

Applicable Drugs: Andembry (garadacimab-gxii), Berinert (C1 esterase inhibitor [human]), Cinryze (C1 esterase inhibitor [human]), Dawnzera (donidalorsen), Ekterly (sebetralstat), Firazyr (icatibant), Haegarda (C1 esterase inhibitor [human]), icatibant (generic), Kalbitor (ecallantide), Orladeyo (berotralstat), Ruconest (C1 esterase inhibitor [recombinant]), Sajazir (icatibant), Takhzyro (lanadelumab-flyo)

Preferred: icatibant

Non-preferred: Andembry, Berinert, Firazyr, Haegarda, Sajazir, Takhzyro

VSI Exclusions: Cinryze, Dawnzera, Ekterly, Kalbitor, Orladeyo, Ruconest

Date of Origin: 8/20/2022

Date Last Reviewed / Revised: 2/9/2026

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 or II and must meet criterion 1 **OR** 2:
 1. Documented genetic testing showing a pathologic HAE gene mutation (SERPING1 gene mutation).
 2. Documented complement testing results on two separate dates showing:
 - a) C4 level below the lower limit of normal for laboratory reference range.
 - b) C1-INH functional level < 50% below the lower limit of normal for laboratory reference range.
 - c) For patients with HAE-C1-INH subtype I only: C1-INH antigenic 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 **OR** meet criteria 2, 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 two 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. 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** patient has a history of at least two acute HAE attacks per month.
 - 2. Treatment must be prescribed by or in consultation with a board-certified immunologist or allergist with expertise in 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, Cinryze, Ekterly, Firazyf, 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).
 - Firazyr, Sajazir, and icatibant
 - Pregnancy Category C

OTHER CRITERIA

- Generic icatibant is preferred over brand Firazyr and Sajazir. For brand Firazyr and Sajazir requests, there must be documentation of intolerance, contraindication, or inadequate treatment response to generic icatibant at maximum dose.

QUANTITY / DAYS SUPPLY RESTRICTIONS

- Andembry: Loading dose of two 200 mg single-dose injections for the first 30 days, then one 200 mg single-dose injection per 30 days thereafter.
- Berinert: Six 20 IU/kg doses (supplied with 500 IU single-dose vials) per 30 days.
- Cinryze:
 - Prophylaxis:
 - ≥ 12 years: Fifty 500 IU single-dose vials per 30 days.
 - 6–11 years: Twenty 500 IU single-dose vials per 30 days.
 - Acute Treatment:
 - 10–25 kg: Six 500 IU single-dose vials per 30 days.
 - ≥ 25 kg: Twelve 500 IU single-dose vials per 30 days.
- Dawnzera: One 80 mg/0.8 mL single-dose autoinjector per 28 days.
- Ekterly: Twelve 300 mg tablets 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/1 mL 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/1 mL single-dose prefilled syringe per 28 days.

APPROVAL LENGTH

- **Authorization:** 6 months
- **Re-Authorization:** 6 months, with an updated letter of medical necessity or progress notes **AND** must meet all criteria listed:
 - A. Documentation of recent HAE attacks (e.g., dates, duration, severity, location, and detailed course of resolution).
 - B. Documented improvement of HAE attacks (e.g., measured by severity, duration, or functioning).
 - C. For requests for medications for the routine prophylaxis of HAE attacks (when applicable):
 1. 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.
 2. Documented evaluation of prophylactic HAE treatment efficacy (e.g., disease activity, symptom burden, symptom control, and patient preference).

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-nI-C1-INH	Normal	Normal	Normal	Normal	Normal
Abbreviations: HAE, hereditary angioedema; HAE-C1-INH, hereditary angioedema with a deficiency of C1 esterase inhibitor; HAE-nI-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
Ekterly (sebetralstat)	Plasma kallikrein inhibitor	≥ 12 years old	600 mg PO (Maximum: 1,200 mg/24 hours)	Y
Firazyr, Sajazir, generic icatibant	Bradykinin B2 receptor antagonist	≥ 18 years old	30 mg SC in the abdominal area (Maximum: 90 mg /24 hours) [off-label pediatric dosage]: 0.4 mg/kg 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
Andembry (garadacimab- gxii)	Factor XII (FXIIa) inhibitor (monoclonal antibody)	≥ 12 years old	Loading dose 400 mg for the first 30 days, then 200 mg per 30 days	Y
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
Dawnzera (donidalorsen)	Prekallikrein- directed antisense oligonucleotide	≥ 12 years old	80 mg administered subcutaneously every 4 weeks 80 mg administered subcutaneously every 8 weeks may be considered	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 severe hepatic impairment (Child-Pugh B or C), or patients with persistent GI reactions: 1 capsule (110 mg) orally once daily with food	Y
Orladeyo (berotralstat)	Plasma kallikrein inhibitor	≥ 2- <12 years old	12 kg to <24kg : 72 mg packet once daily 24 kg to <32 kg: 96 mg packet once daily 32 kg to <40 kg: 108 mg packet once daily 40 kg or greater: 132 mg packet once daily	Y

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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DISCLAIMER: Medication Policies are developed to help ensure safe, effective and appropriate use of selected medications. They offer a guide to coverage and are not intended to dictate to providers how to practice medicine. Refer to Plan for individual adoption of specific Medication Policies. Providers are expected to exercise their medical judgement in providing the most appropriate care for their patients.