MEDICAL POLICY STATEMENT

Original Effective Date	Next Annual Review Date	Last Review / Revision Date
12/12/2014	04/21/2016	04/21/2015

Policy Name	Policy Number
Hereditary Angioedema and Pharmacotherapy	**SRx-0020**

Medical Policy Statements prepared by CSMG Co. and its affiliates (including CareSource) are derived from literature based on and supported by clinical guidelines, nationally recognized utilization and technology assessment guidelines, other medical management industry standards, and published MCO clinical policy guidelines. Medically necessary services include, but are not limited to, those health care services or supplies that are proper and necessary for the diagnosis or treatment of disease, illness, or injury and without which the patient can be expected to suffer prolonged, increased or new morbidity, impairment of function, dysfunction of a body organ or part, or significant pain and discomfort. These services meet the standards of good medical practice in the local area, are the lowest cost alternative, and are not provided mainly for the convenience of the member or provider. Medically necessary services also include those services defined in any Evidence of Coverage documents, Medical Policy Statements, Provider Manuals, Member Handbooks, and/or other policies and procedures.

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For Medicare plans please reference the below link to search for Applicable National Coverage Descriptions (NCD) and Local Coverage Descriptions (LCD):

A. SUBJECT

Hereditary Angioedema and Pharmacotherapy

- C1-INH concentrates
  - C1 Esterase Inhibitor [human] (Berinert®)
  - C1 Esterase Inhibitor [human] (Cinryze®)
  - C1 Esterase Inhibitor [recombinant] (Ruconest®)
- Kallikrein inhibitors
  - Ecallantide (Kalbitor®)
- Bradykinin receptor antagonists
  - Icatibant (Firazyr®)

B. BACKGROUND

Hereditary angioedema (HAE) is clinically defined as episodic severe swelling, most commonly in the mucosal tissues of the upper airway and gastrointestinal tract, as well as the limbs and face. It can last 48-72 hours and does not involve urticaria, redness, or pruritus. It is rare; however, this autosomal dominantly inherited disorder can cause fatal asphyxiation if swelling involves the laryngeal area.

The etiology of the disease involves a mutation in the SERPING1 gene that is responsible for encoding the C1 esterase inhibitor (C1-INH) protein that is involved in controlling the complement system; this unregulated compliment system results in an increase in bradykinin, thereby, increasing vascular permeability. There are three subtypes of HAE. Type I HAE occurs when levels of C1-INH proteins are reduced while Type 2 HAE is characterized by adequate, but abnormally functioning, C1-INH. The third subtype of HAE is rare and occurs when there is a defect in the factor XII gene but C1-INH are normal; much is unknown about the etiology of this third subtype. This Medical Policy will focus on Type I and Type II HAE.

Pharmacotherapy can be used to acutely treat and prevent HAE. There are three distinct medication classes used to treat acute HAE attacks which include C1-INH concentrates, kallikrein inhibitors, and bradykinin receptor antagonist. All of the agents in each class have been shown to be efficacious and safe when treating acute HAE attacks. Prophylaxis can be short-term or long-term. Long-term prophylaxis with C1-INH ([human] Cinryze®) in patients with inadequate acute treatment as defined by more than two acute HAE attacks per month can be used. Short-term prophylactic therapy can be used if patients with diagnosed HAE undergo dental, medical, or surgical procedures that are expected to trigger a HAE attack.

Pharmacotherapy for HAE:

- C1-INH concentrates: Exogenous replacement of C1-INH corrects the underlying pathophysiology of HAE by replenishing the deficient or malfunctioning proteins. Pharmacologically increasing the plasma levels of C1-INH can be achieved via intravenous administration of either human plasma-derived C1-INH or recombinant C1-INH. The C1-INHs are commonly used for the acute emergency management of HAE and include [human] Berinert® and [recombinant] Ruconest®. For long-term prophylaxis against HAE, [human] Cinryze® can be administered. Short-term prophylactic therapy can be used if patients with diagnosed HAE undergo dental, medical, or surgical procedures that are expected to trigger a HAE attack. Long-term prophylactic therapy with C1-INH agents given every 3-4 days can be administered to diagnosed HAE patients when considering their frequency & severity of HAE attacks, quality of life, availability of resources, and inadequate control with acute treatment.

