Subject: Cinryze (C1 esterase inhibitor [human])	**Original Effective Date:** 3/11/10
Policy Number: MCP-230	**Revision Date(s):** 1/13/15; 12/13/17
Review Date(s): 12/16/15; 9/15/2016	

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 **Cinryze (C1 esterase inhibitor [human])** for the **routine prophylaxis** against angioedema attacks in adults and adolescents with 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.[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 not 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)

- **Cinryze** is indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE on October 10, 2008 and **first in its class to be FDA-approved for this use in the U.S.**
  - Cinryze is a C1 inhibitor derived from human plasma. C1 inhibitor is a normal constituent of human blood and is one of the serine proteinase inhibitors (serpins). The primary function of C1 inhibitor is to regulate the activation of the complement and intrinsic coagulation (contact system) pathway. C1 inhibitor also regulates the fibrinolytic system. HAE patients have low levels of endogenous or functional C1 inhibitor.
  - The recommended dose of Cinryze for HAE prophylaxis is 1000 units administered intravenously every three or four days. The FDA label includes self-administration instructions for patients that have received training from their healthcare provider.

PIVOTAL TRIAL

Prophylaxis

The efficacy of C1 inhibitor as prophylaxis in HAE was demonstrated in a single randomized, double-blind, placebo-controlled, multicenter, crossover study enrolling 24 patients (mean age, 38.1 years; range, 9 to 73 years of age) from the acute treatment study who had demonstrated a high frequency of HAE attacks (2 or more attacks per month). Patients received C1 inhibitor for 12 weeks followed by 12 weeks of placebo (normal saline), or placebo for 12 weeks followed by 12 weeks of C1 inhibitor. The study medications were administered 2 or 3 times a week by IV infusion. Patients were provided diary cards to record information on HAE attacks and adverse reactions, and were contacted at least once a week by telephone for questioning about HAE attacks and adverse reactions. No changes in other prophylactic medications (androgens or antifibrinolytics) were permitted during the 24 weeks on study medication or the 4 preceding weeks. Open-label C1 inhibitor was administered to patients in either study arm if treatment for an acute attack was necessary. Two patients dropped out of the study before completing both study periods, leaving 22 patients in the analysis (20 women, 2 men). The primary end point was the number of HAE attacks during the 12 weeks while receiving C1 inhibitor compared with the number of attacks while receiving placebo, with each patient serving as his or her own control. The change in attack frequency was highly variable between patients, ranging from a 100% reduction in attack frequency while on C1 inhibitor to an 85% increase in frequency while on C1 inhibitor in 1 subject. The majority of patients had a reduction in

attack frequency while receiving C1 inhibitor therapy. Overall, the mean number of attacks was 6.1 ± 5.4 while receiving therapy with the C1 inhibitor and 12.7 ± 4.8 during the placebo phase; the median number of attacks was 6 with C1 inhibitor therapy (range, 0 to 17) and 13.5 with placebo therapy (range, 6 to 22) (treatment effect, $P < 0.0001$). Attack frequency was reduced by more than 75% with C1 inhibitor in 10 of 22 (45%) patients, reduced by 25% to 75% in 7 of 22 (32%) patients, and reduced by 1% to 25% in 4 of 22 (18%) patients. Two (9%) patients had more attacks during C1 inhibitor treatment than during placebo. The FDA's review of this study suggested that the variability in responsiveness may have been caused by a non-optimal dose of C1 inhibitor. Patients treated with C1 inhibitor had a 66% reduction in days of swelling (10.1 vs 29.6; $P < 0.0001$), and reductions in the average severity of attacks (1.3 vs 1.9 on a 1 to 3 score scale; $P = 0.0006$) and average duration of attacks (2.1 days vs 3.4 days; $P = 0.0023$).[a] A total of 338 open-label C1 inhibitor injections were administered during the placebo period to treat acute attacks, compared with 104 open-label C1 inhibitor injections during the C1 inhibitor period. Every patient received a minimum of 2 open-label C1 inhibitor doses while on placebo; 50% of patients did not require open-label C1 inhibitor treatment during the C1 inhibitor period.[b]

Reference:

- *Zuraw B, et al. Efficacy and safety of long-term prophylaxis with C1 inhibitor (C1INH) concentration in patients with hereditary angioedema (HAE) [abstract]. J Allergy Clin Immunol. 2008;121(2):S272.*
- *Lev Pharmaceuticals, Inc. Blood Products Advisory Committee Meeting briefing document for Cinryze (C1 inhibitor, human) for the prophylactic treatment of HAE. Food and Drug Administration Web site. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4355B2-2.pdf. Published May 2, 2008. Accessed November 26, 2008.*

- Because C1-INH (Berinert, Cinryze, Ruconest), is a therapeutic protein, there is potential for immunogenicity; however, no anti-C1 esterase inhibitor antibiodies have been detected. There is no evidence that resistance develops with C1-INH treatment.

- 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.

CLASSIFICATION: C1 esterase inhibitor (C1-INH) replacement therapies

FDA INDICATIONS

- **Hereditary angioedema (HAE): ROUTINE PROPHYLAXIS**
  For the routine prophylaxis of angioedema attacks in adults and adolescents with HAE

Available as: 500 Units (lyophilized) in an 8 mL vial

FDA Approved: October 10, 2008

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

- *Thrombotic events: Serious arterial and venous thromboembolic events have been reported at recommended IV doses and when used off-label at doses higher than recommended. Risk factors may include the presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives or certain androgens, morbid obesity, and immobility. Consider potential risk of thrombosis with use, and closely monitor patients with preexisting risks for thrombotic events.*
- *Human plasma: Product of human plasma; may potentially contain infectious agents (e.g., viruses, the variant Creutzfeldt-Jakob disease and, theoretically, the Creutzfeldt-Jakob disease agent) that could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Report infections thought to be transmitted by this product to the manufacturer.*

RECOMMENDATIONS/COVERAGE CRITERIA

Cinryze (C1 esterase inhibitor [human]) 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.
  - *Physician specialties criterion as listed for proper diagnosing and assessing the severity of the symptoms.*

- ❒ 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]
Clinical documented diagnosis of (includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis): [ALL]

- ❒ Prescribed for **ROUTINE PROPHYLAXIS** (not for acute treatment) against angioedema attacks
  - *Cinryze 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 icatibant 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

NOTE: In addition to C1-INH (Cinryze), fresh frozen plasma (FFP) or attenuated androgen may also be given prophylactically prior to surgery.

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/Other restrictions [ALL]

- ❒ 13 years of age or older
  - *Safety and efficacy of C1-esterase inhibitor (human) (Cinryze) have not been established in neonates, infants, and children younger than 13 years of age.*

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.

- ❒ Member is NOT concurrently on, or using in combination with, other approved treatments for **prophylaxis** against HAE attacks (i.e. *Haegarda*)
  - *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/Discontinuations

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

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to C1 esterase inhibitor [human] or any of its components (e.g., hives, chest tightness, wheezing, shortness of breath, hypo tension, and anaphylaxis)
- ❒ Younger than 13 years of age

Exclusions [ANY]

Cinryze (C1 esterase inhibitor [human]) for the treatment of the following disease states is excluded: [ANY]

- ❒ Treatment of acute HAE attacks

  Cinryze [C1 esterase inhibitor (human)] is indicated the routine PROPHYLAXIS against angioedema attacks in adults and adolescents with HAE
- ❒ Prescribed for acquired angioedema (AAE)
- ❒ Concomitant therapy, or concurrently prescribed with, other C1 esterase inhibitors indicated for prophylaxis against HAE attacks (i.e. Haegarda)
- ❒ Concurrent use of agents which may exacerbate HAE:
  - ❍ 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.

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

Cinryze (C1 esterase inhibitor [human]) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria AND Prescribed by, or in consultation with, a board-certified immunologist, allergist, hematologist, or physician experienced in the treatment of C1-esterase inhibitor deficiency

- ❒ 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:
  - ❍ Member is compliant in taking the medication as scheduled
  - ❍ Member tolerated the medication
  - ❍ Member did not experience any severe adverse reactions while taking the medication

  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

3. Labs/Reports/Documentation required [ALL]
Reauthorization requires positive response or demonstrated efficacy to Cinryze (C1 esterase inhibitor [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 Cinryze and has an acute attack while on therapy should be re-evaluated to determine if there is an identifiable cause (adherence, misdiagnosis, 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]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❒ Contraindications [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to C1 esterase inhibitor [human] or any of its components (e.g., hives, chest tightness, wheezing, shortness of breath, hypo tension, and anaphylaxis)
- ❒ Exclusions [ANY]

