Neighborhood Health Plan OF RHODE ISLAND™
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Cinryze® (C1 Esterase Inhibitor, Human)
(Intravenous)

Effective Date: 01/01/2020
Review Date: 10/02/2019, 12/18/2019, 1/22/2020, 2/25/2021, 2/10/2022, 3/16/2023, 12/07/2023, 01/10/2024, 07/09/2025
Scope: Medicaid, Commercial, Medicare

I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

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

- 2,500 billable units per 30 days

III. Summary of Evidence

Cinryze is a plasma-derived replacement therapy indicated for routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (≥6 years old) with Hereditary Angioedema (HAE), a rare autosomal dominant disorder caused by C1 inhibitor deficiency. Cinryze's approval is based on a 24-week randomized, double-blind, placebo-controlled, crossover trial in 24 patients aged 9 to 73 years with a history of ≥2 HAE attacks per month. Patients receiving Cinryze (1,000 IU IV every 3–4 days) experienced a 52% reduction in attack frequency (mean 6.1 vs. 12.7; $p<0.0001$), a 66% reduction in swelling days, shorter attack duration (2.1 vs. 3.4 days; $p=0.0023$), and lower severity scores (1.3 vs. 1.9; $p=0.0006$) compared to placebo. The most common adverse reactions (≥5%) include headache, nausea, rash, vomiting, and fever. Serious adverse events such as thromboembolism have occurred, particularly in patients with known risk factors (e.g., indwelling catheters, obesity, oral contraceptives).

IV. Initial Approval Criteria[1]

Coverage is provided in the following conditions:

Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements.

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

Universal Criteria [1,13]

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

- Will not be used in combination with other prophylactic therapies targeting C1 inhibitor or kallikrein (i.e., Haegarda, Orladeyo, Takhzyro, Andembry, etc); **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 or angiotensin II receptor blockers (ARBs); **AND**
  - Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin); **AND**
  - Neprilysin inhibitors (e.g., sacubitril)

Prophylaxis to prevent Hereditary Angioedema (HAE) attacks † Φ [1-14]

- 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 at least one severe HAE attack 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 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 old, 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 17α-alkylated androgen (e.g., danazol) unless contraindicated. Female patients may derive additional benefit from progestins[15,16,17]; **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); **‡** Compendia Recommended Indication(s); **Φ** Orphan Drug

V. Renewal Criteria[1]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria identified in section IV; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe hypersensitivity reactions, serious thromboembolic events (arterial and venous), etc.; **AND**
  - Significant improvement in severity and 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)

VI. Dosage/Administration[1]

Indication	Dose
Prophylaxis of Hereditary Angioedema (HAE) attacks	**Adult/adolescents (at least 12 years of age)** 1,000 units by intravenous injection every 3 to 4 days – *For patients who have not responded adequately to initial dosing, doses up to 2,000 U (not exceeding 80 IU/kg) every 3 or 4 days may be considered based on individual patient response.* **Pediatric patients (6 to 11 years of age)** 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.*

VII. 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

VIII. References

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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: http://www.cms.gov/medicare-coverage-database/search/advanced-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.
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

Policy Rationale: Cinryze was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Cinryze according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For Medicare members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.