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Medication Policy Manual

Policy No: dru535

Topic: Medications for Hereditary Angioedema (HAE)

Date of Origin: July 1, 2018

- Andembry, garadacimab-gxii
- Berinert, plasma-derived C1-INH
- Cinryze, plasma-derived C1-INH
- Dawnzera, donidalorsen
- Ekterly, sebetralstat
- icatibant (generic, Firazyr, Sajazir)
- Kalbitor, ecallantide
- Haegarda, plasma-derived C1-INH
- Orladeyo, berotralstat
- Ruconest, recombinant human C1-INH
- Takhzyro, lanadelumab-flyo

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are used to treat hereditary angioedema (HAE). Administration is different for each medication, and may be a subcutaneous injection (SC), intravenous injection (IV), or oral. Kalbitor (ecallantide), Ekterly (sebetralstat), icatibant (generic, Firazyr, Sajazir), plasma-derived C esterase inhibitor (pdC1-INH, Berinert), and recombinant human C1-INH (rhC1-INH, Ruconest) are approved for the treatment of HAE attacks. Andembry (garadacimab-gxii), an activated factor XII inhibitor, Dawnzera (donidalorsen), Takhzyro (lanadelumab-flyo), and Orladeyo (berotralstat), both kallikrein inhibitors, and two other forms of plasma-derived C1-INH (Haegarda and Cinryze), are approved for the prophylaxis of HAE attacks.

Policy/Criteria

Most contracts require pre-authorization approval of medications used to treat hereditary angioedema (HAE) prior to coverage.

I. Continuation of therapy (COT): Medications used to treat HAE may be considered medically necessary for COT when criterion A and B below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a through e must be met:

a. The patient was established on therapy prior to current health plan membership AND documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim. NOTE: The use of *prophylactic* agents (as listed in *Table 4*) for the treatment of HAE with normal C1-INH (HAE-nl-C1-INH), formerly type III HAE, are not coverable.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.
NOTE: Please include baseline HAE symptoms (prior to use of HAE-specific therapy), as well as current symptoms, for establishing documentation of clinical benefit.

AND

c. **For use of branded Firazyr or Sajazir only**: There is clinical documentation (such as chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication, icatibant.

AND

d. The quantity is within the coverable limit (per *Table 3 and 4*, Quantity and Authorization Limits). NOTE: For doses above those listed in Initial Quantities, documentation of need for higher dosing must be met, as detailed in the table.

AND

e. The requested treatment is not used for any indication listed in the Investigational Uses section (see *section IV*).

OR

3. Both of the following (a and b):

a. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

b. **For use of branded Firazyr or Sajazir only**: There is clinical documentation (such as chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication, icatibant.

AND

B. **For Cinryze (plasma-derived C1-INH) only**: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications used to treat hereditary angioedema (HAE) may be considered medically necessary when there is clinical documentation (such as chart notes or laboratory reports) that criterion A, B, or C below is met.

A. **HAE, acute treatments**: Criteria 1 through 4 below are met.

1. **Drug**: Request is for Ekterly, icatibant (generic, Firazyr, Sajazir), Berinert, Kalbitor, or Ruconest (as listed in *Table 3*).

2. **Diagnosis**: For Ekterly, diagnostic criteria are met for type I HAE or type II HAE. For all other acute treatments, diagnostic criteria are met for type I HAE, type II HAE, or HAE with normal C1-INH (HAE-nl-C1-INH) (see *Table 1*).

3. **Concurrent therapy**: The treatment is not used in conjunction with other HAE-specific acute therapies (as listed in *Table 3*) for the HAE attacks (i.e., only one abortive therapy is used per attack).

4. **Product choice**: Preferred product criteria are met (see *Table 2*).

OR

B. **HAE, prophylactic treatments**: Criteria 1 through 7 below are met.

1. **Drug**: Request is for Andembry, Cinryze, Dawnzera, Haegarda, Orladeyo, or Takhzyro (as listed in *Table 4*).

2. **Diagnosis**: Diagnostic criteria are met for type I HAE or type II HAE (see *Table 1*).

3. **Severity**: History of attacks that are considered severe with swelling of the face, throat, or gastrointestinal tract.

Severe is defined as events that significantly interrupt usual daily activity despite short term symptomatic treatment, as documented in clinical documentation (such as chart notes or HAE calendar).

4. **Trigger Management**: Patient has been evaluated for potentially treatable triggers of HAE attacks and is maximally managed with respect to avoiding triggers.

5. **Concurrent therapy**: The treatment is not used in conjunction with other HAE-specific prophylactic therapies (as listed in *Table 4*) for the prophylaxis of HAE attacks.
6. **Product choice**: The preferred product criteria are met (see *Table 2*).
7. **Site of Care**: **For Cinryze (plasma-derived C1-INH) only**: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

OR

C. **Acquired Angioedema (AAE)**: Criteria 1 through 4 below are met.

1. **Drug**: Request is for icatibant (generic, Firazyr, Sajazir) or Kalbitor.
2. **Diagnosis**: Diagnostic criteria are met for Acquired Angioedema [*see Table 1*].
3. **Concurrent therapy**: The treatment is not used in conjunction with other HAE-specific acute therapies (as listed in *Table 3*) for the HAE attacks; i.e., only one abortive therapy is used per attack.
4. **Product choice**: Preferred product criteria are met (see *Table 2*).

Table 1. Diagnostic Criteria

Drug	Criteria
Type I HAE, type II HAE	Clinical documentation (such as chart notes and laboratory reports) that establishes **all** of the following (criteria 1 through 3): **1.** The diagnosis has been established by an allergist, immunologist, or hematologist. **2.** A comprehensive evaluation performed by the specialist to rule out all other causes of angioedema. *Other causes may include but are not limited to mast-cell mediated angioedema, idiopathic angioedema, allergic reactions/anaphylaxis, drug-induced angioedema, allergic contact dermatitis, autoimmune conditions.* **3.** Based on the laboratory's normal reference range, **all** of the following (criteria a through d) are met: **a.** Low serum C4 protein level **b.** Low C1-INH function (reported by labs as a percentage, %) **c.** Low C1-INH protein level (type I) OR normal/high C1-INH protein level (type II) **d.** Normal level of serum C1q protein OR a family history of HAE

Drug	Criteria
HAE-nl-C1-INH (formerly type III HAE)	Clinical documentation (such as chart notes and laboratory reports) that establishes **all** of the following (criteria 1 through 3): **1.** The diagnosis has been established by an allergist, immunologist, or hematologist. **2.** A comprehensive evaluation performed by the specialist has ruled out all other causes of angioedema. *Other causes may include but are not limited to mast-cell mediated angioedema, idiopathic angioedema, allergic reactions/anaphylaxis, drug-induced angioedema, allergic contact dermatitis, autoimmune conditions.* **3.** Based on the laboratory's normal reference range, **all** of the following criteria (a through d) are met: **a.** Normal serum C4 protein level **b.** Normal C1-INH function (reported by labs as a percentage, %) **c.** Normal C1-INH protein level **d.** Normal level of serum C1q protein OR a family history of HAE.
Acquired Angioedema	Clinical documentation (such as chart notes and laboratory reports) that establishes **all** of the following (criteria 1 through 4): **1.** The diagnosis has been established by an allergist, immunologist, or hematologist. **2.** A comprehensive evaluation performed by the specialist has ruled out all other causes of angioedema. *Other causes may include but are not limited to mast-cell mediated angioedema, idiopathic angioedema, allergic reactions/anaphylaxis, drug-induced angioedema, allergic contact dermatitis, autoimmune conditions.* **3.** Based on the laboratory's normal reference range, **all** of the following (criteria a through d) are met: **a.** Low serum C4 protein level **b.** Low C1-INH function (reported by labs as a percentage, %) **c.** Normal or low C1-INH protein level **d.** Low serum C1q protein level **4.** The patient has been evaluated for an underlying B-cell lymphoproliferative disorder.

