**CLASSIFICATION:** Blood Product Derivative; C1 Esterase Inhibitor
**Hereditary angioedema (HAE): ROUTINE PROPHYLAXIS**

Haegarda is indicated for the routine prophylaxis of angioedema attacks in adults and adolescents with hereditary angioedema.

Available as: Subcutaneous Powder for Solution: 2000 IU, 3000 IU (supplied as a kit with a white lyophilized powder in single-use vials containing 2,000 or 3,000 IU of C1-INH with sterile water for injection and one Mix2Vial® filter transfer set for reconstitution)

FDA Approved: June 2017

Black Box Warnings: *None at the time of this writing*

REMS: *None at the time of this writing*

**Warnings/Precautions**

- **Hypersensitivity:** Severe hypersensitivity reactions may occur including hives, tightness of the chest, difficulty breathing, wheezing, hypotension, and/or anaphylaxis during or after injection. Epinephrine should be immediately available for treatment of severe hypersensitivity reactions.
- **Thromboembolic Events:** At the recommended dose, a causal relationship between thromboembolic events and the use of Haegarda has not been established. Thrombosis has occurred in treatment attempts with high doses of intravenous (IV) C1-INH for prevention or therapy of capillary leak syndrome before, during, or after cardiac surgery (non-FDA approved indication and dose).
- **Transmissible Infectious Agents:** Since Haegarda is made from human blood, it may carry a risk of transmitting infectious agents. The risk has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viruses, and by processes demonstrated to inactivate and/or remove certain viruses during manufacturing. Despite these measures, the risk of transmission of infectious agents cannot be totally eliminated.

*FDA-approved indication does not, in itself, dictate coverage. Molina coverage Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare. The covered FDA-approved indications are conditions that are considered medically necessary; however it is not inclusive of all conditions which may be approved by the Medical Reviewer. At the discretion of the Medical Director and on a case-by-case basis, Molina Healthcare may consider authorization of the biologic therapy addressed in this Policy for members with exceptional circumstances and for members with severe disease who may fall outside of the defined criteria. Molina Healthcare reserves the right to update this Policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.*
Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) may be authorized for members who meet ALL of the following criteria [ALL]

1. Prescriber specialty [ONE]
   - 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]
   - Documentation of diagnosis required and may include clinical notes from the member’s medical records including any relevant labs and/or tests, supporting the diagnosis [ALL]
     - Prescribed for routine PROPHYLAXIS (not for acute treatment) against angioedema attacks
       - Haegarda [C1 inhibitor (human)] is not indicated for the treatment of HAE attacks.
     - 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%)

   Informational Note: 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 Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) in patients with Type III HAE.
Prescribed for **SHORT-term** or **LONG-term** prophylaxis: **[ONE: 1 OR 2]**

1) **SHORT-TERM PROPHYLAXIS [ALL]**

- Requested **PRIOR** to medical, surgical or dental procedure
- Short-term prophylaxis may be authorized for ONE (1) procedure or ONE (1) month only

*Informational Note: Short-term prophylaxis can be achieved by using fresh frozen plasma (FFP), C1INH replacement, or short-term, high-dose anabolic androgen therapy (AAAI/ACAAI/AAI, Zuraw, 2013b).*

2) **LONG-TERM PROPHYLAXIS [ALL]**

- History of HAE attacks is consistent with at least **ONE** of the following criteria: **[ONE]**
  - History of at least TWO (2) severe HAE attacks per month (i.e. history of attacks that are considered severe with swelling of the face, throat, or gastrointestinal tract)
  - Severe is defined as events that significantly interrupt usual daily activity despite short-term symptomatic treatment.
  - Emergency medical care related to HAE per year
  - Disabled at least 5 days per month due to HAE
  - Recent hospitalization for severe episode of angioedema

- Insufficient therapeutic response, intolerance, contraindication* or inappropriateness to the following therapy for HAE prophylaxis. Documentation required: **[ONE]**

  - ATTENUATED ANDROGENS (synthetic 17-alpha-alkylated androgens) **[ONE]**
    - danazol
    - oxandrolone
    - methyltestosterone
    - stanozolol (*not available commercially in the U.S., available by prescription; may be available via compounding pharmacies*)

*EXCEPTIONS [ANY]*
Androgens are contraindicated in following conditions/individuals and therefore an exception to this criterion applies to members meeting **ANY** of the following: **[ANY]**

- Hypersensitivity to the attenuated androgen(s)
- Under 13 years of age
- Hepatic or renal impairment
- Pregnancy or breast-feeding
- Androgen-dependent tumor: Males with carcinoma of the breast; males or with known or suspected carcinoma of the prostate gland
- Serious cardiac, hepatic or renal disease
- Hypercalcemia
- Porphyria (may induce aminolevulinic acid (ALA) synthetase activity and porphyrin metabolism)
- Thromboembolic disease or active thrombosis and history of such events
INFORMATIONAL NOTE

• Reference for prophylaxis treatment recommendation: AAAAI/ACAAI (J Allergy Clin Immunol 2013 Jun;131(6):1491 PDF)
• 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.
• 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).

3. Age/Gender/Restrictions [ALL]

☐ 12 years of age or older
  ∗ Safety and efficacy not established in pediatric patients 12 years of age and younger

4. Conventional Therapy/Concurrent Therapy/Other 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., ACE-I/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 prophylaxis against HAE attacks (i.e. Cinryze)
  ∗ Insufficient evidence to support use of combination therapy with multiple agents

NOTE: If authorized, members will only be authorized for one (1) prophylactic HAE medication* at a time. *Haegarda® and Cinryze® are indicated for the prophylaxis of angioedema attacks in adults and adolescents with HAE.

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**
   
   Authorization will **not** be granted if ANY of the following conditions apply [ANY]
   
   - Non-FDA approved indications
   - History of anaphylactic or life-threatening hypersensitivity reactions to human C1 inhibitor or any component of the formulation
   - Younger 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
   - Treatment of **acute** HAE attacks *(Haegarda is indicated for the ROUTINE PROPHYLAXIS of angioedema attacks in adults and adolescents with HAE)*
   - Acquired angioedema (AAE)
   - Concomitant therapy, or concurrently prescribed with, other C1 esterase inhibitors indicated for prophylaxis against HAE attacks (i.e. Cinryze)
   - Concurrent therapies that may provoke or exacerbate an attack within the previous month, including but not limited to: [ANY]
     - Angiotensin-converting enzyme (ACE) inhibitors
     - Angiotensin II receptor blockers
     - Estrogen-containing medications [i.e. hormone replacement therapy and contraceptives]

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.

   - Member’s current weight to confirm requested dosing is in accordance to the FDA-approved dosing

   **NOTE:** Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.
Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) may be authorized for continuation of therapy if all of the following criteria are met: [ALL]

1. Initial Coverage Criteria

- 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

- Adherence to therapy at least 85% of the time as verified by prescriber and member’s medication fill history (review Rx history for compliance), including:
  - Adherent to the prescribed medication regimen
  - Tolerance to therapy
  - No severe adverse reactions or drug toxicity

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

  NOTE: History of non-compliance or non-adherence as verified by member’s medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL]

Reauthorization requires positive response or demonstrated efficacy to Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) 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: If there has not been at least a 50% reduction in frequency of HAE attacks, this should prompt a discussion with the Prescriber regarding a review of member’s therapy
  - Severity
  - Duration

- Clinical documentation of functional improvement
  NOTE: Members who are authorized for prophylactic therapy with Haegarda [C1 inhibitor (human)] and has an acute attack while on therapy should be re-evaluated to determine if there is an identifiable cause (adherence, etc.) for the breakthrough.

INFORMATIONAL NOTE: The goal of long-term therapy is to decrease or eliminate attacks, and success should be measured by this clinical outcome rather than by laboratory parameters.
4. **Discontinuation of Treatment [ANY]**

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

**Contraindications [ANY]**
- Non-FDA approved indications
- History of anaphylactic or life-threatening hypersensitivity reactions to human C1 inhibitor or any component of the formulation
- Younger 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
- Treatment of acute HAE attacks
  - *Haegarda is indicated for the ROUTINE PROPHYLAXIS of angioedema attacks in adults and adolescents with hereditary angioedema*
- Acquired angioedema (AAE)
- Concomitant therapy, or concurrently prescribed with, other C1 esterase inhibitors indicated for prophylaxis against HAE attacks (i.e. Cinryze)
- Concurrent therapies that may provoke or exacerbate an attack within the previous month, including but not limited to: [ANY]
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin II receptor blockers
  - Estrogen-containing medications [i.e. hormone replacement therapy and contraceptives]
1. **Recommended Dosage [ALL]**

   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.

   - ROUTINE PROPHYLAXIS of angioedema attacks in adults and adolescents with HAE: 60 units/kg **subcutaneously** every 3 or 4 days
     - Epinephrine should be available during self-administration in the event of an acute, severe hypersensitivity reaction. Patient suffering from an acute laryngeal HAE attack and self-administering should be informed to seek immediate medical attention following treatment (potential for airway obstruction to occur).

