Berinert [C1 esterase inhibitor (human)]
Policy Number: C6770-A

CRITERIA EFFECTIVE DATES:

<table>
<thead>
<tr>
<th>ORIGINAL EFFECTIVE DATE</th>
<th>LAST REVIEWED DATE</th>
<th>NEXT REVIEW DATE</th>
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<tr>
<td>3/1/2010</td>
<td>07/17/2019</td>
<td>07/17/2020</td>
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J CODE | TYPE OF CRITERIA | LAST P&T APPROVAL/VERSION
J0597 Injection, c-1 esterase inhibitor (human), berinert, 10 units | RxPA | Q2 2019 | 20190828C6770-A |

PRODUCTS AFFECTED:
Berinert (C1 esterase inhibitor, human)

DRUG CLASS:
C1 Inhibitors

ROUTE OF ADMINISTRATION:
Intravenous

PLACE OF SERVICE:
Specialty Pharmacy or Buy and Bill
The recommendation is that medications in this policy will be for pharmacy benefit coverage and administered in a place of service that is a non-hospital facility based location (i.e., home infusion provider, provider’s office, free-standing ambulatory infusion center) or if trained by self-administration

AVAILABLE DOSAGE FORMS:
Berinert KIT 500UNIT/10ml

FDA-APPROVED USES:
For the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adults and pediatric patients

COMPRENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: hereditary angioedema (HAE)

REQUIRED MEDICAL INFORMATION:
A. TREATMENT OF ACUTE HEREDITARY ANGIOEDEMA ATTACKS:
1. Documentation of HAE diagnosis and subtype confirmed by ONE of the following:
   (a) TYPE 1 OR 2 HAE; Presence of a mutation in the C1INH gene altering protein synthesis and/or function
   OR
   (b) BOTH of the following: (documentation of TWO (2) separate low measurements for each test defined as below the testing laboratory’s lower limit of the normal range): Low serum complement factor 4 (C4) level (< 14 mg/dL) AND Low C1 inhibitor (C1INH) level (C1INH < 19.9 mg/dL), OR Low C1INH functional level (functional C1INH < 72%) OR
Prior Authorization Criteria

(c) TYPE 3 HAE confirmed by BOTH of the following: Normal C4 level, normal C1 inhibitor antigenic protein level and normal C1 inhibitor functional activity AND Member meets EITHER of the following criteria: Tested positive for the F12 gene mutation OR a family history of angioedema

AND

2. Prescribed for ACUTE treatment of acute abdominal, facial, or laryngeal HAE attacks associated with HAE (not for routine prophylaxis)

AND

3. Recurrent history of acute episodes of moderate to severe facial, cutaneous or abdominal attacks and/or airway swelling, tongue swelling, laryngeal edema or pharyngeal edema

AND

4. All other causes and potentially treatable triggers of HAE attacks (i.e. stress, trauma, infection, etc.) have been identified and optimally managed

AND

5. Concurrent therapies that may exacerbate HAE, have been evaluated and has been discontinued as appropriate, including: Estrogen-containing medications [e.g. hormone replacement therapy, contraceptives], ACE-inhibitor (ACEI), Angiotensin II receptor blockers

AND

6. Member is NOT concurrently on, or using in combination with, other approved treatments for ACUTE HAE attacks (e.g. Firazyr®, Ruconest®, and Kalbitor®)

DURATION OF APPROVAL: Initial authorization: 6 months, Continuation of therapy: 6 months

QUANTITY: May authorize up to a sufficient quantity for member to have a cumulative amount on-hand to treat up to 2 acute attacks per month [*5,000 unit (10 vials) per 30 days]

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified immunologist, allergist, hematologist, or physician experienced in the treatment of C1-esterase inhibitor deficiency. Submit consultation notes if applicable.

AGE RESTRICTIONS:
5 years of age or older

GENDER:
Male and female

CONTINUATION OF THERAPY:
A. TREATMENT OF ACUTE HEREDITARY ANGIOEDEMA ATTACKS:
   1. Member currently meets ALL initial coverage criteria

   AND

   2. Subsequent authorizations require re-assessment treatment regimen/plan, an evaluation of the frequency of HAE attacks and complete clinical review of member’s condition to determine if continuation of treatment with requested treatment is medically necessary. Submit all relevant clinical notes, chart notes, and consultation notes (if applicable) for review at least once every 6 months.