Table 2: Preferred Product Criteria

Drug	Criteria
Andembry (garadacimab-gxii)	None
Berinert (plasma-derived C1-INH)	Clinical documentation (such as chart notes) confirming that generic icatibant has been ineffective, not tolerated, or contraindicated.
Cinryze (plasma-derived C1-INH)	Clinical documentation (such as chart notes) confirming that treatment with at least one of the following has been ineffective, not tolerated, or contraindicated: **1.** Andembry (garadacimab-gxii) **OR** **2.** Dawnzera (donidalorsen) **OR** **3.** Haegarda (plasma-derived C1-INH). **OR** **4.** Takhzyro (lanadelumab-flyo).
Dawnzera (donidalorsen)	None
Ekterly (sebetralstat)	Clinical documentation (such as chart notes) confirming that treatment with the following has been ineffective, not tolerated, or contraindicated: **1.** Generic icatibant. **AND** **2.** At least one of the following (a or b): **a.** Berinert (plasma-derived C1-INH) **OR** **b.** Ruconest (recombinant C1-INH)
Haegarda (plasma-derived C1-INH)	None
icatibant (Firazyr, Sajazir)	Clinical documentation (such as chart notes) confirming that there is an intolerance or contraindication to an inactive ingredient in generic icatibant.
icatibant (generic)	None
Kalbitor (ecallantide)	Clinical documentation (such as chart notes) confirming that generic icatibant has been ineffective, not tolerated, or contraindicated.

Drug	Criteria
Orladeyo (berotralstat)	Clinical documentation (such as chart notes) confirming that treatment with at least one of the following has been ineffective, not tolerated, or contraindicated: **1.** Andembry (garadacimab-gxii) **OR** **2.** Dawnzera (donidalorsen) **OR** **3.** Haegarda (plasma-derived C1-INH). **OR** **4.** Takhzyro (lanadelumab-flyo).
Ruconest (recombinant human C1-INH)	Clinical documentation (such as chart notes) confirming that treatment with both of the following has been ineffective, not tolerated, or contraindicated: **1.** Generic icatibant. **AND** **2.** Berinert (plasma-derived C1-INH).
Takhzyro (lanadelumab-flyo)	None

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers HAE treatments covered under the following benefits:

1. **Pharmacy benefit only (as self-administered medications)**: Andembry (garadacimab-gxii), Dawnzera (donidalorsen), Ekterly (sebetralstat), Haegarda (plasma-derived C1-INH), icatibant (generic, Firazyr, Sajazir), Orladeyo (berotralstat), and Takhzyro (lanadelumab-flyo).
2. **Medical benefit only (as a provider-administered medication)**: Kalbitor (ecallantide).
3. **Either the pharmacy benefit (as self-administered medications) OR the medical benefit (as provider-administered medications)**: Berinert (plasma-derived C1-INH), Cinryze (plasma-derived C1-INH), and Ruconest (recombinant human C1-INH).

B. When pre-authorization is approved, each drug may be covered in the following quantities and for the following authorization periods outlined in *Table 3 and 4*.

