



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

Document Number: IC-0018

Last Review Date: 10/03/2022

Date of Origin: 11/28/2011

Dates Reviewed: 12/2011, 01/2013, 08/2013, 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, 10/2018, 10/2019, 03/2020, 10/2020, 10/2021, 10/2022

I. Length of Authorization

Coverage will be provided for 12 weeks and is eligible for renewal (unless otherwise specified).

The cumulative amount of medication(s) the patient has on-hand, indicated for the acute treatment of HAE, will be taken into account when authorizing. The authorization will provide a sufficient quantity in order for the patient to have a cumulative amount of HAE medication(s) on-hand in order to treat up to 4 acute attacks per 4 weeks for the duration of the authorization (unless otherwise specified).

II. Dosing Limits

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

- Berinert 500 IU single-dose vial: 22 vials every 28 days

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

- 1100 billable units per 28 days

III. Initial Approval Criteria ¹

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**
- 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**

Treatment of acute abdominal, facial, or laryngeal attacks of Hereditary Angioedema (HAE) †
1,13,20,21,22

- Patient has a history of moderate to severe cutaneous attacks (without concomitant hives) OR abdominal attacks OR mild to severe airway swelling attacks of HAE (i.e. debilitating cutaneous/gastrointestinal symptoms OR laryngeal/pharyngeal/tongue swelling); **AND**
- Patient has one of the following clinical presentations consistent with a HAE subtype§, which must be confirmed by repeat blood testing (treatment for acute attack should not be delayed for confirmatory testing):

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 old, normal C1q levels, patient does not have underlying disease such as lymphoma or benign monoclonal gammopathy [MGUS], etc.)

HAE II (C1-Inhibitor dysfunction) § 20,22

- 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 (also known as HAE III) § 20,21,22

- Normal C1-INH antigenic level; **AND**
- Normal C4 level; **AND**
- Normal C1-INH functional level; **AND**
- Repeat blood testing during an attack has confirmed the patient does not have abnormal lab values indicative of HAE I or HAE II; **AND**
- Either of the following:
 - Patient has a known HAE-causing mutation (e.g., mutation of coagulation factor XII gene [F12 mutation], mutation in the angiotensin-1 gene, mutation in the plasminogen gene, mutation in the kininogen 1 gene, mutation in the myoferlin gene, mutation in the heparan sulfate 3-O-sulfotransferase 6 gene, etc.); **OR**
 - Patient has a family history of HAE and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (*e.g. cetirizine standard dosing at up to four times daily or an alternative equivalent, given for at least one month or an interval long enough to expect three or more angioedema attacks*) **AND** corticosteroids with or without omalizumab

† FDA Approved Indication(s)

IV. 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 III; **AND**

- Significant improvement in severity and duration of attacks have been achieved and sustained; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe hypersensitivity reactions, serious thromboembolic events (arterial or venous), etc.; **AND**
- The cumulative amount of medication(s) the patient has on-hand, indicated for the acute treatment of HAE, will be taken into account when authorizing. The authorization will provide a sufficient quantity in order for the patient to have a cumulative amount of HAE medication(s) on-hand in order to treat up to 4 acute attacks per 4 weeks for the duration of the authorization (unless otherwise specified).

V. Dosage/Administration ¹

Indication	Dose
Acute Hereditary Angioedema (HAE) attack	Administer 20 international units (IU) per kg body weight by intravenous injection upon recognition of an HAE attack. **Note: Patients may self-administer Berinert after being instructed by their healthcare provider.

VI. Billing Code/Availability Information

HCPCS Code:

- J0597 – Injection, C-1 esterase inhibitor (human), berinert, 10 units; 1 billable unit = 10 units

NDC:

- Berinert 500 IU single-dose carton kit (containing a single-dose vial of Berinert and a 10 mL vial of Sterile Water for Injection): 63833-0825-xx

VII. References

1. Berinert [package insert]. Kankakee, IL; CSL Behring LLC; September 2021. Accessed August 2022.
2. Wasserman RL, Levy RJ, Bewtra AK, et al. Prospective Study of C1 Esterase Inhibitor in the Treatment of Successive Acute Abdominal and Facial Hereditary Angioedema Attacks. *Ann Allergy Asthma Immunol*, 2011, 106(1):62-8.
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, Sargent 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. 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(4):801-808.
19. Craig TJ, Bewtra AK, Bahna SL, et al. C1 esterase inhibitor concentrate in 1085 Hereditary Angioedema attacks--final results of the I.M.P.A.C.T.2 study. *Allergy*. 2011;66(12):1604-1611.

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.
22. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – The 2021 revision and update. Allergy. 2021 Nov 22. doi: 10.1111/all.15214

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/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 (WPS)
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 (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, 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