  This drug class is the preferred treatment for children, pregnant or breastfeeding women.

- Kallikrein inhibitors: This class of medication targets the enzyme kallikrein which cleaves kininogen to form bradykinin. This thereby blocks the production of bradykinin which is the primary mediator of HAE. Ecallantide (Kalbitor®) is only FDA approved medication in this class and it is self-administered subcutaneously to treat acute HAE attacks in patients 12 years and older

- Bradykinin receptor antagonists: This medication class provides a selective competitive antagonist which blocks the bradykinin B_2 receptor, thereby, inhibiting the physiological effects of bradykinin such as swelling, inflammation, and pain. Icatibant (Firazyr®) is only agent in this class and it can be self-administered subcutaneously for acute HAE attacks in patients 18 years and older.

C. DEFINITIONS

N/A

D. POLICY

CareSource will approve the long-term, routine prophylaxis use of [human] Cinryze® and consider its use as medically necessary when ALL the following criteria have been met:

- A diagnosis of Type I or Type II HAE has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology.
- Clinical documentation of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range (for Type I and Type II only).
- Clinical documentation of **ONE** of the following:
  - Family history of HAE
  - Normal level of serum C1q antigenic protein based on the laboratory's normal reference range.

- Patient has been evaluated for potential treatable triggers of HAE attacks & is maximally managed with respect to avoiding those triggers
- A history of attacks that significantly disrupt normal daily activities despite symptomatic treatment with swelling of the face, throat or GI tract
- Previous treatment with at least one of the below was ineffective, not tolerated or all are contraindicated:
  - Androgen therapy, tanexamic acid or aminocaproic acid

Firazyr may be considered medically necessary for the acute treatment of hereditary angioedema (HAE) attacks when there is a confirmed diagnosis of HAE and criteria below are met:

- A diagnosis of Type I, Type II or Type III HAE has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology
- Clinical documentation of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range (for Type I and Type II only)
- Clinical documentation of **ONE** of the following:
  - Family history of HAE
  - Normal level of serum C1q antigenic protein based on the laboratory's normal reference range
  - FXII mutation (Type III only)

Berinert may be considered medically necessary for the acute treatment of hereditary angioedema (HAE) attacks when there is a confirmed diagnosis of HAE and criteria below are met:

- A diagnosis of Type I or Type II HAE has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology
- Clinical documentation of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range (for Type I and Type II only)
- Clinical documentation of **ONE** of the following:
  - Family history of HAE
  - Normal level of serum C1q antigenic protein based on the laboratory's normal reference range

Kalbitor may be considered medically necessary for the acute treatment of hereditary angioedema (HAE) attacks when there is a confirmed diagnosis of HAE and criteria below are met:

- A diagnosis of Type I, Type II or Type III HAE has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology
- Clinical documentation of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range (for Type I and Type II only)
- Clinical documentation of **ONE** of the following:
  - Family history of HAE
  - Normal level of serum C1q antigenic protein based on the laboratory's normal reference range
  - FXII mutation (Type III only)

Ruconest may be considered medically necessary for the acute treatment of hereditary angioedema (HAE) attacks when there is a confirmed diagnosis of HAE and criteria below are met:

- A diagnosis of Type I or Type II HAE has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology

- Clinical documentation of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range (for Type I and Type II only)
- Clinical documentation of **ONE** of the following:
  - Family history of HAE
  - Normal level of serum C1q antigenic protein based on the laboratory's normal reference range

  AND
- Treatment with **ONE** of the following is contraindicated, ineffective, or not tolerated:
  - Ecallantide (Kalbitor)
  - Icatibant (Firazyr)
  - Plasma-derived C1 esterase inhibitor (Berinert)

Appendix A: FDA approved treatments for acute attacks of HAE

Drug	Usual Dose and Route	FDA Approved Age Range	FDA Approved for the Treatment of Laryngeal Attacks	Approved for Self-Administration
Cinryze (C1 Esterase Inhibitor [Human])	1000IU intravenously every 3-4 days. Max Adult and Ped Daily Dose – 1000IU	Age 12 and older	Yes	Yes
Kalbitor (ecallantide)	30 mg injected subcutaneously in three 10 mg injections; Max Adult and Ped Daily – 60 mg	Age 12 and older	Yes	No
Firazyr (icatibant)	30 mg injected subcutaneously to the abdominal area; Max Daily Adult – 90 mg	Age 18 and older	Yes	Yes
Berinert (pdC1-INH)	20 IU per kg injected intravenously; Max Daily Adult – 2,300units Max Daily Ped – 1,400IU	Age 13 and older	Yes	Yes

Ruconest (rhC1-INH)	50 IU per kg injected intravenously; Max Daily Adult dose - 4200IU Max Daily Ped Dose – 3,500IU	Age 13 and older	No	Yes

IU = international units

For Medicare NCD: CMS Publication 100-3, Medicare National Coverage Determinations, Chapter 1, Section 140.2
https://www.cms.gov/manuals/downloads/ncd103c1_Part2.pdf

If there is no NCD or LCD present, reference the CareSource Policy for coverage.

CONDITIONS OF COVERAGE

HCPCS	J0597	Berinert
	J0598	Cinryze
	J1290	ecallantide
	J1744	icatibant
CPT	C9445	Ruconest

PLACE OF SERVICE
Office, Outpatient, Home
*****Preferred place of service is in the home***
This medication can be self-administered and can be billed through the pharmacy benefit.
NOTE: CareSource supports administering inject able medications in various setting, as long as those services are furnished in the most appropriate and cost effective setting that are supportive of the patient's medical condition and unique needs and condition. The decision on the most appropriate setting for administration is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of the specific medication.

AUTHORIZATION PERIOD
Approved authorizations are valid for 1 year. Continued treatment may be considered when the member has shown biological response to treatment. ALL authorizations are subject to continued eligibility.

E. REVIEW/REVISION HISTORY

Date Issued:	12/12/2014
Date Reviewed:	12/12/2014, 03/23/2015, 04/21/2015
Date Revised:	03/23/2015 - Revisions to include AllMed review for HAE and change to quantity limits within policy. 04/21/2015 – Added Appendix A and change of criteria for Firazyr.

F. REFERENCES

1. Cinryze [package insert]. Lexington, MA: ViroPharma Biologics Inc; Revised September 2014.
2. Craig T, Pursun EA, Bork K, Bowen T, et al. World Allergy Organization Guideline for the Management of Hereditary Angioedema. *WAO J*. 2012; 5:182-199.

3. Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired
4. angioedema. Ann Allergy Asthma Immunol. 2012;109:395-402.
5. Lumry W. Management and Prevention of Hereditary Angioedema Attacks. Am J Manag Care. 2013;19:S111-S118.
6. Riedl, MA, Bernstein, JA, Li, H, et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2014 Feb;112(2):163-9 e1. PMID: 24468257
7. Zuraw BL, Bernstein JA, Lang DM, ed. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitorassociated angioedema. J Allergy Clin Immunol. 2013;131:1491-3.
8. Berinert® [package insert]. Marburg, Germany: CSL Behring; Revised February 2015.
9. Kalbitor® [package insert]. Burlington, MA: Dyax Corp.; Revised September 2014.
10. Ruconest® [package insert]. Raleigh, NC: Salix Pharmaceuticals.; Revised February 2015.
11. Firazyr® [package insert]. Lexington, MA: Shire Orphan Therapeutics; Revised August 2013.

"This guideline contains custom content that has been modified from the standard care guidelines and has not been reviewed or approved by MCG Health, LLC."

The medical Policy Statement detailed above has received due consideration as defined in the Medical Policy Statement Policy and is approved.

Independent Medical Review – AllMed 03/23/2015