Table 3. HAE-specific Acute Treatment Quantity and Authorization Limits

DRUG	DOSAGE	LIMITS	REAUTHORIZATION
Ekterly (sebetralstat)	600mg (two 300mg tablets) per dose. An additional 600mg dose may be taken *once* after the first dose if symptoms worsen or recur. Four tablets for the treatment of a single attack should not be exceeded.	**Initial quantities**: Acute treatments for HAE may be authorized in a quantity sufficient for the treatment of three attacks per month. **Higher quantities**: Acute treatments for HAE may be authorized in a quantity sufficient for the treatment of four to six attacks per month when all criteria (1 through 3) below are met: **1.** The patient has been evaluated for potentially treatable triggers of HAE and AAE attacks and is maximally managed with respect to avoiding triggers. **AND** **2.** Documentation of more than three attacks per month, such that additional quantities may be considered medically necessary. **AND** **3.** **For HAE types I and II only**: Documentation that the patient is being evaluated for initiation of prophylactic HAE-specific therapy.	**Initial and reauthorization**: Authorization **shall** be reviewed at least every twelve months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit. Response to as-needed treatment is defined as a reduction in symptoms related to the AAE or HAE attack. Documentation of the current number and severity of attacks must be provided for each reauthorization, which **must** include an attack calendar or specific documentation of attacks and treatments used, to justify the number of doses covered. **For brand icatibant (Firazyr, Sajazir) only**, there must also be documentation of an intolerance or contraindication to an inactive ingredient in generic icatibant.
Berinert (plasma-derived C1-INH)	20 international units (IU) per kg of body weight per dose		
Kalbitor (ecallantide)	Three 10 mg/1 mL vials per dose		
Icatibant (generic, Firazyr, Sajazir)	One 30 mg/3 mL pre-filled syringe per dose		
Ruconest (recombinant human C1-INH)	Two 2100 IU vials per dose		

Table 4. HAE-specific Prophylactic Treatment Quantity and Authorization Limits

DRUG	LIMITS	REAUTHORIZATION
Andembry (garadacimab-gxii)	**Initial quantities**: 400 mg (two injections of the 200 mg/1.2 mL prefilled syringe or autoinjector) as a single loading dose, then 200 mg (one 200 mg/1.2 mL prefilled syringe or autoinjector) every 28 days thereafter. **Maintenance quantities**: 200 mg every month (one 200 mg/1.2 mL prefilled syringe or autoinjector) every 28 days. **Higher quantities**: Higher doses than listed above are **not** coverable.	**Initial and reauthorization**: Authorization **shall** be reviewed at least every twelve months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is effective, including details of disease stability or improvement relative to baseline HAE-related symptoms and frequency/severity of HAE attacks. Response to HAE-specific therapy is defined as at least a 50% decrease in frequency of HAE attacks relative to baseline frequency, significant improvement/stability in severity and duration of attacks, and clinical documentation of functional improvement/stability. Baseline and current number, and severity of HAE attacks must be provided for each reauthorization. Documentation of the current number and severity of attacks must be provided for each reauthorization, which **must** include an attack calendar or specific documentation of attacks and treatments used, to justify the number of doses covered.
Cinryze (plasma-derived C1-INH)	**Initial quantities**: 1,000 units twice per week for a total of 8,000 units (16 of the 500-unit vials) every 28 days. **Higher quantities**: Higher doses than listed above are **not** coverable.	
Dawnzera (donidalorsen)	**Initial quantities**: 80 mg (one injection of the 80 mg/0.8 mL solution in a single-dose autoinjector) every 4 weeks. **Maintenance quantities** **a.** 80 mg (one injection of the 80 mg/0.8 mL solution in a single-dose autoinjector) every **8 weeks**. **OR** **b.** 80 mg (one injection of the 80 mg/0.8 mL solution in a single-dose autoinjector) every **4 weeks** if clinical documentation is provided that demonstrates the patient has continued to experience HAE attacks, defined as ≥1 attack over the last 6 months, while adherent to stable Dawnzera (donidalorsen) therapy. **Higher quantities**: Higher doses than listed above are **not** coverable.	

DRUG	LIMITS	REAUTHORIZATION
Haegarda (plasma-derived C1-INH)	**Initial quantities**: Up to 60 IU per kg body weight twice weekly. **Higher quantities**: Higher doses than listed above are **not** coverable.	
Orladeyo (berotralstat)	**Initial quantities**: Up to 28 capsules or oral pellets every 28 days. **Higher quantities**: Higher doses than listed above are **not** coverable.	
Takhzyro (lanadelumab-flyo)	**Initial quantities**: Up to 300 mg every two weeks, for a total of 600 mg (two of the 300mg/2mL vials OR two 300mg/2mL single dose prefilled syringes OR four of the 150mg/mL prefilled syringes) every 28 days for the first twelve months of treatment. **Maintenance quantities** **a.** Up to 300 mg every **four weeks**, for a total of 300 mg (one of the 300mg/2mL vials OR one 300 mg/2mL single dose prefilled syringe OR two 150mg/mL single dose prefilled syringes) every 28 days. **OR** **b.** Up to 300 mg every **two weeks**, for a total of 600 mg (two of the 300mg/2mL vials OR two 300mg/2mL single dose prefilled syringes OR four 150mg/mL single-dose prefilled syringes) every 28 days if clinical documentation is provided that demonstrates the patient has continued to experience HAE attacks, defined as ≥1 attack over the last 6 months, while adherent to stable Takhzyro (lanadelumab-flyo) therapy. **Higher quantities**: Higher doses than listed above are **not** coverable.	

IV. Not medically necessary uses: The use of Ekterly (sebetralstat) for the treatment of patients with a history of *severe* laryngeal attacks (swelling with airway compromise that impairs breathing or swallowing) is considered not medically necessary.

V. Investigational Uses

A. Combination use of acute treatments for HAE (as listed in *Table 3*) is considered investigational.

B. Combination use of prophylactic treatments for HAE (as listed in *Table 4*) is considered investigational.

C. The use of prophylactic treatments for HAE (as listed in *Table 4*) for the treatment of normal C1-INH (HAE-nl-C1-INH), formerly type III HAE, is considered investigational.

D. Unless otherwise specified, medications included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high-quality data, or lack of positive data, including for doses in excess of those listed in Section III, *Tables 3 and 4* (above). Details of select investigational uses are listed below in *Table 5*.

Table 5. Select Investigational Uses

Acute Treatments • Ekterly (sebetralstat) • Berinert (plasma-derived C1-INH) • Icatibant (generic, Firazyr, Sajazir) • Kalbitor (ecallantide) • Ruconest (recombinant human C1-INH)	**1.** Treatment of angioedema due to causes other than those listed in the coverage criteria above, including but not limited to drug-induced angioedema, acquired angioedema [other than icatibant (generic, Firazyr, Sajazir)], allergic angioedema, mast-cell mediated angioedema, idiopathic angioedema, angiotensin converting enzyme inhibitor (ACEI)-induced angioedema, or any other drug adverse reaction (such as IVIG/SCIG hypersensitivity etc.). **2.** *Prophylactic* treatment of angioedema attacks. **3.** Osteoarthritis. **4.** Ischemic heart disease. **5.** Concurrent use of more than one acute HAE-specific medication. **6.** Ekterly (sebetralstat) only: treatment of normal C1-INH (HAE-nl-C1-INH)
Prophylactic Treatments • Andembry (garadacimab-gxii) • Cinryze (plasma-derived C1-INH) • Dawnzera (donidalorsen) • Haegarda (plasma-derived C1-INH) • Orladeyo (berotralstat)	**1.** Treatment of angioedema due to causes other than those listed in the coverage criteria above, including but not limited to drug-induced angioedema, acquired angioedema, mast-cell mediated angioedema, HAE-nl-C1-INH (also known as HAE type III), allergic angioedema, idiopathic angioedema, angiotensin converting enzyme inhibitor (ACEI)-induced angioedema, or any other drug adverse reaction (such as IVIG/SCIG hypersensitivity etc.). **2.** Myocardial infarction. **3.** Sepsis. **4.** Treatment of graft rejection.

• Takhzyro (lanadelumab-flyo)	**5.** Prevention of transplant rejection. **6.** Stroke **7.** Concurrent use of more than one prophylactic HAE-specific medication. **8.** *Acute* treatment of angioedema attacks.

