MEDICATION POLICY:

Hereditary Angioedema Agents

Generic Name: N/A

Therapeutic Class or Brand Name: Bradykinin B2 receptor antagonist, C1 esterase inhibitor, plasma kallikrein inhibitor

Applicable Drugs (if Therapeutic Class): Berinert® (C1 esterase inhibitor [human]), Cinryze® (C1 esterase inhibitor [human]), Firazyr® (icatibant), Haegarda® (C1 esterase inhibitor [Human]), Icatibant (generic), Kalbitor® (ecallantide), Orladeyo® (berotralstat), Ruconest® (C1 esterase inhibitor [recombinant]), Sajazir™ (icatibant), Takhzyro® (lanadelumab-flyo)

Preferred: N/A

Non-preferred: Berinert® (C1 esterase inhibitor [human]), Cinryze® (C1 esterase inhibitor [human]), Firazyr® (icatibant), Haegarda® (C1 esterase inhibitor [human]), Icatibant (generic), Kalbitor® (ecallantide), Orladeyo® (berotralstat), Ruconest® (C1 esterase inhibitor [recombinant]), Sajazir™ (icatibant), Takhzyro® (lanadelumab-flyo)

Date of Origin: 8/20/2022

Date Last Reviewed / Revised: 10/23/2023

PRIOR AUTHORIZATION CRITERIA

(May be considered medically necessary when criteria I-VI are met)

I. Documented diagnosis of hereditary angioedema (HAE) (A or B) and must meet criteria listed under applicable condition:

   A. HAE with a deficiency of C1 esterase inhibitor (HAE-C1-INH) subtype I must meet criteria 1 **OR** 2 (a, b, and c). HAE subtype II must meet criteria 1 **OR** 2 (a and c).

      1. Documented genetic testing showing a pathologic HAE gene mutation (SERPING1 gene mutation).
      2. Documented complement testing results on 2 separate dates showing:
         a) C4 level below the lower limit of normal for laboratory reference range.
         b) C1-INH antigenic level < 50 % below the lower limit of normal for laboratory reference range.
         c) C1-INH functional level < 50% below the lower limit of normal for laboratory reference range.

   B. HAE with normal C1 esterase inhibitor (HAE-nl-C1INH) must meet criteria 1 and 2 (a, b, and c) **OR** 2 (a, b, and c), 3, and 4.

      1. Documented genetic testing showing a pathologic gene mutation known to cause HAE -nl-C1INH (i.e., factor XII, angiopoietin-1, plasminogen, kininogen-1, myoferlin, or heparan sulfate-glucosamine 3-O-sulfotransferase 6).
      2. Documented complement testing results on 2 separate dates showing:
         a) C4 levels within normal limits for laboratory reference range.

b) C1-INH antigenic level within normal limits for laboratory reference range.

c) C1-INH functional level within normal limits for laboratory reference range.

3. A documented positive family history of recurrent angioedema.
4. A documented ineffectiveness of high-dose antihistamine therapy (e.g., cetirizine 40 mg/day or the equivalent) for at least 1 month or an interval expected to be associated with at least 3 HAE attacks (whichever is longer).

II. Documented history of recurrent HAE attacks without urticaria and notes detailing their severity, duration, frequency, and functional effects.

III. No use of medications known to cause angioedema (e.g., angiotensin-converting enzyme [ACE] inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs], and estrogens).

IV. Documentation of one of the following indications A or B **AND** must meet all criteria listed under applicable indication:

A. Treatment of acute attacks of HAE (On-Demand medications):

1. Documentation of a patient-specific management plan including where the medication will be stored, and who, when, and how the medication will be administered at the planned treatment location. If requested medication will be self-administered, there must be documentation of training.
2. Treatment must be prescribed by or in consultation with a board-certified immunologist or allergist with expertise managing HAE.

