Medical Policy:

Cinryze® (C1 esterase inhibitor, human) intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.75	March 11, 2025	

Length of Authorization

Coverage will be provided for 12 months and may be renewed.

Dosing Limits [Medical Benefit]

Max Units (per dose and over time):

- 2,000 billable units per 30 days

Guideline

I. Initial Approval Criteria

1. <u>Prophylaxis against angioedema attacks of Hereditary Angioedema (HAE) †</u>

A. Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics; **AND**

B. Patient must be at least 6 years of age; **AND**

C. Not used in combination with C1 inhibitor prophylaxis (e.g., Haegarda or Takhzyro); **AND**

D. Confirmation the patient is avoiding the following possible triggers for HAE attacks:

i. Estrogen-containing oral contraceptive agents AND hormone replacement therapy; **AND**
ii. Antihypertensive agents containing ACE inhibitors; **AND**
iii. Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin); **AND**
iv. Neprilysin inhibitors (e.g., sacubitril); **AND**

E. Patient has one of the clinical presentations listed below consistent with a HAE subtype§, which must be confirmed by repeat blood testing (treatment for acute attack should not be delayed for confirmatory testing); **AND**

i. Patient is receiving treatment as short-term HAE prophylaxis prior to a procedure (i.e. dental or medical procedure); **OR**

ii. Patient has a history of one of the following criteria for long-term HAE prophylaxis:

a. History of two (2) or more severe HAE attacks per month (i.e., airway swelling, debilitating cutaneous or gastrointestinal episodes)

b. Patient is disabled more than 5 days per month by HAE

c. History of at least one laryngeal attack caused by HAE

1. Treatment of patient with "on-demand" therapy (i.e., Kalbitor, Firazyr, Ruconest, or Berinert) did not provide satisfactory control or access to "on-demand therapy" is limited

HAE I (C1-Inhibitor deficiency) §
• Low C1 inhibitor (C1-INH) antigenic level (C1-INH antigenic level below the lower limit of normal as defined by the laboratory performing the test); **AND** • Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test); **AND** • Low C1-INH functional level (C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test); **AND** o Patient has a family history of HAE; **OR** o Acquired angioedema has been ruled out (i.e., patient onset of symptoms occur prior to 30 years of age, normal C1q levels, patient does not have underlying disease such as lymphoma or benign monoclonal gammopathy [MGUS], etc.)
HAE II (C1-Inhibitor dysfunction)
• Normal to elevated C1-INH antigenic level; **AND** • Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test); **AND** • Low C1-INH functional level (C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)
HAE with normal C1INH (formerly known as HAE III)
• Prophylaxis for HAE with normal C1-INH is not routinely recommended and will be evaluated on a case by case basis o Prior to consideration of long-term prophylaxis, the patient must have demonstrated: ▪ An inadequate response or intolerance to an adequate trial of prophylactic therapy with an antifibrinolytic agent (e.g., tranexamic acid (TXA) or aminocaproic acid) and/or a 17αalkylated androgen (e.g., danazol) unless contraindicated. Female patients may derive additional benefit from progestins; **AND** ▪ Response to therapy from an agent indicated for the treatment of acute attacks (i.e., C1 ▪ esterase inhibitor, icatibant, ecallantide, etc.)

† FDA Approved Indication(s)

II. Renewal Criteria

1. Patient continues to meet the criteria in Initial Criteria; **AND**
2. Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe hypersensitivity reactions, serious thrombotic events, laryngeal attacks, etc.; **AND**
   A. Significant improvement in severity and duration of attacks have been achieved and sustained; **OR**
   B. Patient requires dose titration due to an inadequate response to therapy (> 1.0 HAE attack/month, regardless of severity/duration)

Dosage/Administration

Indication	Dose
Hereditary Angioedema (HAE)	**Adult/adolescents (≥12 years old)** 1,000 units by intravenous injection every 3 to 4 days – *For patients who have not responded adequately to initial dosing, doses up to 2,500 U (not exceeding 100 U/kg) every 3 or 4 days may be considered based on individual patient response.* **Pediatric patients (6 to 11 years old)** 500 units by intravenous injection every 3 to 4 days – *The dose may be adjusted according to individual patient response, up to 1,000 U every 3 to 4 days.*

Limitations/Exclusions

Cinryze® (C1 Esterase Inhibitor Human) is not considered medically necessary for indications other than those listed above due to insufficient evidence of therapeutic value.

Applicable Procedure Codes

Code	Description
J0598	Injection, C1 esterase inhibitor (human), Cinryze, 10 units

Applicable NDCs

Code	Description
42227-0081-xx	Cinryze 500 units single-dose vial

ICD-10 Diagnoses

Code	Description
D84.1	Defects in the complement system

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	3/11/2025	Dosing Limits updated from 2,500 to 2,000. Updated HAE I criteria. Removed -Patient has one of the following clinical presentations consistent with HAE subtype, which must be confirmed by repeat blood testing.

		Replaced with E. Patient has one of the clinical presentations listed below consistent with a HAE subtype§, which must be confirmed by repeat blood testing (treatment for acute attack should not be delayed for confirmatory testing); AND Patient is receiving treatment as short-term HAE prophylaxis prior to a procedure (i.e. dental or medical procedure); OR
EmblemHealth & ConnectiCare	3/22/2024	Annual Review: No criteria changes
EmblemHealth & ConnectiCare	7/20/2023	Annual Review: Updated dosing limits: removed "1,000 billable units per 30 days" Added "2,500 billable units per 30 days" Prophylaxis against angioedema attacks of Hereditary Angioedema (HAE) Initial Criteria: Added "Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin); AND Neprilysin inhibitors (e.g., sacubitril); AND" to possible triggers for HAE attacks
EmblemHealth & ConnectiCare	4/06/2022	Transferred policy to new template
EmblemHealth & ConnectiCare	1/1/2020	Annual review

References

1. Cinryze [package insert]. Exton, PA; ViroPharma Biologics, Inc; June 2018. Accessed December 2019.
2. Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 International Consensus Algorithm For the Diagnosis, Therapy, and Management of Hereditary Angioedema. J Allergy Clin Immunol. 2004 Sep;114(3):629-37.
3. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol. Mar-Apr 2009;19(2):147-151.
4. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6(1):24.
5. Craig T, Aygören-Pürsün E, Bork K, et al. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 2012 Dec;5(12):182-99.
6. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005;139(3):379.
7. Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 International Consensus Algorithm For the Diagnosis, Therapy, and Management of Hereditary Angioedema. J Allergy Clin Immunol. 2004 Sep;114(3):629-37.
8. Betschel S, Badiou J, Binkley K, et al. Canadian hereditary angioedema guideline. Asthma Clin Immunol. 2014 Oct 24;10(1):50. doi: 10.1186/1710-1492-10-50.
9. Zuraw BL, Bernstein JA, Lang DM, et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. J Allergy Clin Immunol. 2013 Jun;131(6):1491-3. doi: 10.1016/j.jaci.2013.03.034.
10. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. J Allergy Clin Immunol Pract. 2013 Sep-Oct;1(5):458-67.
11. Frank MM, Zuraw B, Banerji A, et al. Management of children with Hereditary Angioedema due to C1 Inhibitor deficiency. Pediatrics. 2016 Nov. 135(5)

12. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel. Allergy Asthma Proc. 2012;33 Suppl 1:145-156.
13. Maurer M, Mager M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018 Jan 10. doi: 10.1111/all.13384.