Subject: Firazyr (icatibant)	**Original Effective Date:** 7/11/2014
Policy Number: MCP-190	**Revision Date(s):** 12/13/17
Review Date(s): 12/16/15; 9/15/2016	

DISCLAIMER

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

SUMMARY

This policy addresses the coverage of **Firazyr (icatibant)** for **the treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years and older** when appropriate criteria are met.

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

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

PHARMACOLOGIC THERAPY

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

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

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

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

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

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

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

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

- **Firazyr (icatibant)**

  Firazyr (icatibant) is a bradykinin B2 receptor antagonist indicated for the treatment of acute attacks of HAE in patients 18 years of age and older and received FDA-approval in August 2011 for this indication. Firazyr is not indicated for the prophylaxis of HAE attacks. **It is the first drug approved by the FDA that allows HAE patients to self-administer treatment** after receiving proper training from a health care professional.

- **PIVOTAL TRIALS**

  For **A**ngioedema **S**ubcutaneous **T**reatment (FAST-1 and FAST-2)

  The efficacy and safety of icatibant 30 mg subcutaneously was evaluated in two phase III randomized, double-blind, controlled clinical trials (FAST-1 vs. placebo; FAST-2 vs. tranexamic acid) in patients with documented HAE (56 patients in FAST-1; 74 patients in FAST-2) who presented *within 6 hours* of an acute attack with cutaneous or abdominal symptoms becoming *moderately severe* in intensity.
  - 130 adults with C1INH deficiency were treated with icatibant for acute laryngeal, gastrointestinal, or cutaneous attacks of moderate-to-severe intensity.
  - Patients were evaluated by rating the severity of three symptoms (cutaneous swelling, cutaneous pain, and abdominal pain) on VAS (0 mm=no symptoms; 100 mm=worst possible symptom severity), with an eligible attack being at least 30 mm for > 1 of the three symptoms.
  - The primary endpoint of the two trials was the median time to clinically significant relief (decrease in VAS score of > 20 to 30 mm for three consecutive measures) of the index symptom (highest VAS score for one of the three specified symptoms).
    - In FAST-1, the primary endpoint (difference in median time to clinically significant relief of the index symptom) did not achieve statistical significance with icatibant 30 mg administered subcutaneously compared to placebo (2.5 hours vs. 4.6 hours, respectively; P=0.14). [Cicardi M et al, 2010]
    - In FAST-2, there was a statistically significant improvement in the primary endpoint with icatibant compared to tranexamic acid (2.0 hours vs. 12.0 hours, respectively; P<0.001). [Cicardi M et al, 2010]

- In a third trial, FAST-3, 83 patients were randomly assigned to receive icatibant or placebo for moderate-to-severe attacks at any location [Lumry WR et al, 2011]. Icatibant significantly reduced median times to ≥50 percent reduction in symptom severity (2 versus 19.8 hours, primary endpoint), onset of primary symptom relief (1.5 versus 18.5 hours, secondary endpoint), or near-complete symptom relief (8 versus 36 hours) and provided a shorter time to initial symptom relief (0.8 versus 3.5 hours). For laryngeal attacks, median times to ≥50 percent reduction in symptom severity were 2.5 and 3.2 hours for icatibant and placebo, respectively. None of the patients receiving icatibant required rescue therapy before symptom relief occurred.

- 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: Selective Bradykinin B2 Receptor Antagonist
Icatibant is a synthetic decapeptide with 5 nonproteinogenic amino acids. It functions in the body as a competitive bradykinin receptor-2 antagonist. Icatibant is selective for the bradykinin B2 receptor and has a receptor affinity similar to bradykinin.Ref Icatibant does not interact with other peptide receptors, such as angiotensin II, substance P, or neurokinin A.

FDA INDICATIONS

- **Hereditary angioedema**
  For the treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years and older

Available as: A single use pre-filled syringe of 30 mg/3 mL

FDA Approved: August 25, 2011
Orphan drug designation: Treatment of angioedema

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

REMS: *None at the time of this writing*

RECOMMENDATIONS/COVERAGE CRITERIA

Firazyr (icatibant) may be authorized for members who meet **ALL** of the following criteria with supporting documentation: **[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]
Clinical documented diagnosis of (includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis):

- ❒ 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 Firazyr (icatibant) in patients with Type III HAE.*

- ❒ Prescribed for the treatment of **acute** HAE attacks (not for prophylaxis)

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

3. Age/Gender/Other restrictions [ALL]

- ❒ 18 years of age or older
  - *Safety and effectiveness of icatibant in the treatment of pediatric patients with HAE have not been established*

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

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

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

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

  Informational Note: Other types of angioedema must be ruled out (e.g., 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 **ACUTE** HAE attacks (e.g. Berinert®, Ruconest®, and Kalbitor®)
  - ◆ *Insufficient evidence to support use of combination therapy with multiple agents*

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

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

5. Contraindications*/Exclusions/Discontinuations

**FDA–approved labeling lists no contraindications for Firazyr (icatibant) therapy*

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

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to icatibant or any of its components
- ❒ Younger than 18 years of age