B. Routine prophylaxis of HAE attacks:

1. Patient has a history of laryngeal edema or airway compromise with an HAE attack **OR** a history of at least two acute HAE attacks per month.
2. Documentation of a patient-specific management plan including where the medication will be stored, and who, when, and how the medication will be administered at the planned treatment location. If requested medication (except for Orladeyo®) will be self-administered, there must be documentation of training.
3. Treatment must be prescribed by or in consultation with a board-certified immunologist or allergist with expertise managing HAE.

V. Request is for a medication with the appropriate FDA labeling. Refer to Table 2 and Table 3 for FDA-approved indications.

VI. Refer to the plan document for the list of preferred products. If the requested agent is not listed as a preferred product, must have documented treatment failure or contraindication to the preferred product(s).

EXCLUSION CRITERIA

- Concomitant use of more than one agent indicated for the treatment of acute HAE attacks (e.g., Berinert®, Firazyr®, Icatibant, Kalbitor®, Ruconest®, or Sajazir™).

- Concomitant use of more than one agent indicated for the routine prophylaxis of HAE attacks (e.g., Cinryze®, Haegarda ®, Orladeyo®, Takhzyro®).
- Drug specific contraindications:
    - Ruconest®:
        - Effectiveness was not established in patients with HAE laryngeal attacks.
    - Orladeyo®
        - Concomitant use with P-glycoprotein inducers (e.g., rifampin, St. John's wort).

OTHER CRITERIA

- Generic icatibant is preferred over brand Firazyr®. For brand Firazyr® requests, there must be documentation of intolerance, contraindication, or inadequate treatment response to generic icatibant.
- For the patient to be considered adherent, the proportion of days covered must be at least 80% for the previous 6 months.

QUANTITY / DAYS SUPPLY RESTRICTIONS

- Berinert®: Three 20 IU/kg doses (supplied with 500 IU single-dose vials) per 30 days.
- Cinryze®:
    - ≥ 12 years: Fifty 500 IU single-dose vials per 30 days.
    - 6 – 11 years: Twenty 500 IU single-dose vials per 30 days.
- Firazyr®: Nine 30 mg/3 mL single-dose prefilled syringes per 30 days.
- Haegarda®: Ten 60 IU/kg doses (supplied with 2000 IU and/or 3000 IU single-dose vials) per 30 days.
- Icatibant: Nine 30 mg/3 mL single-dose prefilled syringes per 30 days.
- Kalbitor®: Eighteen 10 mg/mL single-dose vials per 30 days.
- Orladeyo®: Twenty-eight (28) 110 mg or 150 mg capsules per 28 days.
- Ruconest®:
    - < 84 kg: Six 50 U/kg doses (supplied with 2100 U single-dose vials) per 30 days.
    - ≥ 84 kg: Twelve 2100 U single-dose vials per 30 days.
- Sajazir™: Nine 30 mg/3 mL single-dose prefilled syringes per 30 days.
- Takhzyro®:
    - For patients 12 years of age and older: Two 300 mg/2 mL single-dose vials or syringes per 28 days.

- If attack free for 6 months or longer: One 300 mg/2 mL single dose vial or syringe per 28 days.

- Pediatric patients 6 to less than 12 years of age: Two 150mg/1mL single-dose prefilled syringes per 28 days.
  - If attack free for 6 months or longer: One 150 mg/1 mL single dose syringe per 28 days.
- Pediatric patients 2 to less than 6 years of age: One 150mg/1mL single-dose prefilled syringe per 28 days.

APPROVAL LENGTH

- **Authorization:** 6 months.
- **Re-Authorization:** 12 months, with an updated letter of medical necessity or progress notes **AND** must meet all criteria listed under applicable indication:

A. Treatment of acute attacks of HAE

1. Documented improvement of HAE attacks (e.g., measured by severity, duration, or functioning).
2. Adherence to prophylactic HAE treatment (when applicable). For the patient to be considered adherent, the proportion of days covered must be at least 80% for the previous 6 months.

