

Medical Policy:

Cinryze® (C1 esterase inhibitor, human) intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.75	March 22, 2024	

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The treating physician or primary care provider must submit to EmblemHealth, or ConnectiCare, as applicable (hereinafter jointly referred to as “EmblemHealth”), the clinical evidence that the member meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request preauthorization or post-payment review. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. This clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Health care providers are expected to exercise their medical judgment in rendering appropriate care.

EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary.

If there is a discrepancy between this guideline and a member's benefits program, the benefits program will govern. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid Services (CMS) for Medicare and Medicaid members. All coding and web site links are accurate at time of publication.

EmblemHealth may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. EmblemHealth Services Company, LLC, has adopted this policy in providing management, administrative and other services to EmblemHealth Plan, Inc., EmblemHealth Insurance Company, EmblemHealth Services Company, LLC, and Health Insurance Plan of Greater New York (HIP) related to health benefit plans offered by these entities. ConnectiCare, an EmblemHealth company, has also adopted this policy. All of the aforementioned entities are affiliated companies under common control of EmblemHealth Inc.

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):

- 2,500 billable units per 30 days

Guideline

I. Initial Approval Criteria

1. Prophylaxis against angioedema attacks of Hereditary Angioedema (HAE) †

- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics; **AND**
- Patient must be at least 6 years of age; **AND**
- Patient has a history of one of the following criteria for long-term HAE prophylaxis:

- i. History of two (2) or more severe HAE attacks per month (i.e., airway swelling, debilitating cutaneous or gastrointestinal episodes); **OR**
 - ii. Patient is disabled more than 5 days per month by HAE; **OR**
 - iii. History of at least one laryngeal attack caused by HAE; **AND**
- D. 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; **AND**
- E. Not used in combination with C1 inhibitor prophylaxis (e.g., Haegarda or Takhzyro); **AND**
- F. 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**
- G. Patient has one of the following clinical presentations consistent with HAE subtype, which must be confirmed by repeat blood testing:

HAE I (C1-Inhibitor deficiency)
<ul style="list-style-type: none"> 1. 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 2. Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test); AND 3. Low C1-INH functional level (C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test); AND <ul style="list-style-type: none"> a. Patient has a family history of HAE; OR b. Onset of HAE symptoms occurred before age 30; OR c. Normal C1q level
HAE II (C1-Inhibitor dysfunction)
<ul style="list-style-type: none"> A. Normal to elevated C1-INH antigenic level; AND <p>Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test); AND</p> <p>Low C1-INH functional level (C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)</p>
HAE with normal C1INH (formerly known as HAE III)
<ul style="list-style-type: none"> B. Prophylaxis for HAE with normal C1-INH is not routinely recommended and will be evaluated on a case by case basis

† 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)	<p><u>Adult/adolescents (≥12 years old)</u></p> <p>1,000 units by intravenous injection every 3 to 4 days</p> <p>– 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.</p> <p><u>Pediatric patients (6 to 11 years old)</u></p> <p>500 units by intravenous injection every 3 to 4 days</p> <p>– The dose may be adjusted according to individual patient response, up to 1,000 U every 3 to 4 days.</p>

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	3/22/2024	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 Nephilysin 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.