BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

HEREDITARY ANGIOEDEMA MEDICATION THERAPY: BERINERT® (plasma derived C1 esterase inhibitor) CINRYZE™ (plasma derived C1 esterase inhibitor) FIRAZYR® (icatibant, bradykinin B2 inhibitor) HAEGARDA® (C1 esterase inhibitor) Icatibant Acetate (bradykinin B2 inhibitor) ORLADEYO™ (berotralstat, kallikrein inhibitor) RUCONEST® (recombinant human C1 esterase inhibitor) SAJAZIR™ (icatibant, bradykinin B2 inhibitor) TAKHZYRO™ (lanadelumab-flyo, kallikrein monoclonal antibody)

This Pharmacy Coverage Guideline (PCG):

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope

- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance

- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

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Criteria:

Section A. Acute Attacks of Hereditary Angioedema (HAE):
BERINERT® (plasma derived C1 esterase inhibitor)
FIRAZYR® (icatibant, bradykinin B2 receptor antagonist)
Icatibant (bradykinin B2 receptor antagonist)
RUCONEST® (recombinant human C1 esterase inhibitor)
SAJAZIR™ (icatibant, bradykinin B2 receptor antagonist)

- **Criteria for initial therapy:** Berinert, Icatibant (generic, Firazyr, Sajazir), or Ruconest is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist
  2. Individual's age is consistent with FDA product label for the requested product
  3. Individual has a confirmed diagnosis of acute attacks of angioedema in hereditary angioedema (HAE) that requires therapy
  4. The individual has received and completed **ALL** the following **baseline tests** before initiation of treatment with continued monitoring of the individual as clinically appropriate:
     a. Two sets C1-inhibitor (done at least one month apart) showing low level and or function
     b. Two sets C4 (done at least one month apart) showing low level
  5. Individual does not experience urticaria or pruritus
  6. **ONE** of the following:
     a. Individual has trigger induced **acute** attacks of angioedema from a known precipitant (e.g., medical, surgical, or dental procedures) but does not require long-term prophylactic therapy
     b. Individual has frequent or severe **acute** attacks of angioedema despite use of long-term prophylactic therapy
  7. **Additional criteria for Firazyr (icatibant) only:** Documented failure, contraindication per FDA label, intolerance, or not a candidate for generic icatibant
  8. Individual will **NOT** be using combination therapy with another agent for the treatment of acute attacks of angioedema unless provider submits justification for combination therapy

  Initial approval duration: 6 months, for a quantity that is enough for treatment of two attacks with 1 refill

- **Criteria for continuation of coverage (renewal request):** Berinert, Icatibant (generic, Firazyr, Sajazir), or Ruconest is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered as continuation of therapy)**:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:
    a. Achieved and maintains at least a 50% reduction in the number of acute attacks of HAE
    b. Achieved and maintains at least a 30% in the duration of acute attacks of HAE
    c. Achieved and maintains at least a 60% reduction in the number of days with acute symptoms

3. For continuation of brand product: Individual has failure, contraindication per FDA label, or intolerance to equivalent generic product

4. Individual has been adherent with the medication

5. There is no evidence the individual has developed any significant unacceptable adverse drug effects from use of the agent that may exclude continued use

6. Individual will **NOT** be using combination therapy with another agent for treatment of acute attacks of angioedema unless provider submits justification for combination therapy

Renewal duration: 6 months, for a quantity that is enough for treatment of two attacks with 1 refill

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Section B. Prophylaxis of Attacks of Hereditary Angioedema (HAE): CINRYZE™ (plasma derived C1 esterase inhibitor) HAEGARDA® (plasma derived C1 esterase inhibitor) ORLADEYO™ (berotralstat, kallikrein inhibitor) TAKHZYRO™ (lanadelumab-flyo, kallikrein monoclonal antibody)

- **Criteria for initial therapy:** Cinryze, Haegarda, Orladeyo, or Takhzyro is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual's age is **ONE** of the following:
    a. **For Cinryze or Haegarda:** 6 years of age or older
    b. **For Orladeyo or Takhzyro:** 12 years of age or older