B. Routine prophylaxis of HAE attacks

1. Documented improvement of HAE attacks (e.g., measured by severity, frequency, duration, or functioning). See other criteria for adherence definition.
2. Adherence to prophylactic HAE treatment. For the patient to be considered adherent, the proportion of days covered must be at least 80% for the previous 6 months.

APPENDIX

Table 1. Laboratory features by HAE type

Type	C4	Antigenic C1-INH	Functional C1-INH	C1q	C3
HAE-C1-INH Subtype I	Decreased	Decreased	Decreased	Normal*	Normal
HAE-C1-INH Subtype II	Decreased	Normal	Decreased	Normal*	Normal
HAE-nl-C1-INH	Normal	Normal	Normal	Normal	Normal
Abbreviations: HAE, hereditary angioedema; HAE-C1-INH, hereditary angioedema with a deficiency of C1 esterase inhibitor; HAE-nl-C1INH, hereditary angioedema with normal C1 esterase inhibitor.					

* Rarely decreased in homozygous HAE

Table 2. FDA-approved agents indicated for the treatment of acute HAE attacks.

Brand Name(s) (Generic Name)	Mechanism of Action	Age Restriction	Dose	May be self-administered
Berinert® (C1 esterase Inhibitor [human])	C1 esterase inhibitor	≥ 5 years old	20 IU/kg IV (Maximum: 20 IU/kg)	Y
Firazyr®, Sajazir™, generic icatibant	Bradykinin B2 receptor antagonist	≥ 18 years old	30 mg SC in the abdominal area (Maximum: 90 mg /24 hours)	Y
Kalbitor® (ecallantide)	Plasma kallikrein inhibitor	≥ 12 years old	30 mg SC in abdomen, thigh, or upper arm (Maximum: 60 mg/24 hours)	N
Ruconest® (C1 esterase inhibitor [recombinant])	C1 esterase inhibitor	≥ 13 years old	<84 kg: 50 U/kg IV ≥84 kg: 4200 U IV (Maximum: 4200 U/dose and 2 doses/24 hours)	Y
Abbreviations: HAE, hereditary angioedema; IU, international units; IV, intravenously; SC, subcutaneously; U, units.				

Table 3. FDA-approved agents indicated for the routine prophylaxis of HAE attacks.

Brand Name (Generic Name)	Mechanism of Action	Age Restriction	Dose	May be self-administered
Cinryze® (C1 esterase inhibitor [human])	C1 esterase inhibitor	≥ 6 years old	Age ≥12 years: 1000 U IV every 3-4 days (Maximum: 2500 U [not exceeding 100 U/kg] every 3 – 4 days) Age 6–11 years: 500 U IV every 3 – 4 days (Maximum: 1000 U every 3 – 4 days)	Y
Haegarda® (C1 esterase inhibitor [human])	C1 esterase inhibitor	≥ 6 years old	60 IU/kg SC twice weekly (every 3 or 4 days)	Y
Orladeyo® (berotralstat)	Plasma kallikrein inhibitor	≥ 12 years old	1 capsule (150 mg) orally once daily with food Chronic use with P-gp or BCRP Inhibitors (e.g., cyclosporine), moderate or	Y

			severe hepatic impairment (Child-Pugh B or C), or patients with persistent GI reactions: 1 capsule (110 mg) orally once daily with food	
Takhzyro® (lanadelumab-flyo)	Plasma kallikrein inhibitor	≥ 2 years old	Age ≥12 years: 300 mg SC every 2 weeks (300 mg SC every 4 weeks may be considered if patient is attack free ≥ 6 months) Age 6–11 years: 150 mg SC every 2 weeks (150 mg SC every 4 weeks may be considered if patient is attack free ≥ 6 months) Age 2–5 years: 150 mg SC every 4 weeks	Y
Abbreviations: BCRP, breast cancer resistance protein; GI, gastrointestinal; HAE, hereditary angioedema; IU, international units; IV, intravenously; SC, subcutaneously; U. units.				

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