



## Cinryze® (C1 Esterase Inhibitor, Human) (Intravenous)

Document Number: IC-0168

Last Review Date: 10/01/2021

Date of Origin: 08/27/2013

Dates Reviewed: 06/2014, 09/2014, 03/2015, 06/2015, 09/2015, 12/2015, 03/2016, 06/2016, 09/2016, 12/2016, 03/2017, 06/2017, 09/2017, 12/2017, 03/2018, 06/2018, 07/2018, 10/2018, 10/2019, 03/2020, 10/2020, 10/2021

### I. Length of Authorization

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

### II. Dosing Limits

#### A. Quantity Limit (max daily dose) [NDC Unit]:

- Cinryze 500 unit vial: 50 vials per 30 days

#### B. Max Units (per dose and over time) [HCPCS Unit]:

- 2,500 billable units per 30 days

### III. Initial Approval Criteria <sup>1</sup>

Coverage is provided in the following conditions:

- Patient is at least 6 years of age; **AND**

#### Universal Criteria <sup>1,13,20</sup>

- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics; **AND**
- Not used in combination with other prophylactic therapies targeting C1 inhibitor (i.e., Haegarda) or kallikrein (i.e., Takhzyro or Orladeyo); **AND**
- Confirmation the patient is avoiding the following possible triggers for HAE attacks:
  - Estrogen-containing oral contraceptive agents **AND** hormone replacement therapy; **AND**
  - Antihypertensive agents containing ACE inhibitors; **AND**
  - Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin); **AND**
  - Neprilysin inhibitors (e.g., sacubitril); **AND**

## Prophylaxis against angioedema attacks of Hereditary Angioedema (HAE) † $\Phi$ 1,13,20,21

- Patient has one of the clinical presentations listed below consistent with an 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**
  - Patient has a history of one of the following criteria for long-term HAE prophylaxis:
    - History of two (2) or more severe HAE attacks per month (i.e., airway swelling, debilitating cutaneous or gastrointestinal episodes)
    - Patient is disabled more than 5 days per month by HAE
    - History of at least one laryngeal attack caused by HAE; **AND**
  - 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) § 13,20,21**

- 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**
  - Patient has a family history of HAE; **OR**
  - Acquired angioedema has been ruled out (i.e., patient onset of symptoms occur prior to 30 years old, normal C1q levels, patient does not have underlying disease such as lymphoma or benign monoclonal gammopathy [MGUS], etc.)

### **HAE II (C1-Inhibitor dysfunction) § 20**

- 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) § 20,21**

- Prophylaxis for HAE with normal C1-INH is not routinely recommended and will be evaluated on a case by case basis
  - 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 17 $\alpha$ -alkylated androgen (e.g., danazol) unless contraindicated. Female patients may derive additional benefit from progestins<sup>15,16,17</sup>; **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);  $\Phi$  Orphan Drug

#### IV. Renewal Criteria <sup>1,13,20,21</sup>

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe hypersensitivity reactions, serious thromboembolic events (arterial and venous), etc.; **AND**
  - Significant improvement in severity, frequency, and/or duration of attacks have been achieved and sustained; **OR**
  - Patient requires dose titration due to an inadequate response to therapy (> 1.0 HAE attack/month, regardless of severity/duration)

#### V. Dosage/Administration <sup>1</sup>

Indication	Dose
Prophylaxis of Hereditary Angioedema (HAE) attacks	<b><u>Adult/adolescents (at least 12 years of age)</u></b> 1,000 units by intravenous injection every 3 to 4 days – <i>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.</i>
	<b><u>Pediatric patients (6 to 11 years of age)</u></b> 500 units by intravenous injection every 3 to 4 days – <i>The dose may be adjusted according to individual patient response, up to 1,000 U every 3 to 4 days.</i>
	<b><i>**Note:</i></b> Patients may self-administer Cinryze after being instructed by their healthcare provider.

#### VI. Billing Code/Availability Information

HCPCS Code:

- J0598 – Injection, C1 esterase inhibitor (human), cinryze, 10 units; 1 billable unit = 10 units

NDC:

- Cinryze 500 units single-dose vial: 42227-0081-xx

#### VII. References

1. Cinryze [package insert]. Exton, PA; ViroPharma Biologics, Inc; January 2021. Accessed August 2021.

2. Lumry W, Manning ME, Hurewitz DS, et al. "Nanofiltered C1-Esterase Inhibitor for the Acute Management and Prevention of Hereditary Angioedema Attacks Due to C1-Inhibitor Deficiency in Children," *J Pediatr*, 2013, 162(5):1017-22.
3. 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.
4. 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.
5. 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.
6. 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.
7. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol*. 2005;139(3):379.
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.
14. Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol*. 2012;109:395-402.
15. Wintenberger C, Boccon-Gibod I, Launay D, et al. Tranexamic acid as maintenance treatment for non-histaminergic angioedema: analysis of efficacy and safety in 37 patients. *Clin Exp Immunol*. 2014 Oct; 178(1): 112–117.
16. Saule C, Boccon-Gibod I, Fain O, et al. Benefits of progestin contraception in non-allergic angioedema. *Clin Exp Allergy*. 2013 Apr;43(4):475-82.

17. Frank MM, Sergent JS, Kane MA, et al. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. *N Engl J Med.* 1972;286:808-812.
18. Zuraw B, Busse P, White M, et al. Efficacy and safety of long-term prophylaxis with C1 inhibitor (C1INH) concentrate in patients with hereditary angioedema (HAE). *J Allergy Clin Immunol.* 2008;121(2 Suppl 1):S272.
19. Aygören-Pürsün E, Soteres DF, Nieto-Martinez SA, et al. A randomized trial of human C1 inhibitor prophylaxis in children with hereditary angioedema. *Pediatr Allergy Immunol.* 2019;30(5):553-561.
20. Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol.* 2019; 15: 72. Published online 2019 Nov 25. doi: 10.1186/s13223-019-0376-8.
21. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract.* 2021 Jan;9(1):132-150.e3. doi: 10.1016/j.jaip.2020.08.046.

## Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D84.1	Defects in the complement system

## Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at:

<https://www.cms.gov/medicare-coverage-database/new-search/search.aspx>. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp
N (9)	FL, PR, VI	First Coast Service Options, Inc.

### Medicare Part B Administrative Contractor (MAC) Jurisdictions

Jurisdiction	Applicable State/US Territory	Contractor
J (10)	TN, GA, AL	Palmetto Government Benefit Administrators, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC