Hereditary Angioedema (HAE), Prophylaxis and Acute Treatment

Meets Primary Coverage Criteria Or Is Covered For Contracts Without Primary Coverage Criteria

I. Treatment of HAE Acute Attacks
The below agents meet member benefit certificate primary coverage criteria that there be scientific evidence for effectiveness in the treatment of acute moderate-severe episodes of established HAE with deficient or dysfunctional C1INH or HAE-nl-C1INH (craniofacial, laryngeal, or gastrointestinal angioedema).

Use is limited to one agent. Combination of below agents for treatment of acute attacks are not allowed.

Prior approval allows individuals to have on-demand medication of two (standard doses, FDA approved) for treatment of acute attacks.

The use of **Icatibant (e.g., Firazyr)** is not covered under the medical benefit. Please check the member's pharmacy benefit for coverage. This policy applies to members whose plan utilizes AR BCBS pharmacy and has **Icatibant (e.g., Firazyr)** as a formulary option.

- **pdC1INH (e.g., Berinert)**, indicated for the treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric individuals.
- **rhC1INH (e.g., Ruconest**) indicated for the treatment of acute attacks (including laryngeal edema) in adult and adolescent individuals with hereditary angioedema (HAE).
- **Ecallantide (e.g., Kalbitor)** is a kallikrein inhibitor with a risk of hypersensitivity reactions indicated for treatment of acute attacks of hereditary angioedema (HAE).
- **Icatibant (e.g., Firazyr)** bradykinin B2 receptor antagonist indicated for treatment of acute attacks of hereditary angioedema (HAE).

Request for one of the above medications, **INITIAL APPROVAL STANDARD REVIEW** for up to 12 months if **ALL** the following criteria is met [Busse, GUIDELINES, 2020]:

1. Established diagnosis of HAE-C1INH deficient or dysfunctional HAE (previously type 1 HAE and type 2 HAE) and HAE-nl-C1INH. **Confirmation is based on supportive clinical and physical findings combined with separate results (historical or current testing) of C4 and C1INH antigenic and functional activity.** Submission of the following documentation is expected:
    a. C1 protein (antigenic) (C1INH level).
    b. C1 esterase function (C1INH function)
    c. C4 level
    d. Documentation of familial history of HAE. **AND**
    e. Documentation of previous treatments attempted and failed. **AND**
    f. Medications known to cause angioedema (i.e., ACE inhibitors, estrogens, angiotensin II receptor blockers, DPP-4 inhib) have been evaluated and discontinued where appropriate.
    g. Documentation of weight for weight-based formulations.
    h. Serpine genetic analysis when there is no clear family history, prenatal testing or where biochemical C1INH test results are equivocal. (US HAEA MAB guidelines)

2. There is a documented history of recurrent angioedema in the absence of concomitant urticaria with moderate to severe attacks such as airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, or painful facial distortion. **And**

3. The individual is of appropriate age for the specific drug requested:
    a. **pdC1INH (e.g., Berinert)** – 5 years or older.
    b. **rhC1INH (e.g., Ruconest)** – 12 years or older
    c. **Ecallantide (e.g., Kalbitor)** – 12 years or older
    d. **Icatibant (e.g., Firazyr) –** 18 years or older

4. Medication is being used for treatment of acute attacks, (not prophylaxis).

Concurrent review (approval an additional 6 months or 1 year)

1. Must meet all the initial criteria above.
2. Documentation must be submitted to show that there has been significant improvement/stability in severity and duration of attacks, and clinical documentation of functional improvement/stability as defined by at least a 50% decrease in frequency of HAE attacks after start of therapy,

Dosing and Administration [FDA label; [Busse, GUIDELINES, 2020]:

pdC1INH (e.g., Berinert)

- 20 IU/kg of body weight for the treatment of a HAE acute attack of abdominal, facial, or laryngeal areas in adults or children, administered IV. May be self-administered. A vial contains 500 IU.
- Doses lower than 20 IU/kg should not be administered.

rhC1INH (e.g., Ruconest)

- **Must have failed Berinert and Icatibant prior to use.**
- For individuals <84 kg, give as 50 units/kg IV, (Body weight divided by 3).
- For individuals > 84 kg give 4,200 units IV (2 vials).
- May self-administer.
- A second dose can be administered at the same dosage level if acute attack symptoms persist, but no more than 4,200 units should be given in a 24-hour period.
- 1 vial contains 2100 Units

Ecallantide (e.g., Kalbitor)

- Administered SQ as 30 mg (supplied as 10 mg per vial).
- An additional dose of 30 mg may be administered within a 24-hour period for persistent symptoms.
- This drug should be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.

Icatibant (e.g., Firazyr)

- Administer as 30 mg injected SQ in the abdominal area (supplied as prefilled syringe).