Position Statement

Summary

- HAE is a rare and potentially life-threatening genetic blood disease characterized by inadequate or non-functional C1-INH proteins in the blood. C1-INH protein is a normal component of blood that helps regulate the inflammatory and clotting systems.
- The intent of the policy is to allow for coverage of HAE therapies for the specific diagnoses for which they have been studied when managed by a specialist (as outlined in the coverage criteria), and to limit coverage to doses studied and shown to be safe and effective in clinical trials.
- HAE is diagnosed with clinical presentation, family history, and measurements of specific laboratory markers (C1-INH function, C1-INH protein levels, and C4 protein levels, as detailed in the coverage criteria above).
- Serum C1-INH, C4 and C1q protein *levels* relate to their concentrations in serum and are most often reported by labs in units of mg/dL. C1-INH *function* is reported by labs as a percentage (%) and relates to C1-INH activity relative to normal function; interpretation of function is based on the lab's provided reference range for low or normal function.
- HAE with normal levels of C1-INH (HAE-nl-C1-INH), formerly known as type III HAE, is suspected in patients with HAE clinical presentation, but levels of C1-INH and C4 are normal, family history is present and serum C1q is also normal. Individuals with HAE-nl-C1-INH who present with recurrent episodes of angioedema without urticaria should be further evaluated to exclude other causes of angioedema, especially mast-cell mediated angioedema. If acquired angioedema (AAE) is suspected due to lack of family history or late onset of symptoms (age over 40 years), C1q antigenic protein testing is used to rule out AAE. Serum C1q level is low in patients with AAE but normal in patients with HAE.[1]
- In patients with recurrent episodes of angioedema without urticaria, other causes of angioedema must be excluded.
- The symptoms of HAE attacks vary in location and severity. They are highly unpredictable even within the same individual. Symptoms can range from swelling in the extremities or gastrointestinal tract to cases involving the face and throat which are less frequent but could be life threatening or fatal.
- Treatment strategies for HAE include long-term prevention, short-term prevention, and on-demand treatment for acute HAE attacks. Medications used in HAE management are associated with high healthcare costs.

- Berinert, Ekterly, icatibant (generic, Firazyr, Sajazir), Kalbitor (ecallantide), and Ruconest are FDA-approved for the on-demand treatment of HAE attacks. However, unlike other on-demand treatment options, the effectiveness of Ruconest for the treatment of laryngeal attacks was not established in its pivotal trial but has been since demonstrated in other prospective trials. Generic icatibant is the lowest cost of all available options. The efficacy of Ekterly (sebetralstat) for the treatment of *severe* laryngeal attacks has not been established; this attack type was excluded from treatment with sebetralstat during the pivotal trial (patients received other effective acute treatment standard of care options). [2]
- Andembry (garadacimab-gxii), Cinryze (plasma-derived C1-INH), Dawnzera (donidalorsen), Haegarda (plasma-derived C1-INH), Takhzyro (lanadelumab-flyo), and Orladeyo (berotralstat) are FDA approved for the prophylaxis of HAE attacks. Based on clinical trials, none of the products are superior in terms of safety or efficacy, however, Andembry, Dawnzera, Haegarda, and Takhzyro are the lowest costs. Andembry, Dawnzera, Haegarda, Takhzyro, and Orladeyo may be self-administered.
- For acute attacks, it is recommended that treatment be initiated as early as possible. Treatment options include Berinert (plasma-derived C1-INH), Ekterly (sebetralstat), Kalbitor (ecallantide), icatibant (generic, Firazyr, Sajazir), and Ruconest (recombinant human C1-INH). There are no preferences given to these acute treatment options.[3]
- Patients with frequent attacks, attacks involving swelling of the face or throat, or incapacitating gastrointestinal attacks may benefit from long-term preventive therapy.
- Patients who are not on long-term preventive therapy that are undergoing surgical or dental procedures may benefit from short-term preventive therapy.
- Strategies in managing HAE should be focused on avoiding or treating triggers, patient's quality of life, and availability of health care resources.
- The World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI), the United States Hereditary Angioedema Associate Medical Advisory Board (US HAEA) and the International/Canadian Hereditary Angioedema guidelines all recommend C1-INH, lanadelumab, and berotralstat as first line long-term prophylaxis over attenuated androgens, along with the management of potential triggers[1 4-6].
- HAE-nl-C1-INH (formerly known as type III HAE), is a rare disorder similar to HAE types I and II but is characterized by normal C4 protein levels and normal C1-INH level and function, family history of angioedema, frequent specific mutations that cause angioedema (such as coagulation factor XII gene, the plasminogen gene, etc.) and later onset. Treatment options are limited in HAE-nl-C1-INH as no FDA-approved therapies exist and treatment is extrapolated from HAE type I and II treatment.[1]
- Evidence to support the use of specific acute HAE attack treatments (icatibant [generic, Firazyr, Sajazir], Berinert, Kalbitor, or Ruconest) in patients with normal C1-INH (HAE-nl-C1-INH) is limited and of poorer quality, namely small uncontrolled, observational trials and case reports. However, given the lack of treatment options in normal C1-INH (HAE-nl-C1-INH), the aforementioned treatment options are coverable when coverage criteria are met. There is currently no evidence supporting the use of

