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Department: PHARMACY	**MMC Review/ Approval Date(s):** 5/30/19, 5/12/20, 5/11/21, 12/21/22	**Total Number of Pages: 13**

Policy Number: 021.004
Title: Coverage Determination Policy for C1 Esterase Inhibitors:
C1 esterase inhibitor [human], (Cinryze)
C1 esterase inhibitor [human], (Berinert)
C1 esterase inhibitor [recombinant], (Ruconest)

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA: none

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Coverage Policy Number: 021.004

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Coverage Determination (Initial/New Requests)

NOTE: Angiotensin converting enzyme (ACE) inhibitors and estrogen-containing medications such as hormone replacement therapy and contraceptives have been found to exacerbate the frequency and/or severity of HAE attacks. Thus, it is recommended that patients with confirmed HAE avoid these medications.

Haegarda® (C1 esterase inhibitor [human]) is a self-administered injection and is obtained under the member's pharmacy benefit

WellMed Medical Management will cover **Cinryze® (C1 esterase inhibitor [human]),** as medically necessary when **ALL** of the following are met:

1. Patient has a documented diagnosis of HAE as confirmed by **ONE** of the following:
    - A C1 inhibitor (C1-INH) deficiency or dysfunction (Type I or II HAE) as documented by **ONE** of the following:
        - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal
        - C1-INH functional level below the lower limit of normal

      OR
    - Normal C1 inhibitor levels and **ONE** of the following:
        - Confirmed presence of a FXII, angiopoietin-1, or plasminogen gene mutation
        - Recurring angioedema attacks that are refractory to high-dose antihistamines with confirmed family history of angioedema

      AND
    - Used for prophylaxis against HAE attacks
    - Not used in combination with other products indicated for the prophylaxis against HAE attacks (e.g., Haegarda, Takhzyro)
    - Prescriber attests that patient has experienced attacks of a severity and/or frequency such that they would clinically benefit from prophylactic therapy with Cinryze
    - History of failure, contraindication, or intolerance to Haegarda
    - Dose is consistent with FDA approved dosing

WellMed Medical Management will cover **Berinert® and Ruconest®** as medically necessary when **ALL** of the following are met:

1. Patient has a documented diagnosis of HAE as confirmed by **ONE** of the following:
   - A C1 inhibitor (C1-INH) deficiency or dysfunction (Type I or II HAE) as documented by **ONE** of the following:
     - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal
     - C1-INH functional level below the lower limit of normal

   OR
   - Normal C1 inhibitor levels and **ONE** of the following:
     - Confirmed presence of a FXII, angiopoietin-1, kininogen or plasminogen gene mutation
     - Recurring angioedema attacks that are refractory to high-dose antihistamines with confirmed family history of angioedema

   AND
2. Used for treatment of an acute HAE attack
3. Not used in combination with other approved treatments for acute HAE attacks (e.g., Berinert, Firazyr, Kalbitor, or Ruconest
4. Dose is consistent with FDA approved dosing

Note: Efficacy of Ruconest® in treating HAE patients with laryngeal attacks has not been established

Coverage Determination (Renewal/Continuation of Therapy Requests)

Renewed requests for continued use of **Cinryze** will be approved if **ALL** of the following are met:

1. Documentation of positive clinical response, defined as a clinically significant reduction in the rate and/or number of HAE attacks, while on Cinryze therapy
2. Reduction in the utilization of on-demand therapies used for acute attacks (e.g., Berinert, Firazyr, Ruconest) as determined by claims information, while on Cinryze therapy
3. Not used in combination with other products indicated for prophylaxis against HAE attacks (e.g., Haegarda, Takhzyro)
4. Used for prophylaxis against HAE attacks

Renewed requests for continued use of **Berinert® and Ruconest®** will be approved if **ALL** of the following are met:

1. Documentation of positive clinical response with prior courses of treatment
2. Not used in combination with other approved treatments for acute HAE attacks (e.g., Berinert, Firazyr, Kalbitor, or Ruconest
3. Used for treatment of an acute HAE attack

FDA Approved Dose and Indication:

Name	Indication	Approved Dosing
Cinryze®	HAE prophylaxis	1000 units for 3-4 days; if no adequate response may increase dose up to 2000 units/day DO NOT EXCEED 80 UNITS/KG
Berinert®	HAE	20 IU/kg
Ruconest®	HAE	< 84kg: 50 IU/kg ≥ 84kg: 4200 IU (MAXIMUM 4200 IU/dose) may repeat dose once if symptoms persist (MAXIMUM 8400 IU/24 hours)

General Background:

Hereditary angioedema (HAE) is a disease characterized by recurrent episodes of angioedema, without urticaria or pruritus, which most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. Although the swelling is self-limited and resolves in two to five days without treatment, laryngeal involvement may cause fatal asphyxiation.