- If response is inadequate or symptoms recur, additional injections of 30 mg may be administered at intervals of at least 6 hours not to exceed more than 3 injections in 24 hours.
- May be self-administered.

Please refer to a separate policy on Site of Care or Site of Service Review (policy #2018030) for pharmacologic/biologic medications.

Does Not Meet Primary Coverage Criteria Or Is Investigational For Contracts Without Primary Coverage Criteria

Use of pdC1INH (e.g., Berinert), rhC1INH (e.g., Ruconest), Ecallantide (e.g., Kalbitor), or Icatibant (e.g., Firazyr) does not meet primary coverage criteria that there be scientific evidence of effectiveness for all other indications.

For members with contracts without primary coverage criteria, the use of pdC1INH (e.g., Berinert), rhC1INH (e.g., Ruconest), Ecallantide (e.g., Kalbitor), or Icatibant (e.g., Firazyr) is **investigational and not medically necessary** for all other indications. I**nvestigational** services are specific contract exclusions in most member benefit certificates of coverage.

The combined use of pdC1INH (e.g., Berinert), rhC1INH (e.g., Ruconest), Ecallantide (e.g., Kalbitor), or Icatibant (e.g., Firazyr) does not meet primary coverage criteria that there be scientific evidence of effectiveness for the treatment of acute attacks or any other indication.

For members with contracts without primary coverage criteria, the combined use of pdC1INH (e.g., Berinert), rhC1INH (e.g., Ruconest), Ecallantide (e.g., Kalbitor), or Icatibant (e.g., Firazyr) for the treatment of acute attacks or any other indication is **investigational and not medically necessary. Investigational** services are specific contract exclusions in most member benefit certificates of coverage.

II. Long Term Chronic Prophylaxis for Acute HAE Attacks

The use of long-term prophylaxis for hereditary angioedema meets benefit certificate primary coverage criteria that there be scientific evidence of effectiveness when despite available on-demand acute prophylaxis and/or acute treatment of angioedema attacks, the affected individual continues to experience moderate-to severe attacks despite failure to achieve adequate control of HAE with on-demand (acute treatment or acute prophylaxis) therapy. The use of both attenuated androgens, plasma derived C1INH medications, berotralstat, and lanadelumab-flyo meet primary coverage criteria for use in long term prophylaxis given the existence of high-quality trials and long-term efficacy. **The individual must have used an acute therapy appropriately and per FDA guidelines prior to the authorization of prophylactic therapy.**

All drugs administered for continued treatment of HAE with abnormal C1INH deficiency/defect (Type I and Type II HAE) prophylactic treatments will require Prior Approval (PA). None of the below drugs are approved for HAE-nl-C1INH (previously Type III HAE).

The use of **pdC1INH (e.g., Haegarda)** and **lanadelumab (e.g., Takhzyro), and Berotralstat (e.g., Orladeyo)** are not covered under the medical benefit. Please check the member's pharmacy benefit for coverage. This policy applies to members whose plan utilizes AR BCBS

pharmacy and has **pdC1INH (e.g., Haegarda)**, **lanadelumab (e.g., Takhzyro), and Berotralstat (e.g., Orladeyo)** as formulary options.

- **pdC1INH concentrate (e.g., Cinryze)** is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult individuals.
- **pdC1INH concentrate (e.g., Haegarda)** is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult individuals**.**
- **Lanadelumab-flyo (e.g., Takhzyro)** is a plasma kallikrein inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of hereditary angioedema in individuals 12 years of age and older
- **Berotralstat (e.g., Orladeyo)** orally administered plasma kallikrein inhibitor for individuals 12 years and older for long-term prophylaxis
- **Attenuated androgens** (e.g., danazol per FDA approved labeling) meet member benefit certificate primary coverage criteria

Request for one of the above medications may be approved **initially for 6 months** if **ALL** the following criteria is met [Busse, GUIDELINES, 2020]:

1. Established diagnosis of C1INH deficient or dysfunctional HAE (previously type 1 HAE and type 2 HAE). **Confirmation is based on supportive clinical and physical findings combined with separate results (historical or current testing) of C4 and C1INH antigenic and functional activity.** Submission of the following documentation is expected:
    1. Low C1 protein (antigenic) (C1INH level).
    2. Low C1 esterase function (C1INH function)
    3. C4 level
    4. Documentation of familial history of HAE. **AND**
    5. Documentation of previous treatments attempted and failed. **AND**
    6. Medications known to cause angioedema (i.e., ACE inhibitors, estrogens, angiotensin II receptor blockers, DPP-4 inhibitors, fibrinolytic agents, sirolimus, everolimus, amiodarone, metoprolol, risperidone, paroxetine, etanercept, etc) have been evaluated and discontinued where appropriate.
    7. Documentation of weight for weight-based formulations.
    8. Serpine genetic analysis when there is no clear family history, prenatal testing or where biochemical C1INH test results are equivocal.

