

C1 Esterase Inhibitor (Berinert®)

Medicare Advantage Medical Policy #MNG-040

Original Effective Date: 01/01/2025

Current Effective Date: 01/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider the use of C1 Esterase Inhibitor (Berinert®)‡ for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adult and pediatric patients to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility will be considered for the use of C1 esterase inhibitor (Berinert) for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adult and pediatric patients when the following criteria are met:

- Patient has a diagnosis of hereditary angioedema as confirmed by appropriate lab test(s);
AND
- The drug will be used for the treatment of acute attacks.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of C1 esterase inhibitor (Berinert) for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adult and pediatric patients when patient selection criteria are not met to be **investigational**.*

Background/Overview

Berinert is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1 esterase inhibitor that is indicated for the treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and pediatric patients. Berinert is for intravenous use only. The dose for Berinert is 20 Units per kg of body weight. Berinert is administered at an injection rate of approximately 4 mL per minute. The safety and efficacy of Berinert for prophylactic therapy have not been established.

Hereditary Angioedema

Hereditary angioedema is a potentially life-threatening autosomal dominant genetic disease in which there is inadequate or nonfunctional complement-1 esterase inhibitor (C1-INH) in the blood. Hereditary angioedema is characterized by episodic, sudden, acute attacks of intense localized edema causing swelling. The swelling can occur almost anywhere but is commonly found in the following body parts: extremities, intestines (abdomen), face, larynx and genitals. Swelling attacks can occur unpredictably and vary in severity and frequency.

The prevalence of HAE is uncertain but is estimated to range from 1 in 10,000 to 1 in 50,000 persons worldwide. It is estimated that HAE affects 6,000 to 30,000 individuals in the U.S. Hereditary angioedema has been reported in all races. No sex predominance has been found between the two main types of HAE (Type I and Type II). Type I HAE accounts for 85% of all cases and results in both decreased antigenic and functional levels of C1-inhibitor. Type II HAE accounts for 15% of all cases and results in normal antigenic C1-inhibitor levels but decreased functional C1 inhibitor levels. Type III HAE is found predominantly in women and was initially associated with therapeutic estrogen. It has been suggested that HAE Type III is caused by activating mutations in the gene for coagulation factor XII. Thus, Type III HAE is not a disease of C1-esterase deficiency and will not be considered further in this review. The disease is inherited in an autosomal dominant manner, and family history is a strong predictor of the disease. However, spontaneous mutation accounts for up to 25% of newly diagnosed cases.

Symptoms of HAE can present at any age, but there appears to be an increased occurrence of HAE after puberty and a reduction after menopause, suggesting a hormone-influenced mechanism. Attacks are commonly triggered by stress, hormonal changes, medical procedures, trauma or medications that impact bradykinin or hormone levels, such as angiotensin-converting enzyme (ACE) inhibitors and estrogen-containing medications. In some cases, attacks occur without an apparent trigger. Attacks are usually preceded by a prodrome (usually a tingling sensation or painless, nonpruritic rash, skin tightness, and fatigue), which can occur 30 minutes to several hours before an HAE attack. As vascular permeability increases, swelling worsens gradually for the first 24 hours and subsides 48–72 hours after swelling reaches its peak. Unlike histamine-mediated allergic angioedema, HAE swelling attacks are not symmetrical and often extend locally. Edema may begin, worsen, and end in one anatomical location, or begin in one location and emerge in another location, or occur simultaneously in many locations. Abdominal attacks are thought to be the most debilitating attacks experienced by HAE patients. Severe attacks may cause obstruction of the gastrointestinal tract. Repeated attacks may lead to inadequate biliary/pancreatic drainage causing gallbladder disease or pancreatitis. Swelling involving the airway is less common but is potentially life-threatening. The time from symptom onset to asphyxiation ranges from 20 minutes to 14 hours. It has been reported that at least 50% of HAE patients will have a laryngeal attack at some point in their lives and many have these attacks repeatedly. Mortality rates are estimated at 15–30%, largely due to laryngeal edema.

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Hereditary angioedema is diagnosed by clinical history, diagnostic tests and exclusion of other causes of angioedema. The specific tests required to make the diagnosis include C4, C1q, and C1-INH (antigenic or functional level). Genetic testing is not necessary to confirm the diagnosis of HAE.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Berinert is a C1 esterase inhibitor approved by the FDA in 2009. It was the first drug approved for acute treatment of abdominal attacks and facial swelling associated with HAE. Berinert carries warnings for sensitivity, thrombotic events, and transmissible infectious agents. Severe hypersensitivity reactions may occur. The signs and symptoms of hypersensitivity reactions may include the appearance of hives, urticarial, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of Berinert. Thrombotic events have been reported in association with C1 esterase inhibitor products when used off-label at high doses. Because Berinert is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The safety and efficacy of Berinert in the treatment of acute abdominal or facial attacks in subjects with hereditary angioedema were demonstrated in a placebo-controlled, double-blind, prospective, multinational, randomized, parallel-group, dose-finding, 3-arm, clinical study, referred to as the randomized clinical trial (RCT). The RCT assessed the efficacy and safety of Berinert in 124 adult and pediatric subjects with C1 esterase inhibitor deficiency that was experiencing an acute moderate to severe attack of abdominal or facial HAE. Subjects ranged in age from 6 to 72 years of age; 67.7% were female and 32.3% were male; and approximately 90% were Caucasian.