   AND

   3. Documenation of significant improvement in the following aspects of HAE attacks have been achieved: Severity, Duration or Clinical documentation of functional improvement

   AND

   4. IF MEMBER IS CONCURRENTLY ON PROPHYLAXIS MEDICATION FOR HAE: Adherence to prophylactic therapy for HAE (with antifibrinolytics, attenuated androgens, or plasma derived C1 inhibitor replacement therapy) NOTE: Adherence to prescribed prophylactic therapy for HAE
must be confirmed by member’s prescription claims. If member is new to Molina and does not have a prescription claims history, Prescriber certify that the member has been adherent to the prescribed prophylactic therapy.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION: All other uses of Berinert (C1 esterase inhibitor, human) are considered experimental/investigational and therefore, will follow Molina’s Off-Label policy. Contraindications include: History of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations

OTHER SPECIAL CONSIDERATIONS: None

BACKGROUND:
Hereditary Angioedema (HAE)
A rare genetic disorder of recurrent attacks of localized subcutaneous or mucosal swelling that affects 1 in 10,000 to 1 in 50,000 individuals in the United States. Attack frequency varies from a few days to decades between attacks and severity ranges from mild to more severe laryngeal edema causing airway obstruction and fatal asphyxiation. Formal diagnosis is often significantly delayed following onset of symptoms and misdiagnosis or medical mismanagement is not uncommon. The two most common forms of HAE (Types I and II) may be managed with prophylaxis or acute treatment depending on attack frequency, severity, and drug tolerability.

Types of HAE
There are four types of HAE in the classification system, Both type I and type II HAEs are caused by mutations in the gene that encodes C1INH (SERPING1). US HAE Association Medical Advisory Board 2013
Type I HAE
• Hereditary C1 inhibitor deficiency indistinguishable clinically from type II HAE
• This is the most common form of the disease (accounts for about 85% of patients with HAE
• Characterized by low quantitative levels of C1-inhibitor (decreased production of C1-INH; low levels of endogenous C1 inhibitor)
• Associated with low complement C4 levels, low C1 inhibitor antigenic levels, and low C1 functional levels
Type II HAE
• Hereditary C1 inhibitor deficiency indistinguishable clinically from type I HAE
• Accounts for about 15% of patients with HAE
• Normal or elevated levels of C1-inhibitor, but the protein does not function properly
• Associated with low complement C4 levels, normal C1 inhibitor antigenic, and low C1 functional levels
Type III HAE
• Occurs primarily in women
• Type III HAE is estrogen-dependent form of angioedema
• Attacks are often associated with increased estrogen levels (pregnancy, oral contraception, hormonal replacement therapy)
• Also known as HAE with normal C1-INH levels, which is the rarest form of this condition

Acquired C1 inhibitor deficiency (C1INH-AAE)
• Not associated with family history of angioedema
• Associated with low complement C4 levels, low C1 inhibitor antigenic, and low C1 functional levels
• May be related to malignancy (mainly lymphoproliferative disorder) or autoantibodies to C1 inhibitor deficiency

Etiology
Types I and II HAE caused by C1 inhibitor deficiency (AAAAI/ACAAI)
Genetic mutation leads to disrupted C1 inhibitor protein secretion or function (AAAAI/ACAAI)
Type 1 HAE: mutation of serpin peptidase inhibitor, clade G (C1 inhibitor), member 1 (SERPING1) results in truncated or misfolded C1 inhibitor proteins that cannot be secreted
Type II HAE, mutation of SERPING1 results in C1 inhibitor proteins that can be secreted but are not functional. More than 275 different mutations have been found for HAE (according to the C1 inhibitor gene mutation database). Most patients with HAE have family history of angioedema, which is inherited with autosomal dominance (AAAAI/ACAAI)

Diagnosis
The diagnosis of HAE is based on the patient’s family history, clinical presentation, and laboratory results. There are three specific blood tests used to confirm Hereditary Angioedema Type I or II: C1-inhibitor quantitative (antigenic), C1-inhibitor functional, C4
Laboratory testing can confirm or rule out the diagnosis. Assess all patients suspected of having HAE-I/II for blood levels of C4, C1 esterase inhibitor (C-I NH) protein, and C1-INH function. (WAO 2013). Almost all patients with HAE have persistently low antigenic C4 levels with normal antigenic C1 and C3 levels. Measurement of C4 levels is often used as a screening test to rule out HAE; subsequent measurement of antigenic and functional C1 inhibitor levels confirms the diagnosis. (Zuraw 2008). The most reliable and cost-effective screening test for HAE is a serum C4 level. The C4 concentration is almost always decreased during attacks and is usually low between attacks. If the C4 level is in the normal range but suspicion for angioedema is high, the test should be repeated. The concentrations of C3 and C1q are normal in patients with HAE, regardless of the clinical status of their disease (Zuraw 2008)

