BlueCross BlueShield
Federal Employee Program
Blue Cross Blue Shield Association
750 9th St NW, Suite 900
Washington, D.C. 20001
1-800-624-5060
Fax 1-877-378-4727

5.85.005

Section:	Prescription Drugs	**Effective Date:**	April 1, 2025
Subsection:	Hematological Agents	**Original Policy Date:**	December 7, 2011
Subject:	Cinryze	**Page:**	1 of 6

Last Review Date: March 7, 2025

Cinryze

Description

Cinryze (C1 esterase inhibitor [human])

Background
Cinryze is a C1-esterase inhibitor used for routine prophylaxis against angioedema attacks in patients with hereditary angioedema (HAE). Hereditary angioedema is caused by having insufficient amounts of a plasma protein called C1-esterase inhibitor. People with HAE can develop rapid swelling of the hands, feet, limbs, face, intestinal tract, or airway. These acute attacks of swelling can occur spontaneously, or can be triggered by stress, surgery or infection. Swelling of the airway is potentially fatal without immediate treatment. Cinryze is intended to restore the level of functional C1-esterase inhibitor in a patient's plasma, thereby preventing the acute attack of swelling (1-4).

Regulatory Status
FDA-approved indication: Cinryze is a C1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6 years of age and older) with Hereditary Angioedema (HAE) (2).

Hypersensitivity reactions may occur. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions following discontinuation of administration (2).

Thrombotic events have been reported at the recommended dose of C1 Esterase Inhibitor (human) products, including Cinryze, following treatment of HAE. Monitor closely patients with known risk factors for thrombotic events (2).

Cinryze is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (2).

Related policies
Berinert, Haegarda, Icatibant, Kalbitor, Orladeyo, Ruconest, Takhzyro

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Cinryze may be considered **medically necessary** if the conditions indicated below are met.

Cinryze may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 6 years of age and older

Diagnosis

Patient must have **ALL** of the following:

1. Hereditary Angioedema (HAE) with **ONE** of the following:
    a. Patient has a C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing **AND ALL** of the following:
        i. C4 level below the lower limit of normal as defined by the laboratory performing the test
        ii. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test **OR** normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)
    b. Patient has normal C1 inhibitor as confirmed by laboratory testing **AND ONE** of the following:
        i. F12, angiopoietin-1, plasminogen, or kininogen-1 (KNG1) gene mutation as confirmed by genetic testing

ii. Documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (e.g., cetirizine) for at least one month

AND ALL of the following:

a. Routine prevention of hereditary angioedema attacks
b. **NO** dual therapy with other agents for the prevention of hereditary angioedema attacks (e.g., Haegarda, Orladeyo, Takhzyro)
c. Inadequate treatment response or intolerance to a short-term course (5-days or less) of an androgen such as danazol, or a contraindication to one such as:
    i. Undiagnosed abnormal genital bleeding
    ii. Markedly impaired hepatic, renal, or cardiac function
    iii. Pregnancy (member is currently pregnant or may become pregnant)
    iv. Breast feeding
    v. Porphyria
    vi. Androgen-dependent tumor
    vii. Active thrombosis or history of thromboembolic disease
    viii. Prepubertal child

Prior – Approval *Renewal* Requirements

Age 6 years of age and older

Diagnosis

Patient must have **ALL** of the following:

1. Hereditary Angioedema (HAE)
    a. Routine prevention of hereditary angioedema attacks
    b. Patient has experienced a significant reduction in frequency of hereditary angioedema attacks since starting treatment
    c. **NO** dual therapy with other agents for the prevention of hereditary angioedema attacks (e.g., Haegarda, Orladeyo, Takhzyro)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Cinryze is a C1-esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE). HAE symptoms include episodes of edema (swelling) in various body parts including the hands, feet, face, and airway. HAE is caused by mutations to C1-esterase-inhibitor (C1-INH). Serious arterial and venous thromboembolic (VTE) events have been reported at the recommended dose of plasma derived C1 esterase inhibitor products in patients with risk factors. The safety and efficacy of Cinryze in children less than 6 years of age has not been established. Persons who experience frequent and/or severe episodes may be candidates for prophylactic treatment (1-4).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Cinryze while maintaining optimal therapeutic outcomes.

References

1. Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. Sep 4 2008;359(10):1027-36.2.
2. Cinryze [package insert]. Lexington, MA: Takeda Pharmaceuticals USA, Inc.; November 2024.
3. 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: In Practice. 2013; 1(5): 458-467.
4. 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; 178:112.

Policy History

Date	Action
December 2011	New policy
September 2012	Annual Review with editorial and reference update
March 2013	Annual editorial review and reference update
March 2014	Annual review and reference update
December 2014	Annual editorial review and reference update
December 2015	Annual editorial review
December 2016	Annual editorial review and reference update Policy code changed from 5.10.05 to 5.85.05
September 2017	Annual review and reference update
December 2017	Annual editorial review and reference update Addition of no dual therapy with other C1-esterase inhibitors for the prevention of angioedema attacks Addition of inadequate treatment response, intolerance, or contraindication to a danazol or tranexamic acid per SME
March 2018	Annual review
July 2018	Change in age from 12 years of age and older to 6 years of age and older
August 2018	Changed wording of no dual therapy requirement
September 2018	Annual review
November 2018	Annual review. Removal of requirement to try and fail tranexamic acid and reworded danazol or androgen trial requirement per SME
September 2019	Annual review
September 2020	Annual review
March 2021	Annual editorial review and reference update
April 2021	Added initiation requirements including C1 inhibitor testing, C4 testing, C1-INH testing, gene mutation testing, or documented family history of refractory angioedema and continuation requirement for significant reduction in frequency of HAE attacks since starting therapy per FEP
June 2021	Annual review
March 2022	Annual review
March 2023	Annual review. Changed policy number to 5.85.005
December 2023	Annual review and reference update
March 2024	Annual review
December 2024	Annual review
March 2025	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 7, 2025 and is effective on April 1, 2025.