  Cinryze (C1 esterase inhibitor [human]) for the treatment of the following disease states is excluded: [ANY]
  - ❍ Treatment of acute HAE attacks
    - *Cinryze [C1 esterase inhibitor (human)] is indicated the routine PROPHYLAXIS against angioedema attacks in adults and adolescents with HAE*
  - ❍ Prescribed for acquired angioedema (AAE)
  - ❍ Concomitant therapy, or concurrently prescribed with, other C1 esterase inhibitors indicated for prophylaxis against HAE attacks (i.e. Haegarda)
  - ❍ Concurrent use of agents which may exacerbate HAE:
    - Angiotensin-converting enzyme (ACE) inhibitors
    - Angiotensin II receptor blockers
    - Estrogen-containing medications [i.e. hormone replacement therapy and contraceptives]

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 [ALL]

- ❒ 1,000 unit dose (2 vials) every 3 or 4 days for routine prophylaxis
- ❒ Lack of adequate response: Doses up to 2,500 unit IV (not exceeding 100 units/kg) every 3 or 4 days may be considered based on individual patient response

2. Authorization Limit [ALL]

- ❒ Quantity limit: [ONE]
  - ❍ Long-term prophylaxis: Up to **10,000 unit (20 vials)* per 30 days** for HAE prophylaxis (for a total up to 1,000 units per dose given every 3 to 4 days)
    **Calculated per CDC 90 percentile for weight in adults*
  - ❍ Short-term prophylaxis: **ONE (1) time authorization only.** May authorize 1,000 dosage unit (2 of the 500-unit vials) per one (1) procedure **OR** 20 vials per 30 days for one (1) month only.
    NOTE: Additional procedure(s) must be re-authorized.
- ❒ Dispensing limit: Only a **ONE (1) month** supply may be dispensed at a time
- ❒ Duration of initial authorization: May authorize **THREE (3) month** initially
- ❒ Continuation of treatment: [AS APPLICABLE]
  - ❍ For long-term prophylaxis: Re-authorization for continuation of treatment is required every **SIX (6) months** to determine medically necessity based on clinical documentation of functional improvement, a decrease in frequency of HAE attack, and an improvement in severity and duration of attacks
  - ❍ For short-term prophylaxis: No additional continuation of treatment authorizations. All requests must be re-submitted for review and meet 'Initial Coverage Criteria.'

3. Route of Administration [ALL]

- ❒ **Cinryze (C1 esterase inhibitor [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. Therefore, 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 for member.
- ❒ 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.

COVERAGE EXCLUSIONS

This policy only addresses the indication of **Cinryze (C1 esterase inhibitor [human])** for the routine prophylaxis against angioedema attacks in adults and adolescents with HAE when appropriate criteria are met.

All other uses of Cinryze (C1 esterase 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 <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*

- **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:
    - Estrogen-dependent form of angioedema
    - Occurs primarily in women
    - 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

PROPHYLAXIS

The efficacy of C1 inhibitor (Cinryze) in preventing HAE attacks was evaluated based on the number of HAE attacks during the 12-week treatment period with Cinryze compared with the number of attacks during the 12-week placebo treatment period.

- Phase 3, multicenter, randomized, double-blind, placebo-controlled, crossover trial of 24 patients
- Subjects: 24 patients with HAE and a history of at least two HAE attacks per month. Age range in the study was nine to 73 years.
  - Mean age 38.1 years, range 9 to 73; 90.9% female; 95.5% Caucasian) with HAE
  - HAE defined as: low C4 and a low C1 inhibitor antigenic level, or normal C1 inhibitor antigenic level and low C1 inhibitor functional level, or known HAE C1 inhibitor mutation), normal C1q levels, and frequent attacks of angioedema (> 2 per month),
  - Patients were randomized to one of two treatment groups: either C1 inhibitor prophylaxis for 12 weeks followed by 12 weeks of placebo prophylaxis; placebo prophylaxis for 12 weeks followed by 12 weeks of C1 inhibitor prophylaxis
  - Doses were administered twice weekly (every three to four days)
  - Patients were permitted to continue their treatment with either danazol or epsilon aminocaproic acid (EACA); although, dose adjustments were not allowed. Two patients dropped from the trial. Treatment with C1 inhibitor significantly ($p<0.0001$) reduced the primary endpoint of the number of attacks per patient (defined as swelling reported by the patient when swelling was not reported on the previous day)
  - Patients received C1 inhibitor for 12 weeks followed by 12 weeks of placebo (normal saline), or placebo for 12 weeks followed by 12 weeks of C1 inhibitor.
  - Patients kept a daily record of any new angioedema symptoms that were not present the previous day and recorded information on HAE attacks and adverse reactions
  - No changes in other prophylactic medications (androgens or antifibrinolytics) were permitted during the 24 weeks on study medication or the 4 preceding weeks.
  - Open-label C1 inhibitor was administered to patients in either study arm if treatment for an acute attack was necessary. Two patients dropped out of the study before completing both study periods, leaving 22 patients in the analysis (20 women, 2 men).
- The primary end point was the number of HAE attacks during the 12 weeks while receiving C1 inhibitor compared with the number of attacks while receiving placebo, with each patient serving as his or her own control. The change in attack frequency was highly variable between patients, ranging from a 100% reduction in attack frequency while on C1 inhibitor to an 85% increase in frequency while on C1 inhibitor in 1 subject. The majority of patients had a reduction in attack frequency while receiving C1 inhibitor therapy.