Type III HAE (HAE with normal C1INH)-Exerpts from A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema
A third form of HAE with normal C1INH has been described; however, there are currently no valid diagnostic tests for this form and the diagnosis is based on exclusion. Familial recurrent angioedema characterized by normal C1INH function can be present; however, there are no commonly agreeupon criteria for diagnosing HAE with normal C1INH levels at this time (C). Some kindreds with HAE with normal C1INH levels appear to require high estrogen levels for the angioedema to manifest. (C) HAE with normal C1INH levels can be caused by increased bradykinin signaling. (C) Drugs developed for patients with HAE with reduced C1INH levels have been reported to be effective in some patients with HAE with normal C1INH levels. (C) Annotation 7: HAE with normal C1INH levels. An additional form of inherited angioedema has been described in which multiple generations are involved in a pattern consistent with autosomal dominant inheritance; however, the C1INH gene and protein levels are completely normal. The clinical pattern of angioedema attacks is similar to that seen in patients with HAE with prolonged angioedema episodes and marked differences in severity from patient to patient. At the current time, there is no definitive laboratory or clinical parameter to confirm a diagnosis of HAE with normal C1INH levels, and the diagnosis can only be considered in patients with a strong family
history suggestive of an autosomal dominant pattern. The original descriptions of HAE with normal C1INH levels were of families in which all the affected subjects were women. Furthermore, attacks of angioedema were believed to mirror states of high endogenous estrogen (ie, pregnancy) or administration of exogenous estrogen. Subsequently, a number of families have been described with affected male subjects and with affected female subjects whose angioedema does not depend on high estrogen levels. Summary Statement 30: Familial recurrent angioedema characterized by normal C1INH function might represent HAE with normal C1INH levels; however, there are no agreed upon criteria for diagnosing HAE with normal C1INH levels at this time (C). An additional form of inherited angioedema has been described in which multiple generations are involved in a pattern consistent with an autosomal dominant inheritance; however, levels of the C1INH gene and protein are completely normal. The clinical pattern of angioedema attacks is similar to that seen in patients with HAE with prolonged angioedema episodes and marked differences in severity from patient to patient.112 At the current time, there is no definitive laboratory or clinical parameter to confirm a diagnosis of HAE with normal C1INH levels, and the diagnosis can only be considered in patients with a strong family history suggestive of an autosomal dominant pattern. Summary Statement 31: Some kindreds with HAE with normal C1INH levels appear to require high estrogen levels for the angioedema to manifest. (C) The original descriptions of HAE with normal C1INH levels described families in which all the affected subjects were women. Furthermore, attacks of angioedema were believed to mirror states of high endogenous estrogen (ie, pregnancy) or administration of exogenous estrogen. Subsequently, a number of families have been described with affected male subjects and with affected female subjects whose angioedema does not depend on high estrogen levels. Summary Statement 32: HAE with normal C1INH levels can be caused by increased bradykinin signaling. (C) Recently, several of the kindreds with HAE with normal C1INH levels have been reported to have a gain-of-function mutation in coagulation factor XII that might result in enhanced generation of bradykinin.113-115 However, other families with HAE with normal C1INH levels were screened for this mutation and found not to have it, with the incidence of factor XII mutations in this population being approximately 30%. The prevalence of this factor XII mutation in HAE with normal C1INH patients in the United States appears to be much lower. A more recent study did not confirm that this factor XII mutation caused a gain of function.116 It is possible that HAE with normal C1INH levels is a heterogeneous disease with multiple underlying causes, possible involving kinin-forming enzymes, kininases, or bradykinin receptors. Appropriate laboratory tests to assess this pathway are not generally available at this time. Summary Statement 33: Drugs developed for patients with HAE with reduced C1INH function have been reported to be effective in some patients with HAE with normal C1INH levels. (C) A number of open-label reports have been published showing that patients with HAE with normal C1INH levels might respond to many of the same drugs as do patients with type I and type II HAE. As with type I and type II HAE, corticosteroids and antihistamines are ineffective for HAE with normal C1INH levels. There are reports of successful on-demand treatment with the C1INH concentrates, ecallantide and icatibant. 117-119 In addition, some patients with HAE with normal C1INH levels have been reported to show improvement with long-term prophylactic therapy with danazol, progesterone, or tranexamic acid
APPENDIX:

REFERENCES: