# Hereditary Angioedema Prior Authorization with Quantity Limit Program Summary

BlueCross BlueShield of Alabama

This program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

**OBJECTIVE**

The intent of the Hereditary Angioedema Prior Authorization (PA) program is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling. The policy will consider these agents appropriate for patients with FDA labeled indication(s) or indications supported in clinical studies and/or clinical guidelines. Dosing will be limited to the FDA labeled or clinically supported dosage for the specific indication. Utilization of more than one agent approved to treat acute attacks or prophylaxis will not be supported.

**TARGET AGENTS**

**Berinert®** (C1 Esterase Inhibitor [Human])
**Cinryze®** (C1 Esterase Inhibitor [Human])
**Firazyr®** (icatibant)
**Haegarda®** (C1 Esterase Inhibitor [Human])
**Kalbitor®** (ecallantide)
**Ruconest®** (C1 Esterase Inhibitor [Recombinant])

**QUANTITY LIMITS**

| Brand (generic) | GPI | Quantity Limit | Multisource Code |
|---|---|---|---|
| **Berinert®** (C1 Esterase Inhibitor [Human]) | | | |
| 500 Internationals Units/10 mL | 85802022006420 | 5,000 International Units (10 vials)/30 days* | M, N, O, or Y |
| **Cinryze®** (C1 Esterase Inhibitor [Human]) | | | |
| 500 Units/10 mL | 85802022002120 | 10,000 Units (20 vials)/30 days* | M, N, O, or Y |
| **Firazyr® (icatibant)** | | | |
| 30 mg/3 mL syringe | 85820040102020 | 6 syringes/30 days | M, N, O, or Y |
| **Haegarda®** (C1 Esterase Inhibitor [Human]) | | | |
| 2000 International Unit single use vials | 85802022002130 | 24 vials/30 days* | M, N, O, or Y |
| 3000 International Unit single use vial | 85802022002140 | 16 vials/30 days* | M, N, O, or Y |
| **Kalbitor® (ecallantide)** | | | |
| 3 - 10 mg/mL single use vials | 85840030002020 | 4 kits per30 days | M, N, O, or Y |
| **Ruconest®** (C1 Esterase Inhibitor [Recombinant]) | | | |
| 2100 unit single use vials | 85802022102130 | 8 vials per30 days* | M, N, O, or Y |

*calculation based on CDC 90 percentile for weight in adults and averaged for men and women to 238 lbs (108 kg). Haegarda is rounded down to reduce waste.

**Berinert, Firazyr, Kalbitor, or Ruconest**
**Initial Evaluation**

The requested agent will be approved when the following are met:

1. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   **AND**
2. The patient has a diagnosis of Type I or Type II hereditary angioedema (HAE) evidenced by ONE of the following:
   A. BOTH of the following (there must be TWO separate low measurements for each test defined as below the testing laboratory's lower limit of the normal range):
      i. Low Serum complement factor 4 (C4) level
      **AND**
      ii. EITHER Low C1-INH antigenic level **OR** Low C1-INH functional level
   **OR**
   B. The patient has a mutation in the C1INH gene altering protein synthesis and/or function
   **AND**
3. Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate
   **AND**
4. The requested agent will be used to treat HAE acute attacks
   **AND**
5. ONE of the following:
   A. The patient is receiving only ONE agent indicated for treatment of acute HAE attacks
   **OR**
   B. The other agent being used for acute HAE attacks will be discontinued before starting the requested agent
   **AND**
6. ONE of the following:
   A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist)
   **OR**
   B. The prescriber has consulted with a specialist in the area of the patient's diagnosis
   **AND**
7. ONE of the following:
   A. The dose is within the program quantity limit (allows for 2 acute attacks per month)
   **OR**
   B. The quantity (dose) requested is greater than the program quantity limit and prescriber has submitted documentation (e.g. frequency of attacks within the past 3 months has been >2 attacks per month) in support of therapy with a higher quantity which has been reviewed and approved by the Clinical Review pharmacist

**Length of Approval:** 12 months

**Renewal Evaluation**

1. The patient has been previously approved for therapy through the Prime Therapeutics PA process
   **AND**
2. ONE of the following:
   A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist)
   **OR**
   B. The prescriber has consulted with a specialist in the area of the patient's diagnosis
   **AND**
3. ONE of the following:

a. The patient is receiving only ONE agent indicated for treatment of acute HAE attacks
**OR**
b. The other agent being used for acute HAE attacks will be discontinued before starting the requested agent