   **NOTE:** Member’s current weight to confirm requested dosing is in accordance to the FDA-approved dosing **[DOCUMENTATION REQUIRED]**

2. **Authorization Limit [ALL]**

   - Quantity limit: [ALL]
     - 16 vials per 28 days (defined as the combined total amount of 2000 unit vials AND 3000 unit vials)
     - Two (2) treatments per week OR eight (8) treatments per month

   - Dispensing limit: Only a **ONE (1) month** supply may be dispensed at a time
     **NOTE:** The number of vial(s) used must correspond with the **smallest dose (vial)** available from the manufacturer which provides the appropriate dose for the member to ensure the minimum amount of drug wastage.

   - Duration of Authorization: [AS APPLICABLE]
     - **For long-term prophylaxis:** [ONE]
       - Initial authorization: May authorize **THREE (3) months** initially
       - Re-authorization for continuation of treatment is required **every SIX (6) months** to determine continued need based on clinical documentation of functional improvement, a decrease in frequency of HAE attack, and an improvement in severity and duration of attacks.

     - **Short-term prophylaxis:** No additional authorizations for short-term prophylaxis; all requests must be re-submitted for review and meet ‘Initial Coverage Criteria.’

3. **Route of Administration [ALL]**

   - Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) may be authorized for **self-administration** or administration by a caregiver (i.e., not a healthcare professional) following training under the guidance of a healthcare professional.
     Coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility will not be authorized. **All authorizations are subject to utilization of the most cost-effective site of care.**

   - If member meets all criteria and authorization for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider. These agents must be dispensed through a participating pharmacy.
This policy only addresses the indication of Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) for the routine prophylaxis against angioedema attacks in adults and adolescents with HAE when appropriate criteria are met.

All other uses of Haegarda [C1 inhibitor (human)] 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 not 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**

**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 asphyxiations.
- 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

- 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

COMPACT (Clinical Studies for Optimal Management in Preventing Angioedema with low-volume subcutaneous C1-inhibitor replacement Therapy) trial
The safety and efficacy of Haegarda were established in the Phase III COMPACT (Clinical Studies for Optimal Management in Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy) trial, which indicated that at the approved dose of 60 IU/kg, Haegarda reduced the median number of HAE attacks by 95% compared with placebo. In addition, the use of rescue medication was reduced by more than 99% versus placebo.

Subcutaneous C1 inhibitor (CSL830) reduces the number of acute attacks in patients with Type I or II HAE
- Based on randomized crossover trial: Multicenter, randomized, double-blind, placebo-controlled, crossover study of 90 adult and adolescent subjects with HAE type I or II
- Subjects: 90 patients ≥ 12 years old (mean age 40 years, 67% female) with types I or II HAE and ≥ 4 attacks over 2 month period within previous 3 months were randomized to 1 of 2 crossover self-administered treatment groups
- Trial Design:
  - Subjects randomized to receive either 60 IU/kg or 40 IU/kg in one 16-week treatment period and placebo in the other 16-week placebo period
  - Subjects self-administered Haegarda or placebo SC two times per week. Efficacy was evaluated for the last 14 weeks of each treatment period
• Rescue medication or pre-procedure prophylaxis with IV C1 inhibitor concentrate, icatibant, ecallantide, or fresh-frozen plasma was allowed for all patients
• Protocol was amended during trial to include patients receiving stable doses of prophylactic oral medication for > 3 months, with oral prophylaxis continued throughout trial

Exclusions
• C1 inhibitory activity ≥ 50%
• normal C4 antigen levels
• features of acquired C1-inhibitor deficiency
• history of arterial or venous thrombosis requiring anticoagulant therapy
• clinically significant risk of pro-thrombotic events
• history of poor response to C1 inhibitor therapy
• disease adequately managed by on-demand pharmacological treatment
• routine use of IV C1 inhibitor prophylaxis within previous 3 months or planned use during trial

Patients progressed to trial completion or to next treatment period at investigator's discretion if ≥ 12 attacks during 4 consecutive weeks after first 4 weeks of a treatment period
• 88% completed both treatment periods; 95.6% of possible data points included in intention-to-treat analysis
• Symptoms, use of trial medication, and use of rescue therapy were reported by patient in daily electronic diary

