

## Corporate Medical Policy

### Treatment of Hereditary Angioedema

**File Name:** treatment\_of\_hereditary\_angioedema  
**Origination:** 7/2012  
**Last CAP Review:** 11/2019  
**Next CAP Review:** 11/2020  
**Last Review:** 11/2019

#### Description of Procedure or Service

---

Hereditary angioedema (HAE) is an autosomal dominant disorder of C1 inhibitor (C1-INH) deficiency characterized by recurrent episodes of severe swelling (angioedema). The most common areas of the body to develop swelling are the limbs, face, intestinal tract, and airway. Minor trauma or stress may trigger an attack, but swelling often occurs without a known trigger. Episodes involving the intestinal tract cause severe abdominal pain, nausea, and vomiting. Swelling in the airway can restrict breathing and lead to life-threatening obstruction of the airway. Patients may develop urticaria, although this only occurs in approximately 30 percent of the affected population.

HAE is estimated to affect 1 in 50,000 people. Type I is the most common, accounting for 85 percent of cases. Type II occurs in 15 percent of cases, and type III is extremely rare. Types I and II result from mutations in the gene encoding C1 inhibitor protein (C1-INH, SERPING1), whereas type III involves mutations in the F12 gene, encoding coagulation factor XII (Hageman factor). Type I HAE is characterized by low plasma levels of a normal C1-INH protein, type II HAE is characterized by the presence of normal or elevated levels of a dysfunctional C1-INH, whereas type III HAE has been recently identified as an estrogen-dependent form of angioedema occurring mainly in women with normal functional and quantitative levels of C1-INH.

Until recently, no effective agent for acute attacks of HAE existed in the United States. Commonly employed drugs for prophylaxis and treatment of these patients include 17 alpha-alkylated androgens (e.g., danazol and stanozolol), antifibrinolytic agents (e.g., epsilon aminocaproic acid tranexamic acid), and infusion of C1-INH concentrate. Additionally, fresh frozen plasma is also an option to be considered for short-term prophylaxis or treatment of acute attacks.

This policy addresses five new products that have been approved by the Food and Drug Administration (FDA) as treatments for HAE. Cinryze® is a C1 esterase inhibitor (human) indicated for routine prophylaxis against angioedema attacks in pediatric (6 years of age and older), adolescent, and adult patients with HAE. Berinert® is a plasma-derived concentrate of C1 esterase inhibitor (human) indicated for the treatment of acute abdominal, facial, or laryngeal attacks of HAE. Kalbitor® (ecallantide) a plasma kallikrein inhibitor, is indicated for treatment of acute attacks of hereditary angioedema. Firazyr® (icatibant) is a specific peptidomimetic bradykinin 2 receptor antagonist which inhibits the effects of bradykinin, and is indicated for the treatment of acute HAE attacks. Ruconest®/Rhucin®, a recombinant analogue of human complement component 1 esterase inhibitor, is indicated for the treatment of acute angioedema attacks in patients with hereditary angioedema.

#### **Related Policies:**

Place of Service for Medical Infusion

# Treatment of Hereditary Angioedema

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Policy

---

**BCBSNC will provide coverage for treatment of Hereditary Angioedema when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

## Benefits Application

---

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Treatment of Hereditary Angioedema is covered

---

Cinryze<sup>®</sup> may be considered medically necessary for **prophylaxis** against angioedema attacks in adolescents, adults, and pediatric patients (6 years of age and older) with hereditary angioedema (HAE) when the following criteria are met:

1. Patient has a history of moderate to severe HAE attacks (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability); **and**
2. Diagnosis of HAE is documented based on evidence of a normal C1 level and a low C4 level as defined by the laboratory performing the test, **with any of the following indicators:**
  - a. C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test
  - b. C1INH functional level below the lower limit of normal as defined by the laboratory performing the test
  - c. known HAE-causing C1INH mutation.

Berinert<sup>®</sup> may be considered medically necessary for the treatment of **acute** abdominal, laryngeal or facial HAE attacks, in patients 13 years of age or older, when the following criteria are met:

1. Patient must be experiencing at least one symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability); **and**
2. Diagnosis of HAE is documented based on evidenced of a normal C1 level and a C4 level below the lower limit of normal as defined by the laboratory performing the test **with either of the following indicators:**
  - a. C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test
  - b. C1INH functional level below the lower limit of normal as defined by the laboratory performing the test

Kalbitor<sup>®</sup> (ecallantide) may be considered medically necessary for the treatment of **acute** HAE attacks, in patients 12 years of age or older, when the following criteria are met:

1. Patient must be experiencing at least one symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability) **and**

# Treatment of Hereditary Angioedema

2. Diagnosis of HAE is documented based on evidenced of a normal C1 level and a C4 level below the lower limit of normal as defined by the laboratory performing the test **with either of the following indicators:**
  - a. C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test
  - b. C1INH functional level below the lower limit of normal as defined by the laboratory performing the test

Firazyr® (icatibant) may be considered medically necessary for the treatment of **acute** attacks of HAE in people aged 18 years and older when the following criteria are met:

1. Patient must be experiencing at least one symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability) **and**
2. Diagnosis of HAE is documented based on evidenced of a normal C1 level and a C4 level below the lower limit of normal as defined by the laboratory performing the test **with either of the following indicators:**
  - a. C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test
  - b. C1INH functional level below the lower limit of normal as defined by the laboratory performing the test

Ruconest® may be considered medically necessary for the treatment of **acute** attacks in adult and adolescent patients with hereditary angioedema (HAE) aged 13 years and older when the following criteria are met:

1. Patient must be experiencing at least one symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability) **and**
2. Diagnosis of HAE is documented based on evidenced of a normal C1 level and a C4 level below the lower limit of normal as defined by the laboratory performing the test **with either of the following indicators:**
  - a. C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test
  - b. C1INH functional level below the lower limit of normal as defined by the laboratory performing the test

## **When Treatment of Hereditary Angioedema is not covered**

Cinryze® is considered investigational for the treatment of **acute** hereditary angioedema attacks and all other indications except those described above.

Berineri® is considered investigational as **prophylaxis** against angioedema attacks and all other indications except as described above.

Kalbitor® (ecallantide) is considered investigational as **prophylaxis** against angioedema attacks and all other indications except as described above.

Firazyr® (icatibant) is considered investigational as **prophylaxis** against angioedema attacks and all other indications except as described above.

Ruconest® is considered investigational as **prophylaxis** against angioedema attacks and all other indications except as described above.

# Treatment of Hereditary Angioedema

## Policy Guidelines

---

Therapy for HAE consists of long-term prophylaxis for patients with frequent or severe attacks, short-term prophylaxis for administration when a patient will be exposed to a known trigger (e.g., planned dental or minor surgical procedure), and rescue treatment for acute attacks. Standard treatments for other types of angioedema (e.g., epinephrine, corticosteroids, anti-histamines) are not effective for treating HAE. The optimal treatment plan for patients with HAE varies and is individualized based on patient-specific factors (e.g. age, comorbidities, emergency medical access, past patient experience) and preferences.

Antifibrinolytics and attenuated androgens are commonly used for prophylaxis or treatment of HAE, however a number of patients either do not respond sufficiently to these agents or are unable to tolerate adverse events associated with their use. Fresh frozen plasma is also used for prophylaxis or acute treatment for HAE attacks. C1-inhibitor products are used for long-term prophylaxis, short-term prophylaxis, and rescue treatment in other parts of the world. Cinryze® is the only C1-inhibitor available in the U.S., and is currently only labeled for long-term prophylaxis of HAE. Cinryze® has been used as a treatment for cerebral ischemic injury, cytokine-induced vascular leak syndrome, myocardial infarction, and sepsis. Effectiveness of Cinryze® for these indications has not been established in the available scientific literature.

Berinert®, Kalbitor®, Ruconest® and Firazyr® are FDA approved only in cases of acute hereditary angioedema attacks. These products are not approved for use as prophylaxis. Firazyr has been proposed as a treatment for acute pancreatitis, airways disease, thermal injury, drug-induced angioedema, and refractory ascites in persons with liver cirrhosis; however, Firazyr's effectiveness has not been established for these clinical indications. Kalbitor has been proposed as a treatment to reduce blood loss during surgery; however Kalbitor's effectiveness for this indication has not been established.

An FDA Black Box warning has been issued for Kalbitor which states: "Anaphylaxis has been reported after administration of Kalbitor. Because of the risk of anaphylaxis, Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer Kalbitor to patients with known clinical hypersensitivity to Kalbitor."

Ruconest is contraindicated in patients with a history of allergy to rabbits or rabbit-derived products. Ruconest is contraindicated in patients with a history of life-threatening immediate hypersensitivity reactions to C1 esterase inhibitor preparations, including anaphylaxis. Ruconest is not indicated for use in children under the age of 13 years.