**AND**

4. The prescriber has submitted documentation that the patient continues to have acute HAE attacks
**AND**
5. The prescriber has communicated (via any means) with the patient regarding frequency and severity of attacks and has verified that the patient does not have >1 month supply (sufficient for 2 acute attacks) currently on-hand
**AND**
6. The patient does not have any FDA labeled contraindications to therapy with the requested agent
**AND**
7. ONE of the following:
    a. The dose is within the program quantity limit (quantity limits allow for 2 acute attacks per month)
    **OR**
    b. The quantity (dose) requested is greater than the program quantity limit and prescriber has submitted documentation (e.g. frequency of attacks within the past 3 months has been >2 attacks per month) in support of therapy with a higher quantity which has been reviewed and approved by the Clinical Review pharmacist

**Length of Approval**: 12 months

**Cinryze or Haegarda**
**Initial Evaluation**
The requested agent will be approved when the following are met:

1. The patient does not have any FDA labeled contraindications to therapy with the requested agent
**AND**
2. ALL of the following:
    A. The patient has a diagnosis of Type I or Type II hereditary angioedema (HAE) evidenced by ONE of the following:
        i. BOTH of the following (there must be TWO separate low measurements for each test defined as below the testing laboratory's lower limit of the normal range):
            a. Low Serum complement factor 4 (C4) level
            **AND**
            b. EITHER Low C1-INH antigenic level **OR** Low C1-INH functional level
        **OR**
        ii. The patient has a mutation in the C1INH gene altering protein synthesis and/or function
    **AND**
    B. ONE of the following:
        i. The requested agent is Cinryze and will be used to treat HAE acute attacks AND ONE of the following:
            a. The patient is receiving only ONE agent indicated for treatment of acute HAE attacks
            **OR**
            b. The other agent being used for acute HAE attacks will be discontinued before starting the requested agent

**OR**

ii. The agent will be used for prophylaxis against HAE attacks AND ALL of the following:
    a. ONE of the following:
        1. The patient is receiving only ONE HAE agent indicated for treatment for prophylaxis against HAE attacks
        **OR**
        2. The other agent being used for prophylaxis will be discontinued before starting the requested agent
    **AND**
    b. The patient has had at least 2 acute severe (e.g. swelling of the throat, incapacitating abdominal or cutaneous swelling) attacks per month
    **AND**
    c. ONE of the following:
        1. The patient has tried and failed danazol, aminocaproic acid, or tranexamic acid
        **OR**
        2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to danazol, aminocaproic acid, or tranexamic acid

**AND**

3. Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate
**AND**
4. ONE of the following:
    a. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist)
    **OR**
    b. The prescriber has consulted with a specialist in the area of the patient's diagnosis
**AND**
5. ONE of the following:
    a. The dose is within the FDA labeled or clinically supported dose AND within the quantity limit
    **OR**
    b. The quantity (dose) requested is greater than the program quantity limit and prescriber has submitted documentation in support of therapy with a higher quantity which has been reviewed and approved by the Clinical Review pharmacist

**Length of Approval**: 3 months for HAE prophylaxis treatment
12 months for acute HAE attack treatment

**Renewal Evaluation**

1. The patient has been previously approved for therapy through Prime Therapeutics PA process
**AND**
2. ONE of the following:
    a. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist)
    **OR**
    b. The prescriber has consulted with a specialist in the area of the patient's diagnosis
**AND**
3. ONE of the following:
    a. The requested agent was initially approved for acute HAE attacks and ALL of the following:

i. ONE of the following:
   1. The patient is receiving only ONE agent indicated for treatment of acute HAE attacks
      **OR**
   2. The other agent being used for acute HAE attacks will be discontinued before starting the requested agent

   **AND**

ii. The prescriber has submitted documentation that the patient continues to have acute HAE attacks

   **AND**

iii. The prescriber has communicated (via any means) with the patient regarding frequency and severity of attacks and has verified that the patient does not have >1 month supply (sufficient for 2 acute attacks) currently on-hand

**OR**

b. The requested agent was initially approved for prophylaxis of HAE attacks and BOTH of the following:
   i. ONE of the following:
      1. The patient is receiving only ONE agent indicated for prophylaxis of HAE attacks
         **OR**
      2. The other agent being used for prophylaxis will be discontinued before starting the requested agent

   **AND**

   ii. The patient has had a decrease in the frequency of acute attacks from baseline (prior to treatment)

**AND**

4. The patient does not have any FDA labeled contraindications to therapy with the requested agent

   **AND**

5. ONE of the following:
   a. The dose is within the FDA labeled dose or clinically supported dose and within the quantity limit
      **OR**
   b. The quantity (dose) requested is greater than the program quantity limit and prescriber has submitted documentation in support of therapy with a higher quantity which has been reviewed and approved by the Clinical Review pharmacist

**Length of Approval**: 12 months

**FDA Approved Products for Acute Attacks and Routine Prophylaxis of Hereditary Angioedema (HAE)**[1-5,16]

| Medication | Indications | Recommended Dose |
|---|---|---|
| Berinert (C1 esterase inhibitor, [human]) | • Treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adults and pediatric patients | • 20 IU/kg IV administered at 4 mL/minute. Supplied as 500 IU in 10 mL.<br>• Patient may self-administer |
| Cinryze (C1 esterase inhibitor, [human]) | • Treatment for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE | • 1,000 Units IV administered at 1 mL/min every 3 to 4 days.<br>• Patient may self-administer |
| Firazyr (icatibant) | • Treatment of acute attacks of HAE in adults 18 years of age and older | • 30 mg SQ in abdominal area. Additional doses may be given at least 6 hours apart up to a maximum of 3 doses in 24 hours.<br>• Patient may self-administer |
| Haegarda (C1esterase inhibitor [human]) | • Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients | • Administer 60 IU/kg body weight SQ twice weekly (every 3 or 4 days)<br>• Patient may self-administer |
| Kalbitor (ecallantide) | • Treatment of acute attacks of HAE in patients 12 years of age and older | • 30 mg (3mL) administered subcutaneously in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24 hour period.<br>• Must be administered by a health care provider. |
| Ruconest (C1 esterase inhibitor, [recombinant]) | • Treatment of acute attacks of HAE in adults and adolescents<br>• Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks | • 50 IU/kg (maximum 4200 IU) administered via slow intravenous infusion over approximately five minutes. A second dose may be administered if symptoms persist (maximum 2 doses in 24 hours).<br>• Patient may self-administer |

**CLINICAL RATIONALE**[4,6-14]

Hereditary Angioedema (HAE) is an autosomal dominant disease occurring in approximately 1 in 50,000 persons without known differences between the sexes or ethnic groups. It is characterized by recurrent episodes/attacks of nonpruritic, nonpitting, subcutaneous or submucosal edema that may involve the extremities, bowels, genitalia, trunk, face, tongue, or larynx. Attacks result in progressive swelling without erythema over the first 24 hours and then the swelling gradually subsides during the following 48 to 72 hours. Symptoms of HAE typically begin in the first or second decade of life and persist throughout; however, any acute attack has the potential to be life-threatening. An acute attack that causes death is most often a result of abdominal or laryngeal involvement. Triggers for attacks vary and may be traceable to a source (e.g. minor trauma or stress); however, episodes often occur without a defined precipitating factor.

Three types of HAE have been identified. Type I accounts for approximately 85% of all cases and is characterized by deficient levels of C1 esterase inhibitor (C1-INH) protein. This is in

contrast to Type II (approximately 15% of all cases) where a normal level of C1-INH protein is found, but there is diminished C1-INH activity (i.e. dysfunctional C1-INH protein). Type III HAE, characterized by both normal C1-INH protein and functional levels, is rare.

Types I and II occur as a result of a mutation in the SERPING1 gene that codes for C1-INH and ultimately leads to the increased generation of bradykinin. Bradykinin has been credited in all types for involvement in attacks through increasing vascular permeability via the B2 receptor. Although Type III pathophysiology has not been fully elucidated, mutations in coagulation factor XII and effects of estrogen that affect bradykinin have been associated. The US HAE Association Medical Advisory Board (2013) recommends that current medications that affect bradykinin and can cause angioedema (e.g. angiotensin converting-enzyme inhibitors and estrogen replacement) be evaluated and stopped when appropriate.

In addition to clinical presentation and an assessment of family history, HAE diagnosis typically includes a laboratory workup of C4, C1-INH antigenic level, and C1-INH function. C4, the natural substrate for C1 esterase, is considered the single best screening test for C1INH deficiency. At least 95% of patients with C1INH deficiency will always have a reduced C4 even between attacks. If the patient has a normal C4, repeating the C4 during an attack increases the probability (nearly 100% of patients) that the patient's C4 will be low. In order to further distinguish between Type I and Type II HAE, the C1-INH antigenic level and/or functional activity is measured. It is recommended to repeat the blood tests to confirm diagnosis.

Prior to C1 inhibitors, icatibant, and ecallantide, treatment of acute attacks involved fresh frozen plasma and fluid/ventilation support. Currently, clinical evidence supporting the use of more than one agent used to treat acute attacks at the same time is lacking. For patients requiring prophylaxis, there are medications that are considered beneficial. Danazol and other 17 alpha-alkylated androgens have been used for long term prophylaxis with success and are still recommended for use. However, androgens have undesirable side effects (e.g. liver toxicity) and have limited use in pregnancy. Beyond 17 alpha-alkylated androgens, Cinryze (C1 esterase inhibitor, [human]) is approved in the U.S. for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE. The pivotal clinical trials required patients to have at least 2 HAE attacks per month prior to moving to prophylaxis. Guidelines recommend Cinryze as first-line long term prophylaxis (LTP) for pregnant or lactating HAE patients. Outside of the United States aminocaproic acid and tranexamic acid are approved for long-term prophylaxis of HAE.