Angiotensin-converting enzyme inhibitors are contraindicated in patients known to have HAE because they increase the half-life of bradykinin and can thus precipitate symptoms. Oral contraceptive agent use should also be avoided because it can precipitate attacks in some individuals with HAE.

C1 inhibitor (C1INH) is an acute-phase reactant and a member of the "serpin" superfamily of serine protease inhibitors. C1INH inhibits steps in the classical and lectin complement pathways, as well as of the intrinsic coagulation (contact system), fibrinolytic, and kinin-generating pathways. Within these different pathways, C1INH inhibits several plasma proteases: C1r and C1s, mannose-binding lectin-associated serine proteases (MASP1 and MASP2), coagulation factor XII (Hageman factor), coagulation factor XI, plasma kallikrein, and plasmin [3-6]. The function of C1INH in the kinin-generating pathway is most directly related to the pathogenesis of HAE.

HAE type I is due to C1 inhibitor (C1INH) deficiency, and type II is caused by C1INH dysfunction. Together, these two disorders are called HAE with C1INH deficiency (C1INH-HAE). C1 esterase inhibitors are administered intravenously for treatment of acute attacks. Plasma derived C1 inhibitors (pdC1INH) are the best studied first-line therapy for acute episodes of angioedema in patients with HAE.

Cinryze® (C1 esterase inhibitor [human]), 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).
Berinert® (C1 esterase inhibitor [human]), is a plasma-derived C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients.
Ruconest® is a C1 esterase inhibitor [recombinant] indicated for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE).

Medicare does not have a National Coverage Determination (NCD) for Cinryze® (C1 esterase inhibitor [human]), Berinert® (C1 esterase inhibitor [human]), or Ruconest® (C1 esterase inhibitor [recombinant]).There are no Local Coverage Determinations (LCD) that address Cinryze® (C1 esterase inhibitor [human]), Berinert® (C1 esterase inhibitor [human]), or Ruconest® (C1 esterase inhibitor [recombinant]) for Texas at the time of this policy creation.

Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks.

Clinical Evidence:

The efficacy of pdC1INH for treatment of acute attacks of HAE has been well demonstrated in randomized trials.

The US Food and Drug Administration (FDA) has not approved Cinryze ® for treatment of acute attacks (only for prophylaxis). However, there is no empiric reason to suspect that Cinryze ® would be less effective than the C1INH products used for years in Europe. The Cinryze® dose approved in the European Union for acute attacks is 1000 units, with the possibility of another 1000 units if not improving. In the absence of trials to determine optimal dosing of Cinryze® in acute attacks, either this dosing or weight-based dosing is acceptable.

●A randomized trial of pdC1INH (Cinryze®) for the treatment of acute attacks involved 68 patients assigned to either 1000 units of pdC1INH (regardless of weight, with the possibility of another 1000 units after one hour based on clinician and patient assessment of need) or placebo for nonlaryngeal attacks. The median time to onset of unequivocal relief (the primary endpoint) was two hours in the pdC1INH group, compared with over four hours in the placebo group.

●A subsequent randomized trial of 125 patients with acute gastrointestinal or facial cutaneous attacks compared pdC1INH (Berinert®) at doses of 10 units/kg or 20 units/kg with placebo [21]. Patients were treated within five hours of the symptoms reaching moderate intensity. Median time to onset of relief was significantly shorter with the higher dose of pdC1INH (0.5 hours), compared with the lower dose of pdC1INH (1.2 hours) or placebo (1.5 hours).

●A retrospective comparison of data from 881 acute laryngeal attacks treated with any of the available first-line therapies found that weight-adjusted pdC1INH appeared to give the best outcomes, with time to onset of relief ranging from 15 minutes to two hours and none of the 48 attacks requiring a second dose [8]. A subsequent nonrandomized trial also confirmed the efficacy of weight-based pdC1INH (Berinert®) (20 units/kg) in patients with laryngeal edema.

Data from a multicenter registry found that the response could be improved when patients were able to self-administer pdC1INH at home at the first sign of swelling (pdC1INH "on demand") and that this practice was safe. In a small study, 12 patients reported initiation of relief in a mean of approximately 40 minutes after the onset of symptoms when pdC1INH was self-administered, as compared with about 2.5 hours when the patients were dependent on a health care facility for administration.

