MEDICAL MUTUAL®

Drug Policy

Policy: **SD**	**201020-MRx (10-22)**	**Initial Effective Date: 04/21/2016** **Annual Review Date: 12/21/2023** **Last Revised Date: 12/21/2023**
Code(s):	**HCPCS J0597**	
SUBJECT:	**Berinert ® (C1 esterase inhibitor [human]) injection for intravenous use** **Prior Approval Criteria**	

☒Subject to Site of Care

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

Initial and renewal requests for the medication(s) listed in this policy are subject to site of care management. When billed under the medical benefit, administration of the medication will be restricted to a non-hospital facility-based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless the member meets the site of care exception criteria. To view the exception criteria and a list of medications subject to site of care management please click here.

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 meets one of the following:
  - Patient has tried the preferred product, Ruconest **[documentation required];** OR
  - Patient has had a history of at least one laryngeal attack that had been treated with Berinert, as per the prescriber; OR
  - Patient has an allergy to rabbits or rabbit-derived products; OR
  - Patient is less than 13 years of age; 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** 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) § [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 angiopoietin-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**
- Patient meets one of the following:
  - Patient has tried the preferred product, Ruconest **[documentation required];** OR
  - Patient has had a history of at least one laryngeal attack that had been treated with Berinert, as per the prescriber; OR
  - Patient has an allergy to rabbits or rabbit-derived products; OR
  - Patient is less than 13 years of age; 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 Alergy 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, Sergent 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

Documentation Requirements:
The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

Prior approval is required for HCPCS Code J0597

Edits and Denials:

Prior approval: Prior approval is required for Berinert **(HCPCS Code J0597)**. Requests for prior approval will be authorized by a nurse reviewer if submitted documentation meets criteria outlined within the Corporate Medical Policy.

Requests for prior approval will be forwarded to a qualified physician reviewer if submitted documentation does not meet criteria outlined within Corporate Medical Policy.

TOPPS: Claims received with **HCPCS Codes J0597** will pend with **Remark Code M3M or M4M** and will be adjudicated in accordance with the Corporate Medical Policy.

Liability: A participating provider will be required to write off charges denied as not medically necessary.