*Pivotal clinical trial data for each of the products can be accessed in the prescribing information

**Safety**[1-5,16]

C1 esterase inhibitor products [(human-Berinert, Cinryze, Haegarda); (recombinant-Ruconest)] are contraindicated in patients who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations. Serious hypersensitivity reactions, including anaphylaxis may occur. Epinephrine should be immediately available for treatment of acute hypersensitivity reactions. Since Ruconest is made from the milk of transgenic rabbits, its use is contraindicated in patients with allergies to rabbits or rabbit derived products. Thrombotic events have been reported following administration of C1-INH products when used off-label at higher than labeled doses.

Anaphylaxis has been reported after administration of ecallantide (Kalbitor). The prescribing information contains a boxed warning for this, and it requires administration by a healthcare professional with appropriate medical support. Anaphylaxis occurred in 3.9% of treated patients in clinical trials.

Given the potential for airway obstruction during acute laryngeal HAE attacks, patients should be advised to seek medical attention in an appropriate healthcare facility immediately in addition to treatment with Berinert, Firazyr, or Kalbitor.

*Further safety information for each agent can be found by accessing the agent's specific prescribing information.

**Guidelines**[8-14]
Consensus guidelines from HAE International Working Group recommend with a high level of evidence that all patients have access to at least one of the plasma-derived/recombinant C1-INHs, icatibant, or ecallantide. They also recommend that patients should have on-demand medicine to treat acute attacks at home and should be trained to self-administer when possible and supported by product labeling. Additionally, several guidelines note that some patients will need long term prophylaxis (LTP) in addition to on demand treatment.

A focused parameter update developed by a joint task force representing the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of allergy, Asthma and Immunology (2013) supports:

- HAE attacks: symptomatic treatment, efficacy of fresh frozen plasma often, and safety and efficacy of C1-INHs, plasma kallikrein inhibitor, or bradykinin B2 receptor antagonist.
- HAE Prophylaxis: anabolic androgens as effective and relatively safe; antifibrinolytic agents as somewhat effective and relatively safe but generically less effective than androgens; and C1-INH as safe and effective.

An international consensus from AAAAI, ACAAI, WAO, and the European Association of Allergy and Clinical Immunology recommend the following:

- HAE attacks: C1-INH, ecallantide, and icatibant are all efficacious and safe; fresh frozen plasma should be used when no other treatments are available.
- HAE prophylaxis: patients not treated successfully with on-demand therapy should be considered for long-term prophylaxis. C1-INH is effective; 17 alpha-alkylated androgens may decrease frequency and severity of HAE attacks but have potential adverse effects if used long term; antifibrinolytic agents have been used but are less effective.

US HAE Association Medical Advisory Board 2013 recommends:

- HAE attacks: early treatment of acute attacks with C1-INH, ecallantide, icatibant, or fresh frozen plasma. The medication selection should be individualized based on patient response and all attacks should be considered for treatment irrespective of anatomical location. Patients should have access to at least two doses of medicine for on-demand treatment of acute attacks.
- HAE prophylaxis: the decision to initiate long term prophylaxis should be individualized and consider attack severity, frequency, comorbid conditions, and patient experience/preference. Medication options include C1-INH as well as older alternatives of danazol, stanozolol, orandralone, methyl-testosterone, aminocaproic acid, or tranexamic acid. Short term prophylaxis with C1-INH or anabolic androgens may be indicated before medical, surgical, or dental procedures.
- Attack frequency and severity should be evaluated by the physician on an ongoing basis. The US HAEA MAB recommends that patients keep a record of all of their attacks, regardless of severity (mild, moderate, or severe). These logs or attack records should be maintained in a format (e.g., electronic, paper) that is decided upon between the patient and physician and is easy for the patient to complete. Regardless of format, these records should specifically identify the following 3 domains: description of attack, treatment of attack, and response to treatment. Physician knowledge of the patient's HAE attack frequency and severity is critical to determine the ongoing management of HAE. Data captured from the attack logs are considered vital information to be documented in the patient's medical records. This attack diary should be provided to the treating physicians and reviewed on a regular basis by a means (i.e., in person or electronically) predetermined between the patient and the physician.

- Physician knowledge of when patients may require and when they have administered on-demand treatment is a key aspect of optimal management of HAE and highlights the importance of a strong patient-physician partnership and communication. When patients self-administer or receive on-demand medications, there must be a plan to have the patient report this use in a timely manner, as discussed above.
  The MAB recommends that potential triggers of HAE be reviewed when patients come into the office for visits. This includes an updated list of current medications to ensure that patients are not taking an angiotensin-converting enzyme inhibitor or estrogen replacement. For patients who are well controlled, return visits may occur once every 6-12 months.

**REFERENCES**


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