The study objectives were to evaluate whether Berinert shortens the time to onset of relief of symptoms of an abdominal or facial attack compared to placebo and to compare the efficacy of two different doses of Berinert. The time to onset of relief of symptoms was determined by the subject's response to a standard question posed at appropriate time intervals for as long as 24 hours after start of treatment, taking into account all single HAE symptoms. In addition, the severity of the single HAE symptoms was assessed over time.

Subjects were randomized to receive a single 10 unit/kg body weight dose of Berinert (39 subjects), a single 20 unit/kg dose of Berinert (43 subjects), or a single dose of placebo (42 subjects) by slow intravenous infusion (recommended to be given at a rate of approximately 4 mL per minute) within

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5 hours of an HAE attack. At least 70% of the subjects in each treatment group were required to be experiencing an abdominal attack.

If a subject experienced no relief or insufficient relief of symptoms by 4 hours after infusion, investigators had the option to administer a second infusion of Berinert (20 units/kg for the placebo group, 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group). This masked (blinded) “rescue study medication” was administered to subjects and they were then followed until complete resolution of symptoms was achieved. Adverse events were collected for up to 7 to 9 days following the initial administration of Berinert or placebo.

In the rare case that a subject developed life-threatening laryngeal edema after inclusion into the study, immediate start of open-label treatment with a 20 unit/kg body weight dose of Berinert was allowed.

All subjects who received confounding medication (rescue medication) before symptom relief were regarded as “non-responders.” Therefore, time to onset of symptom relief was set at 24 hours if a subject received any rescue medication (i.e., rescue study medication, narcotic analgesics, non-narcotic analgesics, anti-emetics, open-label C1 inhibitor, androgens at increased dose, or fresh frozen plasma) between 5 hours before administration of blinded study medication until time to onset of relief.

For the trial to be considered successful, the study protocol specified the following criteria for the differences between the Berinert 20 units/kg and the placebo group:

- The time to onset of relief of symptoms of the HAE attack had to achieve a one-sided p-value of less than 0.0249 for the final analysis, and at least 1 of the following criteria had to demonstrate a trend in favor of Berinert with a one-sided p-value of less than 0.1:
 - The proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment with study medication compared to baseline, or
 - The number of vomiting episodes within 4 hours after start of study treatment.

Subjects treated with 20 IU/kg body weight of Berinert experienced a significant reduction ($p=0.0016$; “Wilcoxon Rank Sum test”) in time to onset of relief from symptoms of an HAE attack as compared to placebo (median of 48 minutes for Berinert 20 IU/kg bodyweight, as compared to a median of > 4 hours for placebo). The time to onset of relief from symptoms of an HAE attack for subjects in the 10 IU/kg dose of Berinert was not statistically significantly different from that of subjects in the placebo group.

References

1. Berinert [C1 Esterase Inhibitor (Human)] US Package Insert. CSL Behring. Kankakee, IL. September 2021.

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2. German Medical Profession's Drugs Committee. Severe thrombus formation of Berinert® HS. *Deutsches Ärzteblatt*. 2000;97:B-864.
3. Horstick, G *et al.* Application of C1-Esterase Inhibitor During Reperfusion of Ischemic Myocardium: Dose-Related Beneficial Versus Detrimental Effects. *Circulation*. 2002;104:3125-3131.
4. Carrell RW, Boswell DR. Serpins: the superfamily of plasma serine proteinase inhibitors. In: Barrett A, Salvesen G, eds. *Proteinase Inhibitors*. Amsterdam: Elsevier. 1986;12:403-420.
5. Harrison RA. Human C1 inhibitor: Improved isolation and preliminary structural characterization. *Biochemistry* 1983;22:5001-5007.
6. Davis AE, The pathophysiology of hereditary angioedema. *Clin Immunol*. 2005; 114:3-9.
7. Nuijens JH, Eerenberg-Belmer AJM, Huijbregts CCM, et al. Proteolytic inactivation of plasma C1 inhibitor in sepsis. *J Clin Invest*. 1989;84:443-450.

Policy History

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10/15/2024 UM Committee review

Next Scheduled Review Date: 10/2025

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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Code Type	Code
CPT	No codes
HCPCS	J0597
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: <https://www.cms.gov/medicare-coverage-database/search.aspx>. You may wish to review the Guide to the MCD Search here: <https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx>.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.