BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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HEREDITARY ANGIOEDEMA MEDICATION THERAPY
FIRAZYR® (icatibant, bradykinin B2 inhibitor) subcutaneous
HAEGARDA® (C1 esterase inhibitor) subcutaneous
TAKHZYRO™ (lanadelumab-flyo, kallikrein monoclonal antibody) subcutaneous

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602)

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864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Section A. Acute Attacks of Hereditary Angioedema (HAE):

FIRAZYR® (icatibant, bradykinin B2 receptor antagonist)

Criteria:

- **Criteria for initial therapy:** Firazyr 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 is 18 years of age or older

  3. A confirmed diagnosis of acute attacks of angioedema in hereditary angioedema (HAE) that requires on-demand therapy with **ALL** of the following:
     - Low C1-inhibitor function
     - Low C4 level
     - No urticarial or pruritus

  4. **ONE** of the following:
     - 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
     - Individual has frequent or severe **acute** attacks of angioedema despite use of long-term prophylactic therapy (See Definitions section for list of agents)

  5. No dual therapy with another injectable agent for treatment of acute attacks of angioedema in HAE unless provider submits justification for dual therapy

  6. No previous life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components

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

- **Criteria for continuation of coverage (renewal request):** Firazyr is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  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
     - Response is defined as: **ONE** of the following:
       - Achieved and maintains at least a 50% reduction in the number of acute attacks of HAE

- Achieved and maintains at least a 30% in the duration of acute attacks of HAE
- Achieved and maintains at least a 60% reduction in the number of days with acute symptoms

3. No dual therapy with another injectable agent for treatment of acute attacks of angioedema in HAE unless provider submits justification for dual therapy

4. No evidence the individual developed any contraindications or significant unacceptable adverse drug effects that may exclude continued use

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

Section B. Prophylaxis of Attacks of Hereditary Angioedema (HAE):

HAEGARDA® (plasma derived C1 esterase inhibitor)
TAKHZYRO™ (lanadelumab-flyo, kallikrein monoclonal antibody)

Criteria:

- **Criteria for initial therapy:** Haegarda, 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 is **ONE** of the following:
   - **For Haegarda:** 12 years of age or older
   - **For Takhzyro:** 12 years of age or older

3. 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:
   - Low C1-inhibitor function
   - Low C4 level
   - No urticarial or pruritus

4. Individual has failed, or is intolerant to an adverse effect, or has a contraindication such that the individual is unable to use long-term prophylactic therapy with **EITHER** danazol or tranexamic acid or aminocaproic acid **or** they are not indicated

5. No dual therapy with another injectable agent for prevention/prophylaxis of attacks of HAE unless provider submits justification for dual therapy

6. No previous life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components

Initial approval duration: 6 months

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- **Criteria for continuation of coverage (renewal request):** Haegarda or Takhzyro is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  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
     - Response is defined as: **ONE** of the following:
       - Achieved and maintains at least a 50% reduction in the number of HAE attacks
       - Achieved and maintains at least a 30% in the duration of HAE attacks
       - Achieved and maintains at least a 60% reduction in the number of days with symptoms
  3. Individual has been adherent with the medication

  4. No dual therapy with another injectable agent for prevention/prophylaxis of attacks of HAE unless provider submits justification for dual therapy

  5. No evidence the individual developed any contraindications or significant unacceptable adverse drug effects that may exclude continued use

  Renewal duration: 12 months

- Firazyr, Haegarda, or Takhzyro for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

Treatment with dosing or frequency outside the FDA-approved dosing and frequency

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.

The three groups of agents used for long-term prophylaxis are: attenuated androgens, antifibrinolytics, and regularly injected C1INH. Attenuated androgens and C1INH concentrate are both highly effective; antifibrinolytics are usually well-tolerated but may be less effective than androgens or C1INH.

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.

Definitions:

Oral agents for HAE:

Androgens for routine prophylaxis of HAE attacks:
- Danazol
- Oxandrolone
- Oxymetholone
- Methyltestosterone

Antifibrinolytic agents for routine prophylaxis of HAE attacks:
- Tranexamic acid
- Aminocaproic acid

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Injectable medications used for treating individuals with hereditary angioedema (HAE):

Drug	Age	Route	Self-Administer	Dose	How supplied
Acute attacks HAE					
Berinert (pdC1INH)	5	IV	Yes	20 IU per kg	500 IU single-use vial
Firazyr (icatibant) [bradykinin B2 RA]	18	SQ	Yes	30 mg injected to the abdominal area Second dose needed in about 10% of patients and can be given 6 hours after first. ***Max of three doses in 24 hours***	Three cartons, each with one single-dose, single-use, prefilled syringe with 30 mg per syringe
Kalbitor (ecallantide) [kallikrein inhibitor]	12	SQ	No	30 mg injected (3 doses of 10 mg 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
Ruconest (rhC1INH)	13	IV	Yes	50 IU per kg; Max dose 4200 IU ***Second dose rarely needed, no more than two doses in 24 hours***	2100 IU single-use vial
Prophylaxis of HAE					
Cinryze (pdC1INH	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
Haegard (pdC1INH)	12	SQ	Yes	60 IU per kg every 3 or 4 days	2000 or 3000 IU single-use vials
Takhzyro (lanadelumab-flyo) [plasma kallikrein inhibitor]	12	SQ	Yes	300 mg every 2 or 4 weeks	300 mg single-use vial

Resources:

Berinert (C1 esterase inhibitor, human) product information accessed 01-21-20 at DailyMed

Cinryze (C1 esterase inhibitor, human) product information accessed 01-21-20 at DailyMed

Cyklokapron (tranexamic acid) product information accessed 01-21-20 at DailyMed

Firazyr (icatibant) product information accessed 01-21-20 at DailyMed

Haegarda (C1 esterase inhibitor, human) product information accessed 01-21-20 at DailyMed

Kalbitor (ecallantide) product information accessed 01-21-20 at DailyMed

Ruconest (C1 esterase inhibitor, recombinant) product information accessed 01-21-20 at DailyMed

Takhzyro (lanadelumab-flyo) product information accessed 01-21-20 at DailyMed

UpToDate: Hereditary angioedema: Treatment of acute attacks. Current through Jul 2018

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UpToDate: Hereditary angioedema: general care and long-term prophylaxis. Current through Jul 2018

UpToDate: Hereditary angioedema: Epidemiology, clinical manifestations, exacerbating factors, and prognosis. Current through Jul 2018

UpToDate: Hereditary angioedema: Pathogenesis and diagnosis. Current through Jul 2018

Maurer M, Magerl M, Ansotegui I, et al.: The International WAO/EAACI Guideline for the management of Hereditary Angioedema – The 2017 revision and update. Allergy 2018; 73:1575-1596

Farkas H, Martinez-Saguer I, Bork K, et al.: International consensus on the diagnosis and management of pediatric patients with Hereditary Angioedema with C1 inhibitor deficiency. Allergy 2017: 300-313. DOI:10.1111/all.13001

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Bowen T. Hereditary Angioedema: Beyond International Consensus – circa 2010 – The Canadian Society of Allery and Clinical Immunology Dr. David McCourtie Lecture. Allergy, Asthma & Clinical Immunology 2011, 7:1

Bowen T, Cicardi M, Farkas H, et al.: 2010 International Consensus algorithm for the diagnosis, therapy, and management of Hereditary Angioedema. Allergy, Asthma & Clinical Immunology 2010, 6:24

Temino VM and Peebles RS. The Spectrum and Treatment of Angioedema. Am J Med 2008; 121:282-286