3. Individual has a confirmed diagnosis of frequent or severe attacks of angioedema in hereditary angioedema (HAE) that requires routine long-term prophylaxis with documentation of **ALL** of the following:
    a. Two sets C1-inhibitor (done at least one month apart) showing low level and or function
    b. Two sets C4 (done at least one month apart) showing low level

4. Individual does not experience urticarial or pruritus

5. Individual has failure, intolerance, contraindication per FDA label **or** they are not indicated to **EITHER** danazol or tranexamic acid or aminocaproic acid

6. **Additional criteria for Orladeyo only:**
    a. Individual does not have end stage renal disease (creatinine clearance of less than 15mL/min or estimated glomerular filtration rate less than 15 mL/min/m^2 or requiring hemodialysis)
    b. Individual is not on P-gp inducing agents such as rifampin, St. John's Wort, etc

7. Individual will **NOT** be using combination therapy with another agent for prevention/prophylaxis of attacks of HAE unless provider submits justification for combination therapy

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cinryze, Haegarda, Orladeyo, or Takhzyro is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered as continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:
    a. Achieved and maintains at least a 50% reduction in the number of HAE attacks
    b. Achieved and maintains at least a 30% in the duration of HAE attacks
    c. Achieved and maintains at least a 60% reduction in the number of days with symptoms

3. Individual has been adherent with the medication

4. **Additional criteria for Orladeyo only:**
    a. Individual does not have end stage renal disease (creatinine clearance of less than 15mL/min or estimated glomerular filtration rate less than 15 mL/min/m^2 or requiring hemodialysis)
    b. Individual is not on P-gp inducing agents such as rifampin, St. John's Wort, etc
    c. The requested dose is **NOT** greater than 150 mg daily

5. There is no evidence the individual has developed any significant unacceptable adverse drug effects from use of the agent that may exclude continued use

6. Individual will **NOT** be using combination therapy with another agent for prevention/prophylaxis of attacks of HAE unless provider submits justification for combination therapy

Renewal duration: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Description:

Hereditary angioedema (HAE) is an autosomal dominant disorder that results from C1 esterase inhibitor (C1INH) deficiency. C1INH regulates the activity of the complement component C1, the first step in the classic complement cascade.

HAE is a disease characterized by recurrent episodes of angioedema, **without** urticaria or pruritus, most often affecting the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. People with HAE can develop rapid painful swelling of the hands, feet, limbs, face, intestinal tract, or airway. Acute attacks of swelling can occur spontaneously, or can be triggered by stress, surgery, medical or dental procedures, or infection. The swelling is often self-limited and resolves in two to five days without treatment, however laryngeal involvement may cause fatal asphyxiation.

The swelling (i.e., angioedema) that occurs in HAE results from excessive production of bradykinin, a potent mediator of vasodilation. Bradykinin also has important vascular permeability-enhancing effects. During episodes of angioedema individuals with HAE have plasma bradykinin levels shown to be substantially higher than normal

HAE is caused by low levels or inadequate function of a plasma protein called C1-esterase inhibitor (C1INH) that is involved in regulating how some portions of the immune system and blood clotting pathways work. The absence or dysfunction of C1INH leads to an increase in bradykinin production. Bradykinin dilates blood vessels which is responsible for the symptoms of HAE.

The angioedema of HAE mediated by bradykinin does not respond to epinephrine, antihistamines, or glucocorticoids.

Therapeutic approaches for HAE include both “on-demand” treatments given at the onset of symptoms to abolish angioedema attacks as well as prophylactic treatment used to prevent or minimize attacks. All individuals require a readily available on-demand treatment to terminate unpredictable angioedema episodes. Short-term prophylaxis is use of medication given before a known trigger such as specific medical or dental procedures. In contrast, long-term prophylaxis is given to decrease the number and length of attacks. An integral part of treatment is trigger avoidance, if possible.

Therapies that are minimally effective or have no benefit at all in the treatment of acute angioedema in HAE include androgens, tranexamic acid, and treatments for allergic (histaminergic) angioedema such as epinephrine. Glucocorticoids and antihistamines are NOT effective for angioedema associated with disorders of C1INH and should not be given once the diagnosis of a C1INH disorder has been made.

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Definitions:

Androgens for routine prophylaxis of HAE attacks:

- Danazol
- Oxandrolone
- Oxymetholone
- Methyltestosterone

Antifibrinolytic agents for routine prophylaxis of HAE attacks:

- Tranexamic acid
- Aminocaproic acid

Other medications used for treating individuals with HAE:

Drug	Age	Route	Self-Administer	Dose	How supplied
Acute attacks HAE					
Plasma derived C1 esterase inhibitor: **Berinert**	5	IV	Yes	20 IU per kg ***A second dose can be given within 4 hours after the initial dose***	500 IU single-use vial
Recombinant C1 esterase inhibitor: **Ruconest**	13	IV	Yes	< 84 kg: 50 IU per kg ≥ 84 kg: 4200 units (2 vials) Max dose 4200 IU per dose ***No more than two doses in 24 hours, however a second dose rarely needed***	2100 IU single-use vial
Bradykinin B2 Receptor antagonist: **Firazyr (icatibant)** **Icatibant** **Sajazir (icatibant)**	18	SQ	Yes	30 mg injected to the abdominal area Additional doses can be given 6 hours after each attack. ***Max of three doses in 24 hours***	Single-dose, single-use, prefilled syringe with 30 mg per syringe packaged as single carton with one syringe or pack of three cartons each with one syringe
Kallikrein inhibitor: **Kalbitor (ecallantide)**	12	SQ	No	30 mg injected (3 doses of 10 mg (1 mL) each) given at three separate sites. ***A second dose can be given within 24 hours after the initial dose***	Three 10 mg/mL single-use vials packaged in a carton
Prophylaxis of HAE					
Plasma derived C1 esterase inhibitor: **Cinryze**	6	IV	Yes	12 years and older: 1,000 units every 3 or 4 days Up to 2,500 units (100 U/kg) every 3 or 4 days 6-11 years of age: 500 units every 3 or 4 days Up to 1,000 units every 3 or 4 days	500 IU single-use vial
Plasma derived C1 esterase inhibitor: **Haegarda**	6	SQ	Yes	60 IU per kg twice weekly (every 3 or 4 days)	2000 or 3000 IU single-use vials

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Oral kallikrein inhibitor: **Orladeyo (berotralstat)**	12	PO	Yes	150 mg orally once daily 110 mg orally once daily in patients with moderate or severe hepatic impairment; persistent GI events; and certain drug-drug interactions ***Additional doses or doses higher than 150 mg once daily are not recommended due to QT prolongation***	110 mg, 150 mg capsule
Kallikrein inhibitor monoclonal antibody: **Takhzyro (lanadelumab-flyo)**	12	SQ	Yes	300 mg every 2 or 4 weeks	300 mg single-use vial

Treatments used for acute episodes of hereditary angioedema (HAE):

	Laryngeal attack	Abdominal attack	Cutaneous attack	
			Extremities, trunk	Face, neck
C1INH concentrate (plasma derived or recombinant) given intravenously	Yes	Yes	Yes, unless swelling is extensively mild and not causing disability	Yes
Kalbitor (ecallantide)	Yes	Yes	Yes, unless extensively mild	Yes
Icatibant	Yes	Yes	Yes, unless extensively mild	Yes
Plasma (solvent / detergent treated or fresh frozen)	Yes, if first line therapies are not available	Yes, if first line therapies are not available	Yes, if severe and first line therapies are not available	Yes
Intubation, transfer to ICU	Yes, consider early intubation if above agents are not available	Not applicable	Not applicable	May be necessary if attack spreads to involve upper airway
Wait and see for spontaneous resolution	Not sufficient	Not recommended unless symptoms are mild and first line therapies are not available	Acceptable if mild	Not sufficient because angioedema can spread to involve airway

Choices of prophylactic agent for hereditary angioedema (HAE) in specific patient groups

Patient population	Preferred agents	Alternate agents	Agents to avoid	Other notes
Pre-pubertal children (male and female)	Plasma-derived C1-INH* (Cinryze, Haegarda)	Tranexamic acid (less effective but may be sufficient for mild disease)	Androgens¶	Lanadelumab and berotralstat not studied or approved for children under 12 years of age

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Adult women not considering pregnancy and post-pubertal girls	Plasma-derived C1-INH* (Cinryze, Haegarda) Lanadelumab (Takhzyro) Berotralstat (Orladeyo)	Tranexamic acid (less effective but may be sufficient for mild disease)	Androgens (multiple side effects and virilization)	
Adult men and post-pubertal boys	Plasma-derived C1-INH* (Cinryze, Haegarda) Lanadelumab Berotralstat	Tranexamic acid (less effective but may be sufficient for mild disease) Androgens (multiple side effects but virilization less of an issue for men)		
Pregnant and lactating women	Plasma-derived C1-INH* (Cinryze, Haegarda) – have the most safety data	Tranexamic acid (less effective but history of safe use)	Androgens Δ	Lanadelumab and berotralstat not recommended because they have not been studied in pregnancy
The choice of which long-term prophylactic agent to use is influenced both by patient characteristics (age, gender, pregnancy/lactation), as shown in the table, as well as regulatory requirements in different countries. * Plasma-derived C1-INH can be given subcutaneously or intravenously. Subcutaneous is more convenient and appears to be more effective based on preliminary evidence. ¶ Androgens are contraindicated in pre-pubertal children because they can cause premature closure of the growth plates. Δ Androgens are avoided in pregnancy because they can result in virilization of female fetuses, although if a woman with HAE is carrying a male fetus, androgens have been successfully used with supervision by an endocrinologist.				

Resources:

Berinert (C1 esterase inhibitor, human) product information, revised by CSL Behring GmbH 09-2021, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Cinryze (C1 esterase inhibitor, human) product information, revised by ViroPharma Biologics, LLC. 04-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Haegarda (C1 esterase inhibitor, human) product information, revised by CSL Behring GmbH 01-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Ruconest (C1 esterase inhibitor, recombinant) product information, revised by Pharming Healthcare, Inc. 04-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Firazyr (icatibant) product information, revised by Takeda Pharmaceuticals America, Inc. 10-2021, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Sajazir (icatibant) product information, revised by Cycle Pharmaceuticals Ltd-UK. 05-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Icatibant product information, revised by Teva Pharmaceuticals USA, Inc. 04-2020, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Orladeyo (berotralstat) product information, revised by BioCryst Pharmaceuticals, Inc. 03-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Takhzyro (lanadelumab-flyo) product information, revised by Takeda Pharmaceuticals America. 02-2022, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Kalbitor (ecallantide) product information, revised by Takeda Pharmaceuticals America, Inc. 11-2021, at DailyMed http://dailymed.nlm.nih.gov. Accessed September 17, 2022.

Zuraw B, Farkas H. Hereditary angioedema (due to C1 inhibitor deficiency): Pathogenesis and diagnosis. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated February 08, 2022. Accessed September 19, 2022.

Zuraw B, Farkas H. Hereditary angioedema: Acute treatment of angioedema attacks. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated July 19, 2021. Accessed September 19, 2022.

Zuraw B, Farkas H. Hereditary angioedema: Short-term prophylaxis before procedures or stressful events to prevent angioedema episodes. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated March 21, 2022. Accessed September 19, 2022.

Zuraw B, Farkas H. Hereditary angioedema (due to C1 inhibitor deficiency): General care and long-term prophylaxis. In: UpToDate, Saini S, Feldweg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated August 01, 2022. Accessed September 19, 2022.