Exclusions [ANY]

- ❒ Concomitant therapy, or concurrently prescribed with drugs which may exacerbate HAE: [ANY]
  - ❍ Angiotensin-converting enzyme (ACE) inhibitors
  - ❍ Angiotensin II receptor blockers
  - ❍ Estrogen-containing medications [i.e. hormone replacement therapy and contraceptives]
- ❒ Prescribed for treatment of the following: [ANY]
  - ❍ ROUTINE PROPHYLAXIS against HAE attacks
  - ❍ Acquired angioedema (AAE)

6. Labs/Reports/Documentation required [ALL]

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

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

CONTINUATION OF THERAPY

Firazyr (icatibant) 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

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

2. Compliance: N/A

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

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

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

  - ❍ **Severity**

  - ❍ **Duration**

- ❒ Clinical documentation of functional improvement

- ❑ Documentation of ONE (1) of the following: [ONE]
  - ❍ Adherence to prophylactic therapy for HAE (with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy), IF APPLICABLE
    NOTE: Adherence to prescribed prophylactic therapy for HAE must be confirmed by member's prescription claims. For member is new to Molina and does not have a prescription claims history, Prescriber certify that the member has been adherent to the prescribed prophylactic therapy.

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

4. Discontinuation of Treatment [ANY]

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

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to icatibant or any of its components
- ❒ Younger than 18 years of age

Exclusions [ANY]

- ❒ Poor response to treatment as evidenced by physical findings and/or clinical symptoms following the initial authorization period
- ❒ Intolerable adverse effects or drug toxicity (i.e. injection site reactions, pyrexia, transaminase increase, dizziness, and rash)
- ❒ Concomitant therapy, or concurrently prescribed with drugs which may exacerbate HAE: [ANY]
  - ❍ Angiotensin-converting enzyme (ACE) inhibitors
  - ❍ Angiotensin II receptor blockers
  - ❍ Estrogen-containing medications [i.e. hormone replacement therapy and contraceptives]
- ❒ Prescribed for treatment of the following: [ANY]
  - ❍ ROUTINE PROPHYLAXIS against HAE attacks
  - ❍ Acquired angioedema (AAE)

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

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

1. Recommended Dosage [ALL]

- ❒ 30 mg (3 mL) administered by **subcutaneous injection** in the abdominal area. Additional doses may be administered at intervals of at least six hours if response is inadequate or if symptoms recur. **No more than three doses may be administered in any 24 hour period.**

- ❒ Maximum of 3 injections (90 mg or 9 mL) in 24 hours if response is inadequate or symptoms recur

2. Authorization Limit [ALL]

- ❒ Quantity limit: [ALL]
  - ❍ 3 injections (90 mg or 9 mL) in 24 hours (as per FDA-approved labeling)
  - ❍ May authorize up to a sufficient quantity for member to have a cumulative amount on-hand to treat up to **2 acute attacks per month [6 syringes per 30 days]**

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

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

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

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

- ❒ Duration of Authorization: [AS APPLICABLE]
  - ❍ Initial authorization: **THREE (3) months**
  - ❍ Re-authorization for continuation of treatment is required **SIX (6) months** to determine continued need based on documented clinical response

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

3. Route of Administration [ALL]

- ❑ Firazyr (icatibant) is considered to be **self-administered by subcutaneous injection** upon recognition of an HAE attack after training under the policy of a healthcare professional (the drug should not be administered IV or IM) until information from the manufacturer, scientific literature, practice standards, or governing State or Federal agency indicates otherwise.

- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy addresses the coverage of Firazyr (icatibant) for **the treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years and older** when appropriate criteria are met.

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

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

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

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

SUMMARY

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

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

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

PIVOTAL TRIALS

For **A**ngioedema **S**ubcutaneous **T**reatment [FAST-1, FAST-2, FAST-3]

The efficacy and safety of Firazyr (icatibant) for the treatment of acute attacks of HAE in adults were studied in three controlled clinical trials.

- **FAST-1, FAST-2:** The efficacy and safety of icatibant 30 mg subcutaneously was evaluated in two phase III randomized, double-blind, controlled clinical trials (FAST-1 vs. placebo; FAST-2 vs. tranexamic acid) in patients with documented HAE (56 patients in FAST-1; 74 patients in FAST-2) who presented within 6 hours of an acute attack with cutaneous or abdominal symptoms becoming moderately severe in intensity. Patients were evaluated by rating the severity of three symptoms (cutaneous swelling, cutaneous pain, and abdominal pain) on VAS (0 mm=no symptoms; 100 mm=worst possible symptom severity), with an eligible attack being at least 30 mm for > 1 of the three symptoms. The primary endpoint of the two trials was the median time to clinically significant relief (decrease in VAS score of > 20 to 30 mm for three consecutive measures) of the index symptom (highest VAS score for one of the three specified symptoms).11

  - **FAST-1** was a randomized, double-blind, placebo-controlled evaluation of subcutaneous icatibant 30mg in the treatment of 56 patients with hereditary angioedema. Seventy-four patients were randomized in the FAST-2 study comparing subcutaneous icatibant 30mg as a single dose and oral tranexamic acid 3 g daily for 2 days.
    - Both studies enrolled patients with HAE presenting with cutaneous or abdominal attacks
    - Inclusion criteria for both studies included:
      - 18 years of age or older
      - Documented Type I or Type II
      - Current edema in the cutaneous, abdominal, and/or laryngeal areas; and
      - Moderate to severe edema according to the investigator's symptom score
      - No later than 6 hours of an acute attack becoming at least moderately severe
    - Exclusion
      - Pregnant or lactating
      - Diagnosis of angioedema other than HAE
      - Serious concomitant illness
      - Received pain medication for the current attack
      - A C1-esterase inhibitor within 3 days before the current attack, or
      - Tranexamic acid within 1 week before the attack
      - Currently receiving angiotensin-converting enzyme (ACE) inhibitors

- Rescue medications (e.g. C1-esterase inhibitor concentrate, antiemetic agents, opiates) were allowed, the patients were included in the analysis, and their data were not censored. They were withheld for as long as possible after the administration of the study, preferably for 8 to 9 hours.

- Primary end point for both studies: the median time to clinically significant relief of the index symptom. A 100-mm visual analogue scale (VAS), with 0 mm indicating no symptoms and 100 mm indicating symptoms of the worst possible severity, was used. Clinically significant relief was defined as a minimum decrease in the VAS score of 20 to 30 mm depending on the initial symptom severity (approximately 30%)
- In clinical trials, ~57% of patients used attenuated androgens, antifibrinolytic agents, or C1 inhibitors for prevention of acute attacks.

- Summary
  - In **FAST-1,** the time to clinically significant relief was 2.5 hours with icatibant compared to 4.6 hours with placebo; a difference that did not achieve statistical significance (P=0.14).
  - In **FAST-2,** the difference in the same primary endpoint was statistically significant, with relief reported at 2.0 hours with icatibant compared to 12.0 hours with tranexamic acid (P<0.001).
  - The authors stated the reason for not achieving statistical significance in the primary endpoint in FAST-1 could have been attributed to using the change in only the index symptom as a marker for symptom relief, and the inclusion of data from patients who received rescue medication in the placebo group (i.e., 45% and 52% of patients on placebo received rescue medication within 12 and 48 hours, respectively; compared to 11% and 22%, respectively, of patients on icatibant). **The difference in the secondary endpoint of time to first improvement as assessed by patient and provider were significantly reduced with icatibant compared to placebo in FAST-1, and compared to tranexamic acid in FAST-2.**

- **FAST-3** evaluated icatibant 30 mg subcutaneously compared to placebo in patients presenting within 6 hours of acute symptoms of HAE (cutaneous and/or abdominal symptoms at least moderate in severity, or mild laryngeal symptoms). There were 10 patients in the laryngeal population; 5 randomized to icatibant or placebo, with 5 that received open-label icatibant. The primary endpoint for the 88 patients in the non-laryngeal population was median time to 50% reduction in symptom severity from baseline for a composite of three symptoms: cutaneous swelling, cutaneous pain, abdominal pain; with a VAS score of > 30 mm for three consecutive measures. Treatment with icatibant significantly reduced the time to the primary endpoint compared to placebo (2.0 vs. 19.8 hours, respectively; P<0.001). The median time to initial onset of symptom relief (secondary endpoint) was also significantly reduced with icatibant compared to placebo, as assessed by both patient and provider.

- <u>Limitations of Clinical Studies</u>

There are some limitations with the evidence supporting the use of icatibant in the treatment of acute HAE.

- The sample sizes in the studies are small but in the context of this orphan indication are considered reasonable.
- The high rate of injection-site reactions experienced by patients receiving icatibant may have compromised blinding.
- The primary outcome used in the clinical studies was based on changes in symptom severity as measured using a VAS.
- There are no accepted standard outcome measures for treatment of HAE, and use of visual analogue scale (VAS) has not been validated for this condition. 'Significant symptoms improvement' was defined differently in FAST-3 (reduction in a composite score of all three main symptoms), compared with FAST-1 and FAST-2 (reduction in an index symptom). The use of the composite score in FAST-3 addressed a criticism that assessment of an index symptom does not account for the range of symptoms that a patient may experience during an attack.

PRACTICE GUIDELINES/PROFESSIONAL SOCIETIES

WORLD ALLERGY ORGANIZATION (WAO)

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

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

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

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

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

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

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

U.S. HEREDITARY ANGIOEDEMA ASSOCIATION (HAEA) ADVISORY BOARD (2012)
HAEA Consensus Document: An approach to diagnosis and treatment of HAE (2012)

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

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

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

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

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

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

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

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; and Gompels MM, et al. J Clin Pathol 2002;55:145–147.		

CODING INFORMATION

CPT	Description
NA	

HCPCS	Description
J-1744	Injection, icatibant, 1 mg

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