### **Treatment of Hereditary Angioedema - Site of Care Eligibility**

1. Administration for treatment of hereditary angioedema may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of hereditary angioedema infusion is not medically necessary.
2. Treatment of Hereditary Angioedema administration in a hospital outpatient setting is considered medically necessary if the following criteria are met:
  - a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.), OR
  - b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
  - c. First infusion, OR
  - d. Less than 3 months since first hereditary angioedema infusion, OR
  - e. First infusion after six months of no hereditary angioedema infusions, OR
  - f. Requirement of a change in hereditary angioedema product.

# Treatment of Hereditary Angioedema

- Members who do not meet the criteria above are appropriate for hereditary angioedema administration in a home-based or physician office setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

## Billing/Coding/Physician Documentation Information

---

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: J0596, J0597, J0598, J1290, J1744, J3490, J3590*

*NOTE: Code J0599 (Haegarda) will be covered under the member's pharmacy benefit; code is effective 1/1/19.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

---

US Food and Drug Administration (FDA). FDA Approves Berinert to Treat Abdominal Attacks, Facial Swelling Associated With Hereditary Angioedema. Retrieved on May 4, 2012, from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm186257.htm>.

US Food and Drug Administration (FDA). FDA Approves Kalbitor for Treating Potentially Life-Threatening Attacks of Hereditary Angioedema. Retrieved on May 4, 2012 from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm192687.htm>

US Food and Drug Administration. Advisory Committee Briefing Document: Kalbitor (ecallantide) For Acute Attacks of Hereditary Angioedema. Retrieved on May 4, 2012, from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM170334.pdf>.

US Food and Drug Administration (FDA). FDA Approves Firazyr to treat acute attacks of hereditary angioedema. Retrieved on May 4, 2012 from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm269616>.

US Food and Drug Administration (FDA). FDA Approves FDA Licenses for Marketing New Therapy for Rare Genetic Disease. Retrieved on May 4, 2012 from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm161477.htm>

Allergy, Asthma and Clinical Immunology (AACI). 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Retrieved on May 4, 2012 from <http://www.aacijournal.com/content/6/1/24>

National Institutes of Health (NIH). Evaluation of the Safety of Self-Administration With Icatibant. (EASSI) Available from: Retrieved on May 4, 2012 from <http://clinicaltrials.gov/show/NCT00997204>.

National Institutes of Health (NIH). A Study of Icatibant in Patients With Acute Attacks of Hereditary Angioedema (FAST-3). Retrieved on May 4, 2012 from <http://clinicaltrials.gov/show/NCT00912093>.

# Treatment of Hereditary Angioedema

National Institutes of Health (NIH). Genetic and Rare Diseases Information Center (GARD) Hereditary Angioedema. Retrieved on May 4, 2012 from [http://rarediseases.info.nih.gov/GARD/Condition/5979/Hereditary\\_angioedema.aspx/Showall](http://rarediseases.info.nih.gov/GARD/Condition/5979/Hereditary_angioedema.aspx/Showall)

Specialty Matched Consultant Advisory Panel review 11/2012

National Institutes of Health (NIH). Efficacy, Safety and Immunogenicity Study of Recombinant Human C1 Inhibitor for the Treatment of Acute HAE Attacks. Retrieved from <http://www.clinicaltrials.gov/ct2/show/NCT01188564?term=recombinant+human+c1+inhibitor&rank=5>

RUCONEST® (recombinant human C1 esterase inhibitor)-Development Products. Retrieved from <http://www.santarus.com./pipeline/development-products.htm>

Specialty Matched Consultant Advisory Panel review 11/2013

Medical Director review 11/2013

US Food and Drug Administration (FDA). Prescribing Information Ecallantide/Kalbitor. <http://www.kalbitor.com/hcp/rems/pdf/KalbitorFullPrescribingInformation.pdf>

US Food and Drug Administration (FDA). FDA Approves Roconest. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm405526.htm>

US Food and Drug Administration (FDA). Prescribing Information. <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM405634.pdf>

Medical Director review 8/2014

Specialty Matched Consultant Advisory Panel review 11/2014

Medical Director review 11/2014

Specialty Matched Consultant Advisory Panel review 11/2015

Medical Director review 11/2015

Specialty Matched Consultant Advisory Panel review 11/2016

Medical Director review 11/2016

Specialty Matched Consultant Advisory Panel review 11/2017

Medical Director review 11/2017

Shire ViroPharma Incorporated. Cinryze (C1 Esterase Inhibitor [Human]), for intravenous use. Highlights of prescribing information. June 2018. Available at: [http://pi.shirecontent.com/PI/PDFs/Cinryze\\_USA\\_ENG.pdf](http://pi.shirecontent.com/PI/PDFs/Cinryze_USA_ENG.pdf). Accessed November 2018.