- Results: The efficacy determination was based the comparison of the number of attacks during the 12-week period while receiving C1 inhibitor versus placebo.
    - Mean number of attacks was 6.1 for the study drug as compared to 12.7 for placebo ($p<0.0001$).
    - Mean duration of HEA attacks reported was 2.1 days for pdC1-INH and 3.4 days for placebo.
    - The number of days swelling reported was 10.1 for pdC1-INH and 29.6 for placebo.
    - Mean severity was less with study drug, 1.3 versus 1.9, based on a three point scoring system (1=mild, 2=moderate, 3=severe).

References:

- *Blood Products Advisory Committee Meeting briefing information for Cinryze (C1-esterase inhibitor (human) nanofiltered (C1INH0nf). Food and Drug Administration Web site. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4355B2-00-index.html. Published May 2, 2008. Accessed October 2017.*
- *Lev Pharmaceuticals, Inc. Blood Products Advisory Committee Meeting briefing document for Cinryze (C1 inhibitor, human) for the prophylactic treatment of HAE. Food and Drug Administration Web site. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4355B2-2.pdf. Published May 2, 2008. Accessed October 2017.*
- *Zuraw B, Busse P, White M, et al. Efficacy and safety of long-term prophylaxis with C1 inhibitor (C1INH) concentration in patients with hereditary angioedema (HAE) [abstract]. J Allergy Clin Immunol. 2008;121(2):S272.*

ACUTE TREATMENT (NOT an FDA-approved indication as of this writing in October 2017)

The efficacy and safety of C1 inhibitor (Cinryze) was evaluated in a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial of 71 patients with HAE attacks.

- 71 patients (6 to 75 years of age) were screened to confirm the diagnosis of HAE and to establish a baseline C4 level. The C1 inhibitor group included 36 patients (27 women, 9 men) and the placebo arm had 35 patients (28 women, 7 men).
- Treatment consisted of IV C1 inhibitor 1,000 units (36 subjects) or normal saline placebo (35 subjects). A second injection could be given 60 minutes after the first if the attack had not started to resolve or was getting worse. Open-label C1 inhibitor could be given as rescue therapy if the subject had not reported onset of relief by 4 hours, or if the subject presented with or progressed to airway involvement at any time. Treated subjects were monitored every 15 minutes for 8.5 hours to record response data, with additional monitoring at the treatment site through 12 hours and with telephone follow-up at 72 hours. In addition, a serum C4 level was measured at treatment; C4 levels at the time of treatment were lower than the baseline level confirmed the presence of an HAE attack and were included in the analysis group.
    - Upon the occurrence of an eligible HAE attack, patients were to travel to the treatment site to receive treatment within 4 hours of the attack onset.
    - Eligible attacks were those of moderate or severe intensity affecting the GI tract, face, or genitourinary system. If the attacks were only in the extremities, the subjects were not randomized or treated for that attack.
    - If there was any indication of laryngeal involvement, the patient was treated with open-label C1 inhibitor and not randomized.
- The primary study end point, the median time to the beginning of unequivocal relief, was 2 hours in the C1 inhibitor group and more than 4 hours in the placebo group ($P = 0.026$). Approximately 70% of patients presented with an attack involving the abdomen. In the intent-to-treat group, the primary endpoint of median time to onset of relief of the defining symptom (first of 3 reports of symptom relief or resolution) in patients treated with C1 inhibitor (n=36) was 2.0 hours compared to greater than 4 hours with placebo (n=35). The success ratio for patients in the C1 inhibitor treatment group was 2.048 (95% CI 1.008 to 4.164; p=0.048) compared to placebo.
- The secondary endpoint of patients who experienced symptom relief within 4 hours was 58.3% of patients who received C1 inhibitor and 42.8% of patients in the placebo group. The median time to complete symptom resolution was 12.3 hours with C1 inhibitor and 31.6 hours with placebo, with a success ratio of 2.717 (95% CI 1.471 to 5.020). Fourteen patients in the C1 inhibitor treatment group received open-label C1 inhibitor as rescue therapy compared to 21 in the placebo group. Among the 83 (71 plus 12 open-label) patients who received C1 inhibitor, 13 reported a treatment emergent adverse event. Sinusitis, decreased blood pressure, and nausea were each reported in 2 patients. Three patients experienced a severe treatment emergent adverse event but this was thought not to be related to the study drug.

Reference: Lev Pharmaceuticals, Inc. Blood Products Advisory Committee Meeting briefing document for Cinryze (C1 inhibitor, human) for the prophylactic treatment of HAE. Food and Drug Administration Web site. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4355B2-2.pdf. Published May 2, 2008.

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 fresh frozen plasma (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

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

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.		

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE 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.

CPT	Description

HCPCS	Description
J0598	Injection, C-1 esterase inhibitor (human), Cinryze, 10 units

ICD-9	Description [For dates of service prior to 10/01/2015]
277.6	Hereditary angioedema/Other deficiencies of circulating enzymes

ICD-10	Description[For dates of service on or after 10/01/2015]
D81.810	Biotinidase deficiency
D84.1	Defects in the complement system

REFERENCES

PACKAGE INSERT, FDA, DRUG COMPENDIA

Cinryze (C1 inhibitor, human) [prescribing information]. Lexington, MA: Shire ViroPharma Biologics; December 2016.

AHFS Drug Information® with AHFS®. (www.statref.com), American Society Of Health-System Pharmacists®, Bethesda, MD. Updated periodically.

DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.

Drug Facts and Comparisons online. (www.drugfacts.com), Wolters Kluwer Health, St. Louis, MO. Updated periodically.

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2012. URL: http://www.clinicalpharmacology.com.

C1 Inhibitor, Human Injection. Lexi-Drugs. Lexicomp Online. Hudson, OH: Wolters Kluwer Clinical Drug Information Inc.http://online.lexi.com. Accessed October 2017.

CLINICAL TRIALS, DEFINITIONS, PEER-REVIEWED PUBLICATIONS

Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: a current state-of-the-art review. VII. Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol 2008;100:Suppl 2:S30-40.

Frank MM, Sergent JS, Kane MA, Alling DW. Epsiolon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. N Engl J Med 1972;286:808-812.

Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol:reversal of clinical and biochemical abnormalities. N Engl J Med 1976;295:1444-8.

Levi M, Choi G, Picavet C, Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. J Allergy Clin Immunol 2006;117:904-8.

Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med 2001;161:2417-29.

Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008;359(10):1027-1036.[PubMed 18768946]

GOVERNMENT AGENCIES, PROFESSIONAL SOCIETIES, OTHER AUTHORITATIVE PUBLICATIONS

Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Available at: Allergy Asthma Clin ImmuAnol. 2010 Jul 28;6(1):24, old version can be found in Ann Allergy Asthma Immunol 2008 Jan;100(1 Suppl 2):S30

Caballero T, Farkas H, Bouillet L, et al. **International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency.** J Allergy Clin Immunol. 2012 Feb;129(2):308-20

Cicardi, M., Bork, K., Caballero, T., Craig, T., Li, H. H., Longhurst, H., Reshef, A., Zuraw, B. and on behalf of **HAWK (Hereditary Angioedema International Working Group) (2012).** Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy, 67: 147–157.

Craig T, Pursun EA, Bork K, Bowen T, et al. **World Allergy Organization** Guideline for the Management of Hereditary Angioedema. WAO J. 2012; 5:182-199.

Grigoriadou S, Longhurst HJ. Clinical Immunology Review Series: An approach to the patient with angioedema. Clin Exp Immunol. 2009 Mar;155(3):367-77

Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. Ann Allergy Asthma Immunol. 2012;109:395-402.

Longhurst HJ, Bork K. Hereditary angioedema: causes, manifestations and treatment. Br J Hosp Med (Lond). 2006;67(12):654–657.

U.S. Hereditary Angioedema Association (HAEA) Advisory Board. HAEA Consensus Document: An approach to diagnosis and treatment of HAE. **2012.** Available at: http://www.angioedemacenter.com/wp-content/uploads/2012/03/HAEA-MAB-Treament-guidelines-v2.pdf. Accessed October 2017

Zuraw BL, Banerji A, Bernstein J, et al. **U.S. Hereditary Angioedema Association (US HAE) Medical Advisory Board 2013** recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. J Allergy Clin Immunol. 2013a; 1(5):458-467. Available at: http://haei.org/wp-content/uploads/2015/04/Zuraw-B-L-US-HAEA-MAB-2013-Recommendations.pdf. Accessed October 2017

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.