Hereditary Angioedema (HAE), Treatment and Prophylaxis

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➲ Instructions for Use

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Related Commercial/Individual Exchange Policies

- Self-Administered Medications (for Commercial Only)
- Self-Administered Medications (for Individual Exchange Only)

Community Plan Policy

- Hereditary Angioedema (HAE), Treatment and Prophylaxis

Application

UnitedHealthcare Commercial

This Medical Drug Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Drug Policy applies to Individual Exchange benefit plans.

Coverage Rationale

➲ See Benefit Considerations

This policy refers only to the following drug products:

- C1 Esterase Inhibitor (human):
  - Berinert® (for intravenous injection)
  - Cinryze® (for intravenous injection)*
- C1 Esterase Inhibitor (recombinant):
  - Ruconest® (for intravenous injection)
- Plasma Kallikrein Inhibitor (human):
  - Kalbitor® (ecallantide, for subcutaneous injection)

Hereditary Angioedema

Berinert, Ruconest, and Kalbitor are proven for the treatment of hereditary angioedema (HAE) when both of the following are met:

- Used for treatment of an acute HAE attack; **and**
- Not used in combination with other approved treatments for acute HAE attacks (e.g., Berinert, Firazyr, Kalbitor, or Ruconest)

Berinert, Ruconest, and Kalbitor are medically necessary for the treatment of hereditary angioedema (HAE) when all of the following criteria are met:

- For **Initial therapy**:

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- Diagnosis of hereditary angioedema (HAE) as confirmed by **one** of the following:
  - A C1 inhibitor (C1-INH) deficiency or dysfunction (Type I or II HAE) as documented by **one** of the following (per laboratory standard):
    - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal; **or**
    - C1-INH functional level below the lower limit of normal

    or
  - Normal C1 inhibitor levels and **one** of the following:
    - Confirmed presence of variant(s) in the gene(s) for factor XII, angiopoietin-1, plasminogen-1, kininogen-1, myoferlin, and heparan sulfate-glucosamine 3-O-sulfotransferase 6; **or**
    - Recurring angioedema attacks that are refractory to high-dose antihistamines with confirmed family history of angioedema; **or**
    - Recurring angioedema attacks that are refractory to high-dose antihistamines with unknown background de-novo mutation(s) (i.e., no family history) (HAE-unknown)

  and
- Used for treatment of an acute HAE attack; **and**
- Not used in combination with other approved treatments for acute HAE attacks (e.g., Berinert, Firazyr, Kalbitor, or Ruconest); **and**
- Prescribed by one of the following specialists:
  - Immunologist; **or**
  - Allergist

  and
- **For Berinert requests only**; submission of medical records documenting a history of failure, contraindication, or intolerance to Ruconest [C1 esterase inhibitor (recombinant)]; **and**
- **For Berinert and Ruconest requests only**; physician attestation that the patient is unable to self-administer or there is no competent caregiver to administer the drug; **and**
- Initial authorization will be for no more than 12 months

- For **continuation of therapy**, all of the following:
  - Documentation of positive clinical response; **and**
  - Used for treatment of an acute HAE attack; **and**
  - Not used in combination with other approved treatments for acute HAE attacks (e.g., Berinert, Firazyr, Kalbitor, or Ruconest); **and**
  - Prescribed by **one** of the following specialists:
    - Immunologist; **or**
    - Allergist

    and
  - **For Berinert and Ruconest requests only**; physician attestation that the patient is unable to self-administer or there is no competent caregiver to administer the drug; **and**
  - Reauthorization will be for no more than 12 months

**Medical Necessity Plans*

Cinryze is not medically necessary for the treatment of hereditary angioedema (HAE). Published clinical evidence does not demonstrate superiority in the efficacy and safety of Cinryze to other available C1 esterase inhibitors (e.g., Berinert, Haegarda).

Non-Medical Necessity Plans

Cinryze is proven for the treatment of hereditary angioedema (HAE) when both of the following are met:

- Used for prophylaxis against HAE attacks; **and**
- Not used in combination with other products indicated for the prophylaxis against HAE attacks (e.g., Haegarda, Takhzyro)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

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HCPCS Code	Description
J0596	Injection, C1 esterase inhibitor (recombinant), Ruconest, 10 units
J0597	Injection, C-1 esterase inhibitor (human), Berinert, 10 units
J0598	Injection, C1 esterase inhibitor (human), Cinryze, 10 units
J1290	Injection, ecallantide, 1 mg

Diagnosis Code	Description
D84.1	Defects in the complement system

Background

C1 Esterase Inhibitor

Human

Cinryze and Berinert are highly purified, pasteurized, nanofiltered, lyophilized C1 inhibitor products prepared from large pools of human plasma from U.S. donors. C1 inhibitor is a normal constituent of human blood and is one of the serine proteinase inhibitors (serpins). The primary function of C1 inhibitor is to regulate the activation of the complement and intrinsic coagulation (contact system) pathway. C1 inhibitor also regulates the fibrinolytic system. HAE patients have low levels of endogenous or functional C1 inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it is thought that increased vascular permeability and the clinical manifestation of HAE attacks are primarily mediated through contact system activation. Suppression of contact system activation by C1 inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin, the main mediator of HAE attacks.