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; 1:458. Available at: <https://www.haea.org/2013Recommendations.pdf>. Accessed November 2018.

# Treatment of Hereditary Angioedema

Specialty Matched Consultant Advisory Panel review 11/2018

Medical Director review 11/2018

Specialty Matched Consultant Advisory Panel review 11/2019

## Policy Implementation/Update Information

---

- 6/29/12 New policy developed to address the FDA approved products used as treatment of Hereditary Angioedema. BCBSNC will provide coverage for Cinryze®, Berinert®, Kalbitor® (Ecallantide), and Firazyr® (Icatibant) when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 6/2012. Notification given 6/29/12 for effective date 10/01/12. (mco)
- 8/7/12 Laryngeal Hereditary Angioedema added as a clinical indication for treatment with Berinert®. Policy remains on 90 day notification with effective date 10/01/2012. (mco)
- 1/1/13 Specialty Matched Consultant Advisory Panel review 11/2012. No changes to Policy Statements. New code added to Billing/Coding section: J1744. (mco)
- 12/10/13 Description section updated. References updated. Specialty Matched Consultant Advisory Panel review 11/2013. Medical Director review 11/2013. No changes to Policy Statements. (mco)
- 5/13/14 Age limitation for Ecallantide/Kalbitor revised from 16 years of age or older to 12 years of age or older. (mco)
- 8/26/14 New FDA approved medication Ruconest® added to policy. Description section updated. Policy Guidelines updated. “When Covered” section updated as follows: “Ruconest® may be considered medically necessary for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE) aged 13 years and older when the following criteria are met: 1.Patient must be experiencing at least one symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion) and 2.Diagnosis of HAE is documented based on evidenced of a normal C1 level and a C4 level below the lower limit of normal as defined by the laboratory performing the test with either of the following indicators: a.C1 inhibitor (C1INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test b.C1INH functional level below the lower limit of normal as defined by the laboratory performing the test.” The “When not Covered” section updated as follows: “Ruconest® is considered investigational as **prophylaxis** against angioedema attacks and all other indications except as described above.” References updated. Added J3490 and J3590 to Billing/Coding section. Medical Director review 8/2014. (mco)
- 12/9/14 References updated. Specialty Matched Consultant Advisory Panel review 11/2014. Medical Director review 11/2014. (td)
- 3/31/15 Billing/Coding section updated: added code C9445. (td)
- 12/30/15 Billing/Coding section updated to delete code C9445 and add code J0956 effective 1/1/16. References updated. Specialty Matched Consultant Advisory Panel review 11/18/2015. Medical Director review 11/2015. (td)

# Treatment of Hereditary Angioedema

- 12/30/16 Specialty Matched Consultant Advisory Panel review 11/2016. Medical Director review 11/2016. (jd)
- 12/29/17 Policy Guidelines updated to include guidelines for “Site of Care Eligibility” related to infusion. Policy notification given 1/1/18, effective 4/1/18. Code C9015 for Haegarda added to policy, to be covered under member’s pharmacy benefit, effective 1/1/18 replacing J0598. Specialty Matched Consultant Advisory Panel review 11/2017. Medical Director review 11/2017. (jd)
- 1/26/18 Added J0598 to Coding section of policy and removed statement regarding Haegarda, “replacing J0598”. (jd)
- 12/14/18 Updated “When Covered” section to extend Cinryze indication to pediatric patients (6 years of age and older). Removed criterion #2 “Patient has contraindication, or intolerance to 17 alpha-alkylated androgens or antifibrinolytic agents for HAE prophylaxis” from Cinryze policy statement. Added the following symptom of HAE attack in policy statement: “extremity swelling causing disability.” Updated indications in Description section and description of patient-specific therapy choice in Policy Guidelines for clarity. References added. Specialty Matched Consultant Advisory Panel review 11/2018. Medical Director review 11/2018. (krc)
- 12/31/18 Added HCPCS code J0599 to Billing/Coding section and deleted code C9015 effective 1/1/19. (krc)
- 12/2/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. No change to policy intent. (krc)

---

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.