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

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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 single-dose vial: 40 vials per 30 days

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

- 2,000 billable units per 30 days

III. Initial Approval Criteria [1]

Submission of medical records (chart notes) related to the medical necessity criteria is REQUIRED on all requests for authorizations. Records will be reviewed at the time of submission. Please provide documentation related to diagnosis, step therapy, and clinical markers (i.e. genetic and mutational testing) supporting initiation when applicable. Medical records may be submitted via direct upload through the PA web portal or by fax.

Coverage is provided in the following conditions:

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

Universal Criteria [1,13,20]

- 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 (e.g., Haegarda etc.) or kallikrein (e.g., Takhzyro, Orladeyo, 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, etc.); **AND**
  - Neprilysin inhibitors (e.g., sacubitril); **AND**

Prophylaxis Against Hereditary Angioedema (HAE) Attacks † Φ [1,3,13,20,21,22]

- 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**
  - 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) § [13,20,21,22]

• 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 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) § [20,22]
• 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) § [20,21,22]
• 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 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

IV. Renewal Criteria [1,13,20-22]

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 [1]

Indication	Dose
Prophylaxis against Hereditary Angioedema (HAE) attacks	**Adult and adolescents (at least 12 years of age)** Administer 1,000 IU* by intravenous injection every 3 to 4 days – *For patients who have not responded adequately to initial dosing, doses up to 2,000 IU (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)** Administer 500 IU* by intravenous injection every 3 to 4 days – *The dose may be adjusted according to individual patient response, up to 1,000 IU every 3 to 4 days.* ** One International Unit (IU) corresponds to the amount of C1 esterase inhibitor present in 1 mL of normal plasma as defined by the WHO international reference standard. Previously, the potency values were expressed in Units (U) and were relative to an in-house reference standard. A conversion factor of 0.83 can be used to recalculate the potency from U to IU, i.e., 100 U = 83 IU.* ***Note:** 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

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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)

The preceding information is intended for non-Medicare coverage determinations. 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 Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is

required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied 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 GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
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