

Clinical Policy: Respiratory Agents: Hereditary Angioedema

Reference Number: OH.PHAR.PPA.86

Effective Date: 01/01/2020

Last Review Date: 01/01/2020

Line of Business: Medicaid

[Coding Implications](#)
[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

RESPIRATORY AGENTS: HEREDITARY ANGIOEDEMA

CLINICAL PA REQUIRED "PREFERRED"	PA REQUIRED "NON-PREFERRED"
HAEGARDA® (C1 esterase inhibitor, plasma derived)	BERINERT® (C1 esterase inhibitor, plasma derived)
RUCONEST® (C1 esterase inhibitor, recombinant)	CINRYZE® (C1 esterase inhibitor, plasma derived)
TAKHZYRO™ (lanadelumab-flyo)	ICATIBANT ACETATE (Generic for Firazyr®)
	KALBITOR® (ecallantide)

Description

The following medications used in the treatment of hereditary angioedema (HAE) require clinical prior authorization: human C1 esterase inhibitors (Haegarda®, Cinryze®, Berinert®), recombinant C1 esterase inhibitors (Ruconest®), ecallantide (Kalbitor®), lanadelumab-flyo (Takhzyro™), and icatibant acetate (Firazyr®)

FDA Approved Indication(s)

- Takhzyro is a kallikrein inhibitor indicated for prophylaxis to prevent attacks of HAE in patients 12 years and older
- Kalbitor is a kallikrein inhibitor indicated for acute attacks of HAE in patients 12 years and older
- Firazyr is a bradykinin B2 receptor antagonist indicated for treatment of acute attacks of HAE in adults 18 years of age or older

C1 esterase inhibitors are indicated for:

- Treatment of acute attacks of HAE in adolescent and adult patients [*Berinert and Ruconest only*]
- Routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE [*Cinryze and Haegarda only*]

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Buckeye Health Plan, an affiliate of Centene Corporation®, that Berinert, Ruconest, Haegarda, Cinryze, Takhzyro, Kalbitor, and Firazyr are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Hereditary Angioedema (must meet all):

1. Diagnosis of HAE confirmed by one of the following (a or b):

- a. Low C4 level and low C1-INH antigenic or functional level (*see Appendix D*);
- b. Normal C4 level and normal C1-INH levels, and both of the following (i and ii):
 - i. History of recurrent angioedema (without urticarial) within the past 6 months
 - ii. Family history of angioedema
2. Member has history of recurrent episodes of abdominal pain and vomiting within the past 6 months
3. Member has history of laryngeal edema within the past 180 days
4. Prescribed by or in consultation with a/an hematologist, allergist, or immunologist;
5. Member meets one of the following (a, b, c, d, or e):
 - a. Age \geq 5 years for Berinert;
 - b. Age \geq 6 years for Cinryze;
 - c. Age \geq 12 years for Haegarda, Takhzyro, Kalbitor;
 - d. Age \geq 13 years for Ruconest;
 - e. Age \geq 18 years for Firazyr;
6. Member meets one of the following (a, b, or c):
 - a. For treatment of acute HAE attacks, meets one of the following (i or ii):
 - i. Request is for Ruconest and member does not experience laryngeal attacks;
 - ii. Request is for Berinert, Kalbitor, or Firazyr and member is unable to use Ruconest due to allergy, contraindication, drug interaction, history of unacceptable/toxic side effects to Ruconest, or there has been one episode of angioedema during use of Ruconest.
 - b. For long-term prophylaxis of HAE attacks, meets all of the following (i and ii):
 - i. Request is for Haegarda or Takhzyro; OR Request is for Cinryze and member is unable to use Haegarda or Takhzyro due to allergy, contraindication, drug interaction, history of unacceptable/toxic side effects, or there has been one episode of angioedema during use of Haegarda or Takhzyro.
 - ii. Member experiences more than one severe event per month OR is disabled more than five days per month OR has a history of previous airway compromise;
 - c. For short-term prophylaxis of HAE attacks, meets both of the following (i and ii):
 - i. Request is for Haegarda; OR Request is for a different plasma-derived C1 esterase inhibitor (Berinert or Cinryze) and member is unable to use Haegarda due to allergy, contraindication, drug interaction, history of unacceptable/toxic side effects, or there has been one episode of angioedema during use of Haegarda
 - ii. Member requires major dental work or surgical procedure;
7. Member is not using the requested product in combination with another FDA-approved product for the same indication (e.g., using both Berinert and Firazyr[®] for acute HAE attacks);
8. Dose does not exceed:
 - a. Berinert: 20 IU/kg of body weight per single dose, up to 2 doses administered in a 24-hour period;
 - b. Cinryze: 2,500 units (5 vials) every 3 to 4 days;

- c. Haegarda: 60 IU/kg of body weight per dose twice weekly;
- d. Ruconest: 4,200 IU per single dose, up to 2 doses administered in a 24-hour period.
- e. Takhzyro: 300 mg every 2 weeks
- f. Kalbitor: 30 mg [1 carton (3 vials)] per dose, with up to 2 doses administered in a 24-hour period
- g. Firazyr: 30 mg (1 syringe) per dose, with up to 3 doses administered in a 24-hour period

Approval duration for short-term prophylaxis: 1 month

Approval duration: 12 months

II. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

- CI-INH: C1 esterase inhibitor
- FDA: Food and Drug Administration
- HAE: Hereditary angioedema
- PA: Prior Authorization

Appendix B: Therapeutic Alternatives

Refer to tertiary resources such as UpToDate or Clinical Pharmacology

Appendix C: Contraindications/Boxed Warnings

Refer to tertiary resources such as UpToDate or Clinical Pharmacology

Appendix D: General Information

Diagnosis of HAE:

- There are two classifications of HAE: HAE with C1-INH deficiency (further broken down into Type 1 and Type II) and HAE of unknown origin (also known as Type III).
- In both Type 1 (~85% of cases) and Type II (~15% of cases), C4 levels are low. C1-INH antigenic levels are low in Type I while C1-INH functional levels are low in Type II. Diagnosis of Type I and II can be confirmed with laboratory tests. Reference ranges for C4 and C1-INH levels can vary across laboratories (see below for examples); low values confirming diagnosis are those which are below the lower end of normal.

Laboratory Test & Reference Range	Mayo Clinic	Quest Diagnostics	LabCorp
C4	14-40 mg/dL	16-47 mg/dL	9-36 mg/dL
C1-INH, antigenic	19-37 mg/dL	21-39 mg/dL	21-39 mg/dL
C1-INH, functional	Normal: > 67%	Normal: ≥ 68%	Normal: > 67%

Laboratory Test & Reference Range	Mayo Clinic	Quest Diagnostics	LabCorp
	Equivocal: 41-67% Abnormal: < 41%	Equivocal: 41-67% Abnormal: ≤ 40%	Equivocal: 41-67% Abnormal: < 41%

- Type III, on the other hand, presents with normal C4 and C1-INH levels. Some patients have an associated mutation in the FXII gene, while others have no identified genetic indicators. Type III is very rare (number of cases unknown), and there are no laboratory tests to confirm the diagnosis. Instead, the diagnosis is clinical and supported by recurrent episodes of angioedema with a strong family history of angioedema.

IV. Dosage and Administration

Refer to tertiary resources such as UpToDate or Clinical Pharmacology

V. Product Availability

Refer to tertiary resources such as UpToDate or Clinical Pharmacology

VI. References

Refer to manufacturer prescribing information

Reviews, Revisions, and Approvals	Date	P&T Approval Date
New policy	01.01	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

CLINICAL POLICY

Respiratory Agents: Hereditary Angioedema



contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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