Cinryze increases antigenic and functional plasma levels of C1 inhibitor, thereby increasing the deficient C1 inhibitor.

Berinert is a human plasma C1 esterase inhibitor to be reconstituted for intravenous administration. Administration of Berinert to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients.

Recombinant

Ruconest is a serine protease inhibitor which suppresses complement and contact pathway systems by irreversibly binding to and inactivating proteases such as kallikrein and factor XIIa. These actions on the contact pathway system prevent the formation of bradykinin, and regulate vascular permeability that is thought to contribute to hereditary angioedema attacks.

Human Plasma Kallikrein Inhibitor (Human)

Kalbitor is a human plasma kallikrein inhibitor for injection for subcutaneous use to treat symptoms hereditary angioedema (HAE). HAE is a rare genetic disorder caused by mutations to C1-esterase-inhibitor (C1-INH) located on Chromosome 1 1q and inherited as an autosomal dominant trait. HAE is characterized by low levels of C1-INH activity and low levels of C4. C1-INH functions to regulate the activation of the complement and intrinsic coagulation (contact system pathway) and is a major endogenous inhibitor of plasma kallikrein. The kallikrein-kinin system is a complex proteolytic cascade involved in the initiation of both inflammatory and coagulation pathways. One critical aspect of this pathway is the conversion of high molecular weight (HMW) kininogen to bradykinin by the protease plasma kallikrein. In HAE, normal regulation of plasma kallikrein activity and the classical complement cascade is therefore not present. During attacks, unregulated activity of plasma kallikrein results in excessive bradykinin generation. Bradykinin is a vasodilator which is thought by some to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Kalbitor is a potent (Ki = 25 pM), selective, reversible inhibitor of plasma kallikrein. Kalbitor binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of HMW kininogen to bradykinin.

By directly inhibiting plasma kallikrein, Kalbitor reduces the conversion of HMW kininogen to bradykinin and thereby treats symptoms of the disease during acute episodic attacks of HAE.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some

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diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

Proven

HAE (Acute)

Ruconest

Riedl et al. conducted an open-label study in North America to assess the safety and efficacy of recombinant human C1 inhibitor (rhC1INH) (Ruconest) for repeated treatment of acute attacks of hereditary angioedema (HAE). Patients with HAE attacks were treated with an intravenous 50-U/kg dose of rhC1INH with an option for an additional dose of 50-U/kg based on clinical response. Patients used a 100-mm visual analogue scale (VAS) to assess time to beginning of relief. Safety evaluation was based on the clinical laboratory results and adverse events. Sixty-two patients were treated for 168 attacks (range, 1-8 attacks per patient). A total of 90% of the attacks were treated with a single 50-U/kg dose of rhC1INH. Median times to beginning of symptom relief for the first 5 attacks ranged from 37 to 67 minutes. More than 90% of attacks responded within 4 hours after treatment with rhC1INH. Thirty-nine patients (63%) reported at least 1 treatment-emergent adverse event, with most events rated mild to moderate. There were seven severe treatment-emergent adverse events reported, however, all were considered to be unrelated to rhC1INH treatment. The results of this open-label extension support continued efficacy of rhC1INH after repeated treatments for subsequent HAE attacks. Additionally, there were no increases in adverse event reporting after repeated exposure to rhC1INH.

In a phase 3, randomized, placebo-controlled trial, researchers evaluated the efficacy and safety of recombinant human C1 inhibitor (rhC1INH 50 IU/kg to maximum 4,200 IU/treatment) versus placebo in patients with hereditary angioedema (HAE) experiencing peripheral, abdominal, facial, and/or oropharyngeal laryngeal attacks.[23] Seventy-five patients were randomized (3:2) to rhC1INH (n = 44) or placebo (saline; n = 31). Efficacy was assessed by patient responses on both a Treatment Effect Questionnaire (TEQ) and visual analog scale (VAS). Safety also was evaluated. Median (95% CI) time to beginning of symptom relief at the primary attack location was 90 minutes (range: 61-150) in rhC1INH-treated patients vs 152 minutes in placebo-treated patients (p = 0.031) based on the TEQ and 75 minutes (range: 60-105) vs 303 minutes (range: 81-720, p = 0.003) based on a VAS decrease of at least 20 mm. Median time to minimal symptoms was 303 minutes (range: 240-720) in rhC1INH-treated patients vs 483 minutes (range: 300-1,440) in placebo-treated patients based on the TEQ (p = 0.078) and 240 minutes (range: 177-270) vs 362 minutes (p = 0.005), based on an overall VAS less than 20 mm. No thromboembolic events, anaphylaxis, or neutralizing antibodies were reported with rhC1INH treatment. Consistent with previous trial results, relief of symptoms of HAE attacks was achieved faster, and safely, with rhC1INH compared with placebo.

Berinert

Utilizing data obtained during IMPACT-2, researchers performed a retrospective subgroup analysis to evaluate if repeated treatment with C1 esterase inhibitor (C1-INH) concentrate (Berinert) dosed at 20 U/kg for successive attacks had any effect on the treatment response to C1-INH concentrate. Fifty-seven patients were studied in IMPACT-2, and of those 57 patients, 18 patients (32%) were treated with C1-INH concentrate for at least 15 attacks each over a mean duration of 34 months (range, 10-51 months). Of the 18 patients treated for ≥ 15 attacks, 7 patients (39%) had between 15 and 25 HAE attacks and 11 patients (61%) had 25 HAE attacks. The distribution of body locations and the intensity of HAE attacks were similar for each of the first 15 attacks and subsequent attacks. Repeated treatment had no systematic effect on the frequency of HAE attacks, the intensity of HAE attacks, the time to onset of symptom relief, or the time to complete resolution of HAE symptoms (the median of individual linear regression coefficients was not statistically significantly different from 0). Additionally, repeated treatment with C1-INH concentrate is not associated with development of inhibitory anti–C1-INH antibodies. The authors concluded that treatment with 20 U/kg of C1-INH concentrate provided consistent response in patients treated for multiple successive HAE attacks regardless of location.

In a prospective, open-label, uncontrolled, multicenter extension study of IMPACT-1, safety, and efficacy of long-term treatment with C1 esterase inhibitor concentrate (C1-INH) (Berinert) 20 U/kg was evaluated in subsequent hereditary angioedema (HAE) attacks at any body location (IMPACT-2). Patients were eligible if they had any type of HAE attack and had previously participated in IMPACT-1 for which they had to be at least 6 years of age with HAE type I or II. The primary efficacy endpoint was the time from start of treatment to onset of symptom relief, analyzed on a per-patient and per-attack basis. The secondary endpoint was the patient-reported time to complete resolution of HAE symptoms. Adverse events, vital signs, viral safety, and anti-C1-INH antibodies were measured to evaluate safety. During a median study duration of 24 months (range: 0-51 months), 1,085 attacks were treated in 57 patients (10-53 years of age). In the per-patient analysis, the median time to onset of symptom relief on any body location was 0.46 h (shortest for abdominal

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attacks: 0.39 h compared to 0.44 h for laryngeal, 0.43 h for peripheral and 0.48 h for facial); the median time to complete resolution of symptoms was 15.5 h (shortest for laryngeal attacks: 5.8 h compared to 12.8 h for abdominal, 22.7 h for peripheral and 26.6 h for facial attacks). Demographic factors, type of HAE, intensity of attacks, time to treatment, and use of androgens and presence of anti-C1-INH antibodies had no clinically relevant effect on the efficacy outcomes. There were no treatment-related safety concerns. No inhibitory anti-C1-INH antibodies were detected in any patient. Authors conclude that a single dose of 20 U/kg C1-INH concentrate is safe and provides reliable efficacy in the long-term treatment of successive HAE attacks at any body location.

In a randomized, double-blind, placebo-controlled trial, the efficacy of pasteurized C1 esterase inhibitor concentrate (C1-INH) (Berinert) was studied in 125 patients at least 6 years of age with type I or type II hereditary angioedema (HAE) experiencing an acute adnominal or facial attack presenting for treatment within 5 hours of the attack (IMPACT-1). Patients were randomized to receive a single intravenous infusion of C1-INH 10 U/kg (n = 40), C1-INH 20 U/kg (n = 43) or placebo (n = 42). The primary endpoint was time from start of treatment to onset of symptom relief, as determined by patient responses to a standard question posed at appropriate time intervals for as long as 24 hours after the start of treatment. Secondary outcomes were time to complete resolution of all HAE symptoms, proportion of patients with worsened intensity of angioedema symptoms between 2 and 4 hours after treatment, and number of vomiting episodes within 4 hours. Median time to onset of relief was significantly shorter with C1-INH concentrate at a dose of 20 U/kg than with placebo (0.5 vs 1.5 hours; p = 0.0025), whereas with C1-INH 10 U/kg, the time to onset of relief was only slightly shorter than with placebo (1.2 vs 1.5 hours; p = 0.2731). The reduction in time to onset of relief was greatest for severe attacks (0.5 vs 13.5 hour) as compared to placebo. Median time to onset of symptom relief was relatively short for abdominal attacks (placebo, 1.3 hours; C1-INH 10 U/kg, 1.2 hours; C1-INH 20 U/kg, 0.5 hours) compared with facial attacks (placebo, 24.0 hours; C1-INH 10 U/kg, 1.3 hours; C1-INH 20 U/ kg, 0.9 hours). Secondary outcomes consistently supported the efficacy of the 20 U/kg dose. No difference in treatment effect in terms of time to onset of symptom relief could be confirmed by stratified analysis when comparing the efficacy of C1-INH 20 U/kg in facial and abdominal attacks, and in moderate and severe attacks. C1 esterase inhibitor concentrate was safe and well tolerated. No seroconversions were observed for HIV, hepatitis virus, or human B19 virus. Researchers conclude that C1-INH 20 U/kg administered intravenously is a safe and effective treatment for rapidly alleviating symptoms of abdominal and facial HAE attacks.

