OVERVIEW:
Berinert is a C1 esterase inhibitor (C1-INH) isolated from normal human plasma and administered intravenously for treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients. The safety and efficacy of Berinert for prophylactic therapy has not been established.

Hereditary angioedema is a rare, debilitating, potentially life-threatening genetic disorder caused by a deficiency in C1-INH, a plasma protein involved in the regulation of the complement and intrinsic coagulation pathways. Hereditary angioedema is caused by mutations in the C1-INH gene located on chromosome 11q and inherited as an autosomal dominant trait. Two main types of hereditary angioedema exist: mutations causing Type I hereditary angioedema are associated with decreased production of C1-INH leading to decreased functional levels; Type II hereditary angioedema mutations are associated with a dysfunctional C1 inhibitor but the inhibitor level is normal.

HAE is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema associated with pain syndrome, nausea, vomiting, diarrhea, and/or life-threatening airway swelling. Airway obstruction due to swelling is life-threatening if left untreated. There is a wide variation in the frequency and severity of attacks. Clinical experience suggests that minor trauma and/or stress, among other triggers, may precipitate attacks. Untreated attacks typically last over 48 to 96 hours. Short-term prophylaxis with a C1-INH is recommended if more than minor manipulation (e.g., mild dental work) is needed, and prior to intubation or major procedures. The dose for short-term prophylaxis with C1-INH varies from 10 U/kg to 20 U/kg or 1,000 units, 1 to 6 hours before procedure. Long-term prophylaxis should be considered in all severely symptomatic patients, taking into consideration the severity of disease, frequency of attacks, patient’s quality of life, availability of resources, and failure to achieve adequate control by on-demand therapy.

The Site of Care Medical Necessity Criteria applies to initial therapy and reauthorizations.
Medical Necessity: The Company considers Berinert (HCPCS Code J0597) medically necessary and eligible for reimbursement providing that all of the following medical criteria are met:

1. **Hereditary Angioedema (HAE) Type 1 and 2 Treatment of Acute Attacks, Initial Therapy.** Approve Berinert if the patient meets the following criteria (a, b, c, d, e and f):

   a) The patient has HAE as confirmed by following criteria (i or ii):
      i) Patient has low levels of functional C1-INH protein (< 67% of normal) as defined by the laboratory reference values [documentation required]; OR
      ii) Patient has lower than normal serum C4 levels (< 14 mg/dL), as defined by the laboratory reference values AND lower than normal C1-INH level (< 19.9 mg/dL) [documentation required]; AND

   b) The medication is prescribed by or in consultation with an allergist, immunologist, hematologist or a physician that specializes in the treatment of HAE or related disorders; AND

   c) All other causes of acquired angioedema (e.g., medications, auto-immune diseases) have been excluded; AND

   d) Patient has at least ONE of the following criteria (i, ii, or iii) AND
      i) Patient must have history of self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, which is recurrent and lasts >12 hours
      ii) Self-limiting, recurrent abdominal pain without a clear organic cause lasting >6 hours
      iii) A history of laryngeal edema

   e) Berinert is not used in combination with other approved treatments for acute HAE attacks (e.g. Firazyr, Kalbitor, or Ruconest).AND

   f) Site of care medical necessity is met*.

2. **Patient has been started on Berinert.** Approve for, an indication or condition addressed as an approval in the Recommended Authorization Criteria (FDA-Approved Indications), continuation of therapy if the patient meets the following criteria (a, b, c, d, e, f and g)

   a) The patient has HAE as confirmed by following criteria (i or ii):
      i) Patient has low levels of functional C1-INH protein (< 67% of normal) as defined by the laboratory reference values [documentation required]; OR
      ii) Patient has lower than normal serum C4 levels (< 14 mg/dL), as defined by the laboratory reference values AND lower than normal C1-INH level (< 19.9 mg/dL) [documentation required]; AND

   b) The medication is prescribed by or in consultation with an allergist, immunologist, hematologist or a physician that specializes in the treatment of HAE or related disorders; AND

   c) All other causes of acquired angioedema (e.g., medications, auto-immune diseases) have been excluded; AND

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d) Patient has at least ONE of the following criteria (i, ii, or iii); AND
   i.) Patient must have history of self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, which is recurrent and lasts >12 hours
   ii.) Self-limiting, recurrent abdominal pain without a clear organic cause lasting >6 hours
   iii.) A history of laryngeal edema

e) Berinert is not used in combination with other approved treatments for acute HAE attacks (e.g. Firazyr, Kalbitor, or Ruconest); AND

f) Patient has at least 1 annual assessment by an HAE specialist; AND

g) Site of care medical necessity is met*.

Approval Duration: 365 days (1 year)

Dosing in Hereditary Angioedema. The recommended dose of Berinert is 20 International Units (IU) per kg body weight administered by intravenous injection.

The Company considers Berinert (HCPCS Code J0597) for prophylaxis against hereditary angioedema attacks investigational and not eligible for reimbursement.

*MMO Site of Care Medical Necessity Criteria:

- Medications in this policy will be administered in a place of service that identifies the location to be a non-hospital facility based location (i.e., home infusion provider, provider’s office, free-standing ambulatory infusion center) unless at least one of the following are met:

  1. Age less than 21 years; or
  2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
  3. History of a severe adverse event from previous administration of the prescribed medication; or
  4. Requested medication is being administered as follows:
     - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
     - administered with dialysis; or
  5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
  6. Up to 1 dose of medication or re-initiation after at least 12 months; or
  7. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.
**Documentation Requirements:**

The Company reserves the right to request additional documentation and to deny reimbursement when it has determined that the services performed were not medically necessary, investigational and/or a pattern of 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 and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

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<th>Sources of Information</th>
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<tbody>
<tr>
<td>- Berinert® [prescribing information]. Kankakee, IL: CSL Behring LLC; February 2015.</td>
</tr>
<tr>
<td>- Centers for Medicare &amp; Medicaid Services: C1 esterase inhibitor (human) (Berinert®). No national or local coverage determination found in the coverage database. December 09, 2010.</td>
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Longhurst HJ, Farkas H, Craig T, et al. HAE international home therapy consensus document. Allergy, Asthma, and Clinical Immunology

Berinert® [prescribing information]. Kankakee, IL: CSL Behring LLC; September 2015.


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<tr>
<th>HCPCS Code(s):</th>
<th>Description</th>
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<tr>
<td>J0597</td>
<td>Injection, C-1 esterase inhibitor (human), Berinert, 10 units</td>
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