Corporate Medical Policy: Treatment of Hereditary Angioedema **"Notification"** **POLICY EFFECTIVE APRIL 1, 2026**

Restricted Product(s):

- C1 esterase inhibitor (Berinert®) intravenous injection for administration by a healthcare professional
- C1 esterase inhibitor (Cinryze®) intravenous injection for administration by a healthcare professional
- C1 esterase inhibitor (Ruconest®) intravenous injection for administration by a healthcare professional
- ecallantide (Kalbitor®) subcutaneous injection for administration by a healthcare professional
- icatibant (Firazyr®, Sajazir™) subcutaneous injection for administration by a healthcare professional

FDA Approved Use:

- C1 Esterase Inhibitor (Berinert®)
  - For the treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients
  - Limitations of use: Not for prophylactic treatment
- C1 Esterase Inhibitor (Cinryze®)
  - For routine prophylaxis against hereditary angioedema (HAE) attacks in adult, adolescent, and pediatric patients 6 years or older
- C1 Esterase Inhibitor (Ruconest®)
  - For the treatment of acute attacks of hereditary angioedema (HAE) in adult and adolescent patients
  - Limitations of use: Effectiveness not established in HAE patients with laryngeal attacks
- Ecallantide (Kalbitor®)
  - For the treatment of acute attacks of hereditary angioedema (HAE) in patients 12 years or older
- Icatibant (Firazyr®, Sajazir™)
  - For the treatment of acute attacks of hereditary angioedema (HAE) in adult patients 18 years or older

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

Initial Criteria for Approval:

1. The patient has a diagnosis of **hereditary angioedema (HAE)** as confirmed through complement testing demonstrating ONE of the following **[medical record documentation required to demonstrate C4 level, C1-inhibitor (C1-INH) antigen (protein) level, and C1-INH function (activity) level where applicable]**:

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a. The patient has C1-INH deficiency or dysfunction (HAE-C1INH Type 1 or Type 2) as demonstrated by ONE of the following **[medical record documentation required]**:
    i. Type 1 HAE: Low C4 level, low C1-INH antigen level, and low C1-INH function level; **OR**
    ii. Type 2 HAE: Low C4 level, normal or elevated C1-INH antigen level, and low C1-INH function level; **OR**
b. The patient has HAE with normal C1-INH (HAE-nl-C1INH) as demonstrated by BOTH of the following **[medical record documentation required]**:
    i. The patient has a normal C4 level, normal C1-INH antigen level, and normal C1-INH function level; **AND**
    ii. ONE of the following:
        1. Genetic testing confirming presence of a mutation causative of HAE-nl-C1INH (e.g., coagulation factor XII [*F12*], angiopoietin-1 [*ANGPT1*], plasminogen [*PLG*], kininogen-1 [*KNG1*], myoferlin [*MYOF*], or heparan sulfate-glucosamine 3-O-sulfotransferase 6 [*HS3ST6*]) **[medical record documentation required]**; **OR**
        2. The patient has a family history of angioedema; **AND**
            a. The patient has recurring angioedema attacks that are refractory to high-dose second generation H1 antihistamine therapy (i.e., 4 times the standard antihistamine daily dose) for at least one month; **AND**

2. The requested medication is **Cinryze**; **AND**
    a. The patient is 6 years of age or older; **AND**
    b. The requested medication will be used for routine prophylaxis of HAE attacks and will NOT be used for treatment of acute attacks **[medical record documentation required]**; **AND**
    c. The patient will NOT be treated with more than one anti-HAE medication used for the prevention of HAE attacks (e.g., Andembry, Cinryze, Dawnzera, Haegarda, Orladeyo, Takhzyro) **[medical record documentation required]**; **AND**
    d. The 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) (e.g., 2 or more attacks within the last 2 months) **[medical record documentation required]**; **OR**

3. The requested medication is **Berinert**; **AND**
    a. The patient is 5 years of age or older; **AND**
    b. The requested medication will be used to treat acute abdominal, laryngeal, or facial HAE attacks (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability) and will NOT be used for prophylaxis of attacks **[medical record documentation required]**; **AND**
    c. The patient will NOT be treated with more than one anti-HAE medication used for the acute treatment of HAE attacks (e.g., Berinert, Ekterly, Firazyr, generic icatibant, Kalbitor, Ruconest, Sajazir) **[medical record documentation required]**; **OR**

4. The requested medication is **Ruconest**; **AND**

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a. The patient is 13 years of age or older; **AND**
b. The requested medication will be used to treat acute HAE attacks (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability) and will NOT be used for prophylaxis of attacks **[medical record documentation required]**; **AND**
c. The patient will NOT be treated with more than one anti-HAE medication used for the acute treatment of HAE attacks (e.g., Berinert, Ekterly, Firazyr, generic icatibant, Kalbitor, Ruconest, Sajazir) **[medical record documentation required]**; **OR**

5. The requested medication is **Kalbitor**; **AND**
    a. The patient is 12 years of age or older; **AND**
    b. The requested medication will be used to treat acute HAE attacks (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability) and will NOT be used for prophylaxis of attacks **[medical record documentation required]**; **AND**
    c. The patient will NOT be treated with more than one anti-HAE medication used for the acute treatment of HAE attacks (e.g., Berinert, Ekterly, Firazyr, generic icatibant, Kalbitor, Ruconest, Sajazir) **[medical record documentation required]**; **OR**

6. The requested medication is **Firazyr**, **generic icatibant**, or **Sajazir**; **AND**
    a. The patient is 18 years of age or older; **AND**
    b. The requested medication will be used to treat acute HAE attacks (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability) and will NOT be used for prophylaxis of attacks **[medical record documentation required]**; **AND**
    c. The patient will NOT be treated with more than one anti-HAE medication used for the acute treatment of HAE attacks (e.g., Berinert, Ekterly, Firazyr, generic icatibant, Kalbitor, Ruconest, Sajazir) **[medical record documentation required]**; **AND**

7. Medications known to cause angioedema (i.e., angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], dipeptidyl peptidase IV [DPP-IV] inhibitors, estrogens, neprilysin inhibitors) have been evaluated and discontinued when appropriate; **AND**
8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis; **AND**
9. If the request is for brand Firazyr, Sajazir, or Ruconest, ONE of the following:
    a. The patient is 13 to 17 years of age; **OR**
    b. The patient is 18 year of age or older AND ONE of the following:
        i. The patient has tried and had an inadequate response to generic icatibant **[medical record documentation required]**; **OR**
        ii. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to generic icatibant that is NOT expected to occur with the requested product **[medical record documentation required]**; **AND**

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10. The patient has a physical or cognitive limitation that makes the utilization of a self-administered formulation unsafe or otherwise not feasible, as demonstrated by BOTH of the following **[medical record documentation required]**:
    a. Inability to self-administer the medication; **AND**
    b. Lack of caregiver or support system for assistance with administration of self-administered products; **AND**
11. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
12. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

    Duration of Approval: 365 days (1 year)

Continuation Criteria for Approval:

1. The patient was approved through Blue Cross NC initial criteria for approval; **OR**
2. The patient would have met initial criteria for approval at the time they started therapy; **AND**
3. If requested medication is **Cinryze**:
    a. The requested medication will be used for routine prophylaxis of HAE attacks and will NOT be used for treatment of acute attacks **[medical record documentation required]**; **AND**
    b. The patient will NOT be treated with more than one anti-HAE medication used for the prevention of HAE attacks (e.g., Andembry, Cinryze, Dawnzera, Haegarda, Orladeyo, Takhzyro) **[medical record documentation required]**; **AND**
    c. The patient has shown a reduction in HAE attacks since initiation of the requested agent (e.g., decrease in the frequency of acute HAE attacks from baseline or decrease in use of on-demand therapy) **[medical record documentation required]**; **OR**
4. If the requested medication is for acute treatment of HAE attacks (i.e., **Berinert**, **Firazyr**, **generic icatibant**, **Kalbitor**, **Ruconest**, **Sajazir**):
    a. The requested medication will be used to treat acute HAE attacks (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion, extremity swelling causing disability) and will NOT be used for prophylaxis of attacks **[medical record documentation required]**; **AND**
    b. The patient will NOT be treated with more than one anti-HAE medication used for the acute treatment of HAE attacks (e.g., Berinert, Ekterly, Firazyr, generic icatibant, Kalbitor, Ruconest, Sajazir) **[medical record documentation required]**; **AND**
    c. The patient has shown quick symptomatic relief with the requested medication (i.e., decrease in median time to near-complete symptom relief with the patient's HAE attacks) **[medical record documentation required]**; **AND**
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis; **AND**
6. If the request is for brand Firazyr, Sajazir, or Ruconest, ONE of the following:
    a. The patient is 13 to 17 years of age; **OR**
    b. The patient is 18 year of age or older AND ONE of the following:

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   i. The patient has tried and had an inadequate response to generic icatibant **[medical record documentation required]**; **OR**
   ii. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to generic icatibant that is NOT expected to occur with the requested product **[medical record documentation required]**; **AND**
7. The patient has a physical or cognitive limitation that makes the utilization of a self-administered formulation unsafe or otherwise not feasible, as demonstrated by BOTH of the following **[medical record documentation required]**:
   a. Inability to self-administer the medication; **AND**
   b. Lack of caregiver or support system for assistance with administration of self-administered products; **AND**
8. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
9. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
C1 esterase inhibitor (Berinert®) intravenous (IV) injection	Acute treatment of HAE attacks in patients ≥5 years old	IV: 20 International Units (IU) per kg body weight at rate of ~4 mL per minute	J0597	6,000
C1 esterase inhibitor (Cinryze®) intravenous (IV) injection	Routine prophylaxis of HAE attacks in patients ≥6 years old	IV: • 6-11 years old: 500 International Units (IU) every 3 or 4 days at rate of 1 mL per minute (5 minutes); doses up to 1,000 IU every 3 or 4 days may be considered based on individual response • ≥12 years old: 1,000 IU every 3 or 4 days at rate of 1 mL per minute (10 minutes); doses up to 2,000 IU (not exceeding 80 IU/kg) every 3 or 4 days	J0598	12,000

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FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
		may be considered based on individual response		
C1 esterase inhibitor (Ruconest®) intravenous (IV) injection	Acute treatment of HAE attacks (excluding laryngeal) in patients ≥13 years old	IV: Reconstituted vial is 150 Units (U) per mL; inject over ~5 minutes • <84 kg: 50 U per kg (total mL is body weight in kg divided by 3) • ≥84 kg: 4,200 U (2 vials, total of 28 mL) • If the attack symptoms persist, an additional (second) dose can be administered at the recommended dose level. Do not exceed 4,200 U per dose. No more than two doses should be administered within a 24-hour period	J0596	20,160
ecallantide (Kalbitor®) subcutaneous (SC) injection	Acute treatment of HAE attacks in patients ≥12 years old	SC: 30 mg (as three 10 mg [1 mL] injections). If an attack persists, an additional 30 mg dose may be given within a 24-hour period.	J1290	1,440
icatibant (Firazyr®, Sajazir™) subcutaneous (SC) injection	Acute treatment of HAE attacks in patients ≥18 years old	SC: 30 mg injected into the abdominal area. If response is inadequate or symptoms recur, additional 30 mg injections may be given at least 6 hours apart (maximum of 3 injections in 24 hours)	J1744	2,160

***Maximum units allowed for duration of approval**

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***Site of Care Medical Necessity Criteria**

1. For requests for injection or infusion administration in an **inpatient setting**, the injection or infusion may be given if the above medical necessity criteria are met AND the inpatient admission is NOT for the sole purpose of administering the injection or infusion; **OR**
2. For requests for injection or infusion administration in an **outpatient hospital setting**, the injection or infusion may be given if the above medical necessity criteria are met AND ONE of the following must be met:
    a. History of a severe adverse event following the injection or infusion of the requested medication (i.e., anaphylaxis, seizure, thromboembolism, myocardial infarction, renal failure); **OR**
    b. Conditions that cause an increased risk for severe adverse event (i.e., unstable renal function, cardiopulmonary conditions, unstable vascular access); **OR**
    c. History of mild adverse events that have not been successfully managed through mild pre-medication (e.g., diphenhydramine, acetaminophen, steroids, fluids, etc.); **OR**
    d. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity; **OR**
    e. New to therapy, defined as initial injection or infusion OR less than 3 months since initial injection or infusion; **OR**
    f. Re-initiation of therapy, defined as ONE of the following:
        i. First injection or infusion after 6 months of no injections or infusions for drugs with an approved dosing interval less than 6 months duration; **OR**
        ii. First injection or infusion after at least a 1-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration; **OR**
    g. Requirement of a change in the requested restricted product formulation; **AND**
3. If the Site of Care Medical Necessity Criteria in #1 or #2 above are not met, the injection or infusion will be administered in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional.

References: all information referenced is from FDA package insert unless otherwise noted below.

1. 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.
2. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract*. 2021;9:132-150.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – The 2021 revision and update. *Allergy*. 2022;77:1961-1990.
4. Zuraw BL, Bork K, Bouillet L, et al. Hereditary angioedema with normal C1 inhibitor: an updated international consensus paper on diagnosis, pathophysiology, and treatment. *Clinic Rev Allerg Immunol*. 2025;68(24):1-24.

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Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q2 annually.

April 2026: Criteria change: Reformatted diagnostic criteria to align HAE type I and type II with updated guidelines. Renamed HAE type III to HAE with normal C1-INH per updated guidelines and adjusted diagnostic requirements to allow for either documented genetic confirmation or presence of recurring angioedema attacks refractory to high-dose second generation H1 antihistamines in addition to family history of angioedema. For acute treatments, removed requirement that patient must be experiencing at least one symptom of a moderate or severe HAE attack, and adjusted placement of examples of HAE attack symptoms within criteria for each product. Added Sajazir (branded generic of Firazyr [icatibant]) to policy for clarity under existing J1744 HCPCS code. For brand Firazyr, Sajazir, and Ruconest, added requirement of trial and failure of generic icatibant within initial and continuation criteria. Added requirement for use of the self-administered product within initial and continuation criteria unless certain criteria are met. For Cinryze continuation criteria, added required medical record documentation for confirmation of prophylactic use and demonstration of clinical benefit, and added examples of clinical benefit. Added requirement that medications known to cause angioedema have been evaluated and discontinued if appropriate. Added requirement to be prescribed by or in consultation with a specialist. Added examples of medications not to be used in combination for clarity. Adjusted maximum units. Added references. **Policy notification given 2/1/2026 for effective date 4/1/2026**.
November 2025: Criteria change: Updated Site of Care medical necessity criteria to add additional bypass for patients with a history of severe adverse events or conditions that cause an increased risk for severe adverse event to align with the Place of Service for Medical Infusions policy for clarity of intent.
April 2022: Criteria change: Removed requirement of two laboratory levels drawn at separate times for HAE-I diagnostic criteria. For prophylactic use (Cinryze), added additional clarification of 2 or more attacks within the last 2 months for history of moderate to severe HAE attacks. Changed age requirement for Berinert to 5 years of age or older. **Policy notification given 2/3/2022 for effective date 4/4/2022**.
August 2021: Criteria update: Added requirement of no treatment with more than one anti-HAE medication used for the same acute or preventative treatment of HAE attacks as the requested product, for clarity with no change to policy intent.
June 2021: Criteria change: Changed diagnostic requirements; added no use for treatment of laryngeal HAE attacks for Ruconest; added no use with another anti-HAE medication used for prevention or treatment of HAE attacks; continuation criteria added; added maximum units; medical policy formatting change. **Policy notification given 4/16/2021 for effective date 6/16/2021**.
*Further historical criteria changes and updates available upon request from Medical Policy and/or Corporate Pharmacy.

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