Kalbitor

In order to assess the potential risk for attack rebound or relapse following ecallantide treatment, Bernstein et al. conducted a post-hoc analysis of the study population from two pivotal double-blind, placebo-controlled ecallantide studies, EDEMA3-DB and EDEMA4. Measurement of symptoms was assessed by treatment outcome score (TOS), mean symptom complex severity (MSCS) score, and global response. Patients with improvement at 4 hours post-dosing in all three measures followed by any sign of worsening at 24 hours were considered to show potential rebound if worsening was beyond baseline or were considered to show potential relapse if not beyond baseline. Likeliness of rebound or relapse was determined by the number of measures showing worsening and the magnitude of worsening. Patients receiving placebo who met the criteria for rebound/relapse were utilized for descriptive comparison only. At 4 hours, improvement in at least one of three efficacy measures was seen in 51 (72.9%) ecallantide-treated and 37 (52.1%) placebo-treated patients (p = 0.01). Improvement in all three measures (TOS, MSCS score, and global response) was seen in 42 (60%) ecallantide-treated and 26 (37%) placebo-treated patients (p < 0.01). Of the 42 ecallantide-treated patients showing measured improvement, a total of 9 (21.4%) showed signs of worsening at 24 hours and were thus considered potential rebound/relapse. Of the nine ecallantide-treated patients with signs of worsening at 24 hours, none were likely to rebound, one was assessed as possible rebound, one as likely relapse, and two as possible relapse. No patient with potential rebound/relapse experienced new symptoms after dosing. Medical intervention was required in one ecallantide-treated patient (likely relapse, patient received danazol for an abdominal attack). Recognizing that relapse was observed in a small proportion of patients and there was little evidence of rebound, the authors concluded that ecallantide was efficacious for treating acute HAE attacks.

Efficacy and safety of ecallantide in the treatment of acute hereditary angioedema (HAE) attacks was evaluated in a double-blind, placebo-controlled study (EDEMA-4). Patients with moderate to severe HAE attacks were randomized 1:1 to receive subcutaneous ecallantide 30 mg (n = 48) or placebo (n = 48). Patients aged 10 years and older with documented evidence of type I or II HAE who presented within 8 hours of a moderate to severe HAE attack affecting any anatomical location were included. The primary efficacy end point was change from baseline in mean symptom complex severity score (MSCS) 4 hours after dosing. Secondary end points included treatment outcome score (TOS) 4 hours after dosing and maintenance of significant overall improvement through 24 hours. Mean (SD) change from baseline in MSCS score 4 hours after dosing was significantly greater with ecallantide use [-0.8 (SD = 0.6)] compared with placebo use [-0.4 (SD = 0.8)] (p = 0.01 comparing distributions). Ecallantide therapy was also associated with a significantly larger mean (SD) TOS 4 hours after dosing vs placebo use [ecallantide: 53.4 (SD = 49.7); placebo: 8.1 (SD = 63.2); p = 0.003 comparing distributions]. The benefit of ecallantide was apparent within 2 hours after dosing and was maintained through 24 hours after dosing as demonstrated by MSCS score (p = 0.04 comparing the distributions) and TOS (p = 0.03 comparing the

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distributions). A significantly greater proportion of ecallantide-treated patients (44%) maintained significant overall improvement through 24 hours compared with placebo users (21%) (p = 0.02). The safety profile was similar between the treatment groups. Researchers conclude that ecallantide treatment results in a rapid and significant reduction in symptom severity of acute HAE attacks and that this effect is sustained for up to 24 hours.

Efficacy of ecallantide in patients (n = 72) with hereditary angioedema presenting with an acute attack was evaluated in a double-blind, placebo-controlled trial (EDEMA-3).[9] Patients at least 10 years of age with an acute attack were randomly assigned, in a 1:1 ratio, to receive subcutaneous ecallantide 30 mg (n = 36) or placebo (n = 36) and observed for at least 4 hours after administration. Symptoms were assessed every 15 minutes for the first 2 hours, every 30 minutes for the next 2 hours, and finally at 24 hours. Two measures of patient-reported outcomes were used to assess the response: treatment outcome scores, which range from +100 (designated in the protocol as significant improvement in symptoms) to -100 (significant worsening of symptoms), and the change from baseline in the mean symptom complex severity score, which range from +2 (representing a change from mild symptoms at baseline to severe symptoms after) to -3 (representing a change from severe symptoms at baseline to no symptoms after). The primary trial end point was the treatment outcome score 4 hours after study-drug administration and secondary end points included the change from baseline in the mean symptom complex severity score at 4 hours and the time to significant improvement. At 4 hours, the median treatment outcome score was 50.0 in the ecallantide group and 0.0 in the placebo group [interquartile range (IQR), 0.0 to 100.0 in both groups; p = 0.004]. The median change in the mean symptom complex severity score at 4 hours reported was -1.00 (IQR, -1.50 to 0.00) with ecallantide, versus -0.50 (IQR, -1.00 to 0.00) with placebo (p = 0.01). Median time to significant improvement was 165 minutes with ecallantide versus more than 240 minutes with placebo (p = 0.14). There were no deaths, treatment-related serious adverse events, or withdrawals owing to adverse events. Researchers conclude that at four hours after administration of ecallantide or placebo for acute attacks of angioedema in patients with HAE, patient-reported treatment outcome scores and mean symptom complex severity scores were significantly better with ecallantide than with placebo.

HAE (Prophylaxis)

Cinryze

Zuraw et al. conducted an open-label, multicenter extension study to assess the safety and efficacy of prophylactic nanofiltered C1-inhibitor (C1INH-nf) (Cinryze) in a large cohort of patients with hereditary angioedema. A total of 146 patients (age range, 3-82 years) with hereditary angioedema received prophylactic C1INH-nf for up to 2.6 years in centers throughout the United States. The primary efficacy endpoint for each patient was the number of angioedema attacks. Safety was evaluated by the number and severity of adverse events, and changes in clinical laboratory values (viral serology performed every 3 months) and vital signs. Patients experienced a 93.7% reduction in attacks while taking prophylactic C1INH-nf (0.19 attacks per month; interquartile range, 0.00-0.64) compared with the historical rate of attacks. The majority of patients (87.7%) reported an attack frequency of 1 or less attack per month during prophylactic C1INH-nf and 51 patients (34.9%) had no attacks during the study. Twice weekly dosing C1INH-nf resulted in a favorable response rate that varied from 95.7% at 30 days to 70.7% at 120 days. Once-weekly dosing resulted in a favorable response rate that varied from 69.3% at 30 days to 45.7% at 120 days. Twice-weekly dosing had a more favorable response rate than once-weekly dosing at each interval examined. Researchers noted that despite twice-weekly C1INH-nf dosing, 7.5% of patients experienced relatively frequent attacks. No clinical characteristics predicted the response to prophylactic C1INH-nf, including historical attack frequency. C1INH-nf was well tolerated. The authors concluded that prophylactic C1INH-nf treatment is highly effective and safe, and provides durable prophylaxis in the majority of patients with hereditary angioedema. Dosing of C1INH-nf at 1,000 units twice weekly is supported by this study. Additionally, the authors commented that individual patients may benefit from further dose adjustment on the basis of response to therapy and individual treatment goals.

In a 24-week, randomized, double-blind, placebo-controlled, cross-over trial (n = 22), prophylaxis with nanofiltered C1 inhibitor concentrate (Cinryze) was evaluated in preventing attacks of hereditary angioedema (HAE) (LEVP2005-1/B). Patients aged 6 years and older with HAE due to C1 inhibitor deficiency who had been randomized to receive C1 inhibitor concentrate for the treatment of acute attacks in a double-blind, placebo-controlled trial and who had a history of 2 or more attacks per month were eligible for enrollment. Eligible patients received either C1 inhibitor concentrate 1,000 units (n = 11) or placebo (n = 11) every 3 to 4 days for 12 weeks and then switched to the other therapy for the next 12 weeks. The primary efficacy end point was the number of attacks of angioedema during each treatment period. Secondary end points included the average severity of attacks, average duration of attacks, number of open-label injections of C1 inhibitor, and total number of days of swelling. The average number of attacks in a 12-week period (primary endpoint) was 6.26 attacks during the C1 inhibitor concentrate prophylaxis period and 12.73 attacks during the placebo period (attack rate difference, 6.47 attacks; 95% CI, 4.21 to 8.73 attacks; p < 0.001). For attacks which occurred during the C1 inhibitor concentrate prophylaxis period compared with the placebo period, the mean severity score (evaluated using a 3-point scale: mild = 1; moderate = 2; severe = 3) was significantly lower (1.3 ±0.85 vs 1.9 ±0.36, respectively; p < 0.001) and the

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attack duration was significantly shorter (2.1 ±1.13 vs 3.4 ±2.39 days, respectively; p = 0.002). Additionally, fewer rescue C1 inhibitor concentrate injections were required (4.7 ±8.66 vs 15.4 ±8.41 injections; p < 0.001) and fewer days of swelling were reported (10.1 ±10.73 vs 29.6 ±16.9 days; p < 0.001) during the C1 inhibitor concentrate prophylaxis period compared with the placebo period. Adverse events possibly associated with C1 inhibitor concentrate use included 1 report each of pruritus and rash, lightheadedness, and fever. Researchers conclude that nanofiltered C1 inhibitor concentrate significantly reduced the number of attacks compared with placebo in patients with HAE.

Professional Societies

World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) Guideline for the Management of Hereditary Angioedema – 2021 Revision and Update

This revised and updated guideline, from 2017, provides up-to-date guidance for the management of HAE. An international panel of experts reviewed the existing evidence, developed 28 recommendations, and established consensus by an online DELPHI process. The recommendations regarding the treatment and prophylaxis of HAE with the medications listed within the therapeutic class include:

- All attacks are considered for on-demand treatment; 98% agreement, evidence level D.
- Any attack affecting or potentially affecting the upper airway is treated;100% agreement, evidence level C.
- Attacks are treated as early as possible;100% agreement, evidence level B.
- Attacks are treated with either intravenous C1inhibitor, ecallantide or icatibant; 96% agreement, evidence level A.
- All patients have sufficient medication for on-demand treatment of at least two attacks and carry on-demand medication at all times; 100% agreement, evidence level D.
- Consider short-term prophylaxis before medical, surgical, or dental procedures as well as exposure to other angioedema attack-inducing events; 94% agreement, evidence level C.
- The use of intravenous plasma-derived C1 inhibitor as first-line short-term prophylaxis; 91% agreement, evidence level C.
- The use of plasma-derived C1 inhibitor as first-line long-term prophylaxis; 87% agreement, evidence level A.
- The use of lanadelumab as first-line long-term prophylaxis; 89% agreement (strong recommendation), evidence level A.
- The use of berotralstat as first-line long-term prophylaxis; 81% agreement, evidence level A.
- The use of androgens only as second-line long-term prophylaxis; 89% agreement, evidence level C.

Evidence Grades

A. Randomized, double-blind clinical trial of high quality [e.g., sample size calculation, flow chart of patient inclusion, intention-to-treat (ITT) analysis and sufficient sample size].
B. Randomized clinical trial of lesser quality (e.g., only single-blind, limited sample size: at least 15 patients per study arm).
C. Comparative trial with severe methodological limitations (e.g., not blinded, very small sample size and no randomization) or large retrospective observational study, large open-label-study, registry data.
D. Adapted from existing consensus document or statement based on expert opinion voting during consensus conference, evidence non A-C.

World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) Guideline for the Management of Hereditary Angioedema – 2017 Revision and Update

This revised and updated guideline, from 2012, on the diagnosis and management of HAE differs from previous consensus reports and position papers. It results from a complete review of the underlying evidence based on systematic and transparent assessments of the quality of evidence. The recommendations for the treatment and prophylaxis of HAE with the medications listed within the therapeutic class include:

- All attacks are considered for on-demand treatment. We recommend that any attack affecting or potentially affecting the upper airway is treated. Evidence grade: D; strength of recommendation: strong.
- Attacks are treated as early as possible. Evidence grade: B; strength of recommendation: strong.
- HAE attacks are treated with either C1-INH, ecallantide, or icatibant. Evidence grade: A; strength of recommendation: strong.
- All patients have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all times. Evidence grade: D; strength of recommendation: strong.
- Short-term prophylaxis before procedures that can induce an attack. Evidence grade: C; strength of recommendation: strong.

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- Prophylaxis should be considered for patients who face events in life that are associated with increased disease activity. Evidence grade: D; strength of recommendation: strong.
- Use of C1-Inhibitor for first line long term prophylaxis. Evidence grade: A; strength of recommendation: strong.
- Use androgens as second-line long-term prophylaxis. Evidence grade: C; strength of recommendation: weak.
- C1-INH be used for treatment of HAE attacks in children under the age of 12. Evidence grade: C; strength of recommendation: strong.
- C1-INH as the preferred therapy for HAE attacks during pregnancy and lactation. Evidence grade: D; strength of recommendation: strong.
- All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer. Evidence grade: C; strength of recommendation: strong.

Evidence Grades

A. Randomized, double-blind, clinical trial of high quality (e.g., sample size calculation, flow chart of patient inclusion, intention-to-treat analysis, sufficient sample size).
B. Randomized clinical trial of lesser quality (e.g., only single blind and limited sample size: at least 15 patients per study arm).
C. Comparative trial with severe methodological limitations (e.g., not blinded, very small sample size, and no randomization) or large retrospective observational studies.
D. Adapted from existing consensus document or statement based on expert opinion voting during consensus conference.

Hereditary Angioedema International Working Group (HAWK): International Consensus on the Diagnosis and Management of Pediatric Patients With Hereditary Angioedema With C1 Inhibitor Deficiency (2017)

An expert panel convened during the 9th C1 Inhibitor Deficiency Workshop in Budapest (2015), and developed a consensus guideline for the treatment of HAE in pediatric patients. Their recommendations for the treatment of HAE include:

- Indications for short term prophylaxis (STP) in pediatrics include patient-specific triggers, medical and dental procedures.
- For most 'minor interventions,' the recommendation is to choose on-demand treatment if a swelling event is precipitated rather than prophylaxis, provided that a licensed on-demand medication is immediately available in the case of emergency.
- For interventions that involve airway manipulation or that might lead to tissue swelling, prophylaxis with a C1 inhibitor (C1-INH) is recommended.
- If licensed on-demand acute treatment medication is not available with planned procedures, the following treatment options are recommend for STP: oral attenuated androgens (AAs); or antifibrinolytics like tranexamic acid (TA).
- Long term prophylaxis (LTP) should be considered to minimize the impact of HAE on patients' quality of life.
- Most consider tranexamic acid (TA) to be the agent of choice for LTP in pediatrics, but TA is contraindicated for patients with a history of thromboembolism or a known thrombophilia defect.
- When antifibrinolytics fail to achieve the desired improvement or if they are contraindicated or not tolerated, then most recommend plasma derived C1-INH for LTP.
- Upper airway swellings should always receive acute treatment as early as possible followed by immediate assessment in the emergency room.
- Every patient with HAE should be considered for home therapy and self-/caregiver administration training.
- Level I evidence for acute treatment of HAE has been reviewed for plasma derived, recombinant human C1-INH, kallikrein inhibitor ecallantide, and bradykinin B2 receptor antagonist icatibant.
- At present, plasma derived, recombinant human C1-INH and ecallantide are the only agents licensed for pediatric acute treatment. Icatibant is not licensed for pediatric use, but a clinical trial in pediatric patients is ongoing.
- Phase III clinical trials are needed in the pediatric populations so that drug treatments for prophylaxis and acute therapy are approved for all ages.
- New drug protocols should include pediatric age patients for all rare diseases and use these data to power and develop clinical trials specifically for pediatrics.

Canadian Hereditary Angioedema Guidelines (2014)

The Canadian Hereditary Angioedema Guideline Committee, under the auspices of the Canadian Hereditary Angioedema Network/Réseau Canadien d'angioédème héréditaire (CHAEN/RCAH) published guidelines to provide graded

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recommendations for the management of patients in Canada with HAE. Their recommendations for the treatment of HAE include:

- C1 esterase inhibitors (C1-INH), icatibant, and ecallantide are effective therapy options for the treatment of acute attacks.
- Short-term prophylaxis should be considered prior to known patient-specific triggers and for any medical, surgical, or dental procedures.
- Long-term prophylaxis may be appropriate for some patients to reduce frequency, duration, and severity of attacks.
- Attenuated androgens are effective for long-term prophylaxis in some patients.
- Plasma-derived C1-INH is effective for long-term prophylaxis in some patients.
- Anti-fibrinolytics are effective for long-term prophylaxis in some patients.
- All patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies.

The International/Canadian Hereditary Angioedema Guideline (2019 Update)

The update to the 2014 *Canadian Hereditary Angioedema Guideline* expanded the scope to include the management of hereditary angioedema (HAE) patients worldwide. Updates include recommendations for diagnosis and therapies for acute treatment in HAE patients with normal C1-INH as follows:

- The diagnosis of HAE-1/2 should be made by measuring plasma levels of C4, C1-INH antigen and, when necessary, C1-INH function; C4 level alone should not be used to confirm or rule out a diagnosis of HAE-1/2.
- C1 esterase inhibitors (C1-INH), icatibant, and ecallantide are effective therapy options for the treatment of acute attacks.
- Attenuated androgens and tranexamic acid should not be used for treatment of acute attacks.
- Frozen plasma could be used for the acute treatment of attacks if other recommended therapies are not available.
- C1 esterase inhibitors (C1-INH) is the treatment of choice for angioedema attacks in pregnant HAE-1/2 patients.

U.S. Hereditary Angioedema Association Medical Advisory Board 2020 Recommendations for the Management of Hereditary Angioedema Due to C1 Inhibitor Deficiency (2020)

In 2013, the U.S. HAEA partnered with its Medical Advisory Board (MAB) to update and publish a set of guidelines for the treatment of hereditary angioedema. Recommendations include:

- The overall goals of HAE treatment are to reduce morbidity and mortality, and to achieve these goals, an individualized comprehensive management plan must be developed and implemented.
- Because of the complexity and variability of HAE and treatment, it is strongly recommended that every patient with HAE be followed up by a physician who is (1) knowledgeable about the condition, (2) experienced in managing patients with HAE, and (3) familiar with all HAE treatment options.
- These physicians should work with their patients to assure that a defined and individualized HAE management plan is established and should also actively coordinate the patient's care with other health care providers.
- All attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized.
- Androgens should not be used in patients who express a preference for an alternative therapy and should not be required to fail androgen therapy as a prerequisite to receiving prophylactic C1INH concentrate.
- Diagnosis of HAE when diagnosis of HAE-n1-C1INH is suspected based on symptoms and normal C1INH tests, additional genetic tests for factor XII, plasminogen, angiopoetin-1, and kininogen mutations.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. U.S. Food and Drug Administration (FDA) approval alone is not a basis for coverage.

Berinert is a plasma-derived C1 esterase Inhibitor (human) FDA-labeled for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adult and pediatric patients. The safety and efficacy of Berinert for prophylactic therapy have not been established.

Cinryze is a C1 esterase inhibitor (human) FDA-labeled for routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years of age and older) with hereditary angioedema (HAE).

Kalbitor is a plasma kallikrein inhibitor FDA-labeled for treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years of age and older.

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Ruconest is a C1 esterase inhibitor (recombinant) FDA-labeled for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE). The effectiveness of Ruconest has not been established in HAE patients with laryngeal attacks.

References

1. Berinert [prescribing information]. Kankakee, IL: CSL Behring LLC, September 2021.
2. Kalbitor [prescribing information]. Lexington, MA: Dyax Corp., June 2025.
3. Cinryze [prescribing information]. Lexington, MA: Shire ViroPharma, Inc., November 2024.
4. 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 Dec;66(12):1604-11.
5. 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 Oct;124(4):801-8.
6. Riedl MA, Hurewitz DS, Levy R, et al. Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: an open-label trial. Ann Allergy Asthma Immunol. 2012 Jan;108(1):49-53.
7. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010 Aug 5;363(6):513-22.
8. Levy RJ, Lumry WR, McNeil DL, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. Ann Allergy Asthma Immunol. 2010 Jun;104(6):523-9.
9. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. N Engl J Med. 2010 Aug 5;363(6):523-31.
10. Cicardi, M., Bork, K., Caballero, T., Craig, T., Li, H. H., Longhurst, H., Reshef, A., Zuraw, B. and on behalf of HAWK (Hereditary Angioedema International Working Group) (2012), Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy*, 67: 147–157.
11. Riedel MA, Levy RJ, Suez D, et al. Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study. *Ann Allergy Asthma Immunol*. 2013 Apr;110(4):295-9.
12. Craig TJ, Bewtra AK, Hurewitz D, et al. Treatment response after repeated administration of C1 esterase inhibitor for successive acute hereditary angioedema attacks. *Allergy Asthma Proc*. 2012 Jul-Aug;33(4):354-61.
13. Zuraw BL and Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Med*. 2012 Sep;125(9):938.e1-7.
14. Bernstein JA, Shea EP, Koester J, et al. Assessment of rebound and relapse following ecallantide treatment for acute attacks of hereditary angioedema. *Allergy*. 2012 Sep;67(9):1173-80.
15. Ruconest [prescribing information]. Bridgewater, NJ: Pharming Healthcare Inc.; April 2020.
16. Zuraw BL, Banerji A, Bernstein JA, et al. U.S. 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.
17. Riedl MA, Bernstein JA, Li H, Reshef A, Lumry W, Moldovan D, Farkas H, Levy R, Baker J, Hardiman Y, Totoritis MC, Relan A, Cicardi M; Study 1310 Investigators. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. *Ann Allergy Asthma Immunol*. 2014 Feb;112(2):163-169.
18. Maurer M, Magerl 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.
19. Betschel S, Badiou J, Binkley K, et al. Canadian hereditary angioedema guideline. *Allergy Asthma Clin Immunol*. 2014 Oct 24;10(1):50.
20. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014 May;69(5):602-16.
21. Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy 2017; 72: 300–313.
22. Li HH, Reshef A, Baker JW, et al. Efficacy of recombinant human C1 esterase inhibitor for the treatment of severe hereditary angioedema attacks. Allergy Asthma Proc. 2017 Nov 5;38(6):456-461.

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23. Baker JW, Reshef A, Moldovan D, et al. Recombinant Human C1-Esterase Inhibitor to Treat Acute Hereditary Angioedema Attacks in Adolescents. J Allergy Clin Immunol Pract. 2017 Jul - Aug;5(4):1091-1097.
24. Betschel S, Badiou J, Binkley K, et al. The international/Canadian hereditary angioedema guideline. *Allergy Asthma Clin Immunol*. 2019 Oct 25;15(72).
25. Busse P, Christiansen S, Riedl M, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *The Journal of Allergy and Clinical Immunology.* 2020 Sept 05.
26. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77(7):1961–90.

Policy History/Revision Information

Date	Summary of Changes

11/01/2026	**Template Update**
	• Transferred content to shared policy template that applies to both UnitedHealthcare Commercial and Individual Exchange benefit plans
	• Added *Application* section to indicate this policy applies to:
	  ○ UnitedHealthcare Commercial benefit plans
	  ○ Individual Exchange benefit plans
	Supporting Information
	• Archived previous policy versions 2025D0044P and IEXD0044.08

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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