Comparing CSL830 vs. placebo
• Low-dose group: C1 inhibitor (CSL830) 40 units/kg subcutaneous injection twice weekly vs. placebo for 16 weeks, then crossed over to other treatment for 16 weeks without washout
  • mean number of attacks per months 1.19 vs. 3.61 (p < 0.001): The time-normalized number of HAE attacks in subjects dosed with 40 IU/kg was 1.19 attacks per month compared to 3.61 attacks per month while receiving placebo (p<0.001)
  • mean use of rescue medication per month 1.13 vs. 5.55 (p = 0.02)
  • mean number of days with symptoms per month 1.57 vs. 7 (no p value reported)
  • no attacks in 38% vs. 9% (no p value reported)
• High dose group: CSL830 60 units/kg subcutaneous injection twice weekly vs. placebo for 16 weeks, then crossed over to other treatment for 16 weeks without washout
  • mean number of attacks per months 0.52 vs. 4.03 (p < 0.001): The time-normalized number of HAE attacks (the rate of attacks) in subjects dosed with 60 IU/kg was 0.52 attacks per month compared to 4.03 attacks per month while receiving placebo (p<0.001)
  • mean use of rescue medication per month 0.32 vs. 3.89 (p < 0.001)
  • mean number of days with symptoms per month 1.61 vs. 7.51 (no p value reported)
  • no attacks in 40% vs. 0% (no p value reported)
• ≥ 50% reduction in attacks with CSL830 compared to placebo
  The percentage of responders with a 50% or greater reduction in the time-normalized number of HAE attacks on Haegarda relative to placebo was 83%
    • 76% (95% CI 62%-87%) in low dose group
    • 90% (95% CI 77%-96%) in high dose group
  Of the subjects on Haegarda 60 IU/kg, 90% responded to treatment and 76% of subjects on Haegarda 40 IU/kg responded to treatment.
• Adverse events comparing CSL830 vs. placebo (combined dose groups)
  • any adverse event in 69% vs. 66% (no p values reported)
  • serious adverse event in 1% vs. 2% (no p values reported)

SPECIFIC POPULATIONS

- Pregnancy: There are no available data on the use of Haegarda in pregnant women. In an observational registry, data were collected on 11 pregnancies in 10 subjects (age 16 to 40 years) receiving up to 3,000 IU C1-INH (IV administration) to treat or prevent HAE attacks. No adverse events were associated with C1-INH treatment.

- Lactation: There is no information available regarding the excretion of Haegarda in human milk, the effect on the breastfed infant, or the effects on milk production. In a retrospective case collection study, breastfeeding was documented for neonates from 21 of 35 births with a median duration of 4.8 months. Mothers were treated postpartum with C1-INH doses up to 1,000 IU via IV administration for the treatment of acute HAE attacks. No adverse events to the mothers were associated with C1-INH treatment after pregnancy, but no information regarding the effect on the breastfed infant was reported.

- Pediatric Use: The safety and effectiveness of Haegarda® were evaluated in a subgroup of six patients 12 to 17 years of age in the randomized routine prophylaxis trial. Results of the subgroup were consistent with overall study results.

- Geriatric Use: The safety and effectiveness of Haegarda® were evaluated in a subgroup of eight patients 65 to 72 years of age in the randomized routine prophylaxis trial. Results of the subgroup were consistent with overall study results.

HAYES

At the time of this writing, an assessment addressing the prophylaxis treatment of HAE and the place of therapy of Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) is not available.

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 Hereditary Angioedema 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) (AAAAI/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

**Antifibrinolytic agents** such as epsilon aminocaproic acid (EACA) have been used for long-term prophylaxis in patients with HAE, but it is not FDA approved for this indication. It has been suggested that treatment with antifibrinolytic agents may not be as effective as androgen therapy; although, direct comparison trials have not been conducted.

**Danazol**, a synthetic androgen, is approved for use in HAE and prevents attacks involving edema of the face, abdomen, extremities, and airway. 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.
Appendix 1: Laboratory Findings in Hereditary Angioedema

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low C1-INH</td>
<td>High or low C1-INH; however, noted as dysfunctional</td>
<td>Normal C1-INH</td>
</tr>
<tr>
<td>Low C4 and C2</td>
<td>Low C4 and C2</td>
<td>C1-INH functional assay and C4 level normal</td>
</tr>
<tr>
<td>Normal C1q</td>
<td>Normal C1q</td>
<td></td>
</tr>
</tbody>
</table>


CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT Description
NA

HCPCS Description
J3490 Unclassified drugs [when specified as C1 esterase inhibitor (human), Haegarda]

ICD-10 Description [For dates of service on or after 10/01/2015]

REFERENCES

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Clinical Pharmacology [Internet]. Haegarda (C1 esterase inhibitor [Human]). Available from: http://www.clinicalpharmacology.com/ [via subscription only]. Accessed October 2017

**CLINICAL TRIALS, DEFINITIONS, PEER-REVIEWED PUBLICATIONS**

**Disease, Symptoms**


**GOVERNMENT AGENCIES, PROFESSIONAL SOCIETIES, OTHER AUTHORITATIVE PUBLICATIONS**


Zuraw BL, Bernstein JA, Lang DM, et al. **American Academy of Allergy, Asthma & Immunology (AAAAI); American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology.** A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor–associated angioedema. J Allerg Clin Immunol. 2013b; 131(6):1491-1493.