2. Medication is being used for prophylaxis against acute attacks of HAE for either of the following:
    1. Short-term prophylaxis prior to surgery or dental procedures; **OR**
    2. Long-term prophylaxis.

3. The individual is of appropriate age for the specific drug requested:
    1. **pdC1INH (e.g., Cinryze)** – 6 years or older
    2. **pdC1INH (e.g., Haegarda)** – 6 years and older
    3. **Landadelumab (e.g., Takhzyro)** – 12 years and older; not approved in pregnancy
    4. **Berotralstat (e.g., Orladeyo)** - ≥12 years old; not approved in pregnancy

4. Long-term prophylaxis is indicated only when a there is a failure to achieve adequate control of HAE with on-demand (acute treatment or acute prophylaxis) therapy alone [Zuraw, Farkas, 2UTD, 2021]

5. Has >1 moderate-to-severe attacks per month despite optimal management. There is a documented history of recurrent angioedema in the absence of concomitant urticaria with moderate to severe attacks such as airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, or painful facial distortion.

Concurrent review (approval an additional 6 months or 1 year)

1. Must meet all the initial criteria above.
2. Documentation must be submitted to show that there has been significant improvement/stability in severity and duration of attacks, and clinical documentation of functional improvement/stability as defined by at least a 50% decrease in frequency of HAE attacks after start of therapy,
3. For Landadelumab (e.g., Takhzyro) – If the individual is well controlled, (attack free) after 6 months, administration of lanadelumab (Takhzyro) every 4 weeks is to be performed.

Dosage and Administration [FDA, label; Busse, GUIDELINES, 2020]:

pdC1INH (e.g., Cinryze)
- Administer as 1,000 units every 3 to 4 days IV*
- Vials are 500 Units

*In rare circumstances with substantial documentation and trials of lower doses, doses up to 2,500 U (not exceeding 100 U/kg) every 3 or 4 days may be considered based on individual response. Doses at this level will require more frequent re-evaluation.

pdC1INH (e.g., Haegarda)
- Administer 60 IU/kg body weight SQ twice weekly (every 3 or 4 days).
- May be self-administered

Landelumab-flyo (e.g., Takhzyro)
- 300 mg SQ every 2 weeks.
- May be self-administered.
- A trial of 300 mg every 4 weeks is to be attempted after 6 months if the individual is well controlled on every 2-week dosing. (In World HAE guidelines)

Berotralstat (e.g., Orladeyo)
- 150 mg once daily; 110 mg daily dose available for those with toxicity requirement of dose reduction

The use of other FDA-approved products as prophylaxis for type I or type II HAE [including but not limited to danazol, stanozolol, etc.] meets primary coverage criteria when used as single agents and is approved under the pharmacy benefit per FDA-dosing guidelines; the use of tranexamic acid and epsilon aminocaproic acid as prophylaxis for type I or type II HAE also

meets primary coverage criteria when used as single agents under the pharmacy benefit when used according to the referenced guidelines including dosing [Busse, GUIDELINES, 2020].

Please refer to a separate policy on Site of Care or Site of Service Review (policy #2018030) for pharmacologic/biologic medications.

Does Not Meet Primary Coverage Criteria or Is Investigational For Contracts Without Primary Coverage Criteria

Use of pdC1INH (e.g., Cinryze), pdC1INH (e.g., Haegarda), Berotralstat (Orladeyo), and Landelumab-flyo (e.g., Takhzyro) does not meet member benefit certificate primary coverage criteria for all other indications including HAE-nl-C1INH.

For members with contracts without primary coverage criteria, the use of pdC1INH (e.g., Cinryze), pdC1INH (e.g., Haegarda), Berotralstat (e.g., Orladeyo), and Landelumab-flyo (e.g., Takhzyro) is considered **investigational and not medically necessary** for all other indications. Investigational services are specific contract exclusions in most member benefit certificates of coverage.

The combined use of pdC1INH (e.g., Cinryze), pdC1INH (e.g., Haegarda), Berotralstat (e.g., Orladeyo), and Landelumab-flyo (e.g., Takhzyro) does not meet primary coverage criteria that there be scientific evidence of effectiveness for any other indication including HAE-nl-C1INH.

The combined use of pdC1INH (e.g., Cinryze), pdC1INH (e.g., Haegarda), Berotralstat (e.g., Orladeyo), and Landelumab-flyo (e.g., Takhzyro) is considered **investigational. Investigational** services are specific contract exclusions in most member benefit certificates of coverage.