TABLE I. Medications for on-demand treatment of HAE

Generic name (trade name, company)	FDA approval status	Dosage	Mechanism	Efficacy	Storage	Anticipated potential adverse effects
Newer						
Plasma-derived C1INH (Berinert, CSL Behring, King of Prussia, Pa)	Approved for acute attacks in adults and adolescents	20 U/kg intravenous	Inhibit plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	+++	Store between 2°C and 25°C; stable for up to 30 mo	Rare: risk of anaphylaxis; theoretical: transmission of infectious agent
Plasma-derived C1INH (Cinryze; ViroPharma, Exton, Pa)	Not FDA approved for on-demand treatment	1000 U intravenous	(Same as above)	+++	Store between 2°C and 25°C	Rare: risk of anaphylaxis or thrombosis; theoretical: transmission of infectious agent
Recombinant human C1INH (Rhucin, Ruconest, Santarus, San Diego, Calif)	Not FDA approved for on-demand treatment	50 U/kg intravenous	(Same as above)	+++	Store between 2°C and 25°C; stable for up to 4 y	Rare: risk of anaphylaxis
Ecallantide (Kalbitor, Dyax, Burlington, Mass)	Approved for acute attacks in patients ≥16 y old	30 mg subcutaneous	Inhibits plasma kallikrein	+++	Store between 2°C and 8°C; stable for up to 36 mo	Common: prolonged PTT; uncommon: risk of anaphylaxis (must be administered by health care professional)
Icatibant (Firazyr, Shire, Lexington, Mass)	Approved for acute attacks in patients ≥18 y old	30 mg subcutaneous	Bradykinin B2 receptor antagonist	+++	Store between 2°C and 25°C; stable for up to 2 y	Common: discomfort at injection site; theoretical: worsening of an ongoing ischemic event
Older						
Fresh frozen plasma	Not FDA approved for on-demand treatment	2 units	Inhibit plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	++	n/a	Rare: risk of anaphylaxis; possible: transmission of infectious agent; sudden worsening of an attack

++, moderate efficacy; +++, excellent efficacy; *MASP*, mannose-associated serine protease; *n/a*, not available; *PTT*, partial thromboplastin time.

HCPCS Code:

HCPCS Code:	Description:
J0596	Ruconest
J0597	Berinert
J0598	Cinryze

Acronyms:

LCD = Local Coverage Determinations
NCD = National Coverage Determinations
HAE = Hereditary Angioedema

References:

1. Cinryze® [C1 Esterase Inhibitor (human)] [package insert]. Lexington, MA: Shire ViroPharma, Inc; 2022.
2. Berinert® [C1 Esterase Inhibitor (human)] [package insert]. Kankakee, IL: CLS Behring, LLC 2021.
3. Ruconest® (C1 esterase inhibitor [recombinant]) [package insert]. Bridgewater, NJ: Pharming Healthcare Inc.; 2020
4. Cinryze® In: IBM Micromedex® DRUGDEX® (electronic version). IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited: October 10, 2022).
5. Berinert® In: IBM Micromedex® DRUGDEX® (electronic version). IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited: October 10, 2022).
6. Ruconest® In: IBM Micromedex® DRUGDEX® (electronic version). IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (cited: October 10, 2022).
7. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol 2009; 124:801.
8. Agostoni A, Bergamaschini L, Martignoni G, et al. Treatment of acute attacks of hereditary angioedema with C1-inhibitor concentrate. Ann Allergy 1980; 44:299.
9. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. N Engl J Med 1996; 334:1630.
10. Kunschak M, Engl W, Maritsch F, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. Transfusion 1998; 38:540.
11. De Serres J, Gröner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. jean.de.serres@aventis.com. Transfus Apher Sci 2003; 29:247.
12. Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. Arch Intern Med 2001; 161:714.
13. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med 2010; 363:513.
14. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guidelines for the management of hereditary angioedema – The 2017 revision and update. Allergy. 2018; 73:1575–1596. https://doi.org/10.1111/all.13384 1596

15. 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 2013;5:458-467
16. Cicardi M, Zuraw B. Hereditary Angioedema: Treatment of acute attacks In: Up to date.https://www.uptodate.com/ Accessed January 18, 2019
17. Kaplan, AP. Angioedema. World Allergy Organ J. 2008 Jun; 1(6): 103–113.
18. Nzeako UC, Frigas E, Tremaine WJ. Hereditary Angioedema. Arch Intern Med. 2001; 161(20):2417-2429.