Ekterly (sebetralstat) in patients with normal C1-INH (HAE-nl-C1-INH), and its use in normal C1-INH (HAE-nl-C1-INH) is considered investigational.

- Guidelines currently only recommend acute treatment for HAE-nl-C1-INH, as evidence for prophylactic treatment is lacking.
- AAE is a rare disorder similar to HAE, as characterized by recurrent episodes of swelling and a deficiency of C1-INH, although AAE develops in older patients and is often associated with lymphoproliferative disorders.[7-9]
- Treatment options for the management of acquired angioedema (AAE) are limited. There are no FDA-approved therapies for AAE and treatment is extrapolated from that of HAE. While no controlled studies have been performed in patients with AAE, observational data from case studies has demonstrated that Kalbitor (ecallantide), icatibant (generic, Firazyr, Sajazir), Berinert (plasma-derived C1-INH), and Ruconest (recombinant human C1-INH) were successfully used to treat AAE attacks. Expert consensus recommendations include these agents for the treatment of AAE. Additionally, management of the underlying lymphoproliferative disorder may control angioedema symptoms.[8-10]
- Given the high cost of medications for the treatment of HAE and AAE, confirmation of efficacy and that current medical necessity criteria are met is required.

Guidelines [1 2 4-6]

- WAO/EAACI and AAAAI guidelines recommend that HAE attacks be treated as early as possible, and that all attacks including those caused by HAE-nl-C1-INH and acquired angioedema be considered for on-demand treatment. Recommended treatment options include C1-INH formulations, Kalbitor (ecallantide) and icatibant. There is no specific recommendation for selecting one of these options over another. Ekterly (sebetralstat) is not yet addressed in guidelines. Among the available guideline-recommended acute treatment options, generic icatibant provides the best value.
- WAO/EAACI, US HAEA or the International/Canadian guidelines do not specifically recommend when to initiate prophylaxis as the decision should reflect the disease activity, patient's quality of life, and availability of heath care resources. As such patients should be evaluated for long term prophylaxis once per year.
- In these most recent guidelines, C1-INH medications, lanadelumab, and berotralstat, are recommended as first line therapy for long-term prophylaxis (LTP) in HAE types 1 and 2, with attenuated androgens and fibrinolytics recommended as second and third line, respectively. Newer LTP options, such as Andembry (garadacimab-gxii) and Dawnzera (donidalorsen), are not yet addressed in guidelines.
- Guidelines do not recommend one long term prophylaxis agent over the other, therefore Haegarda (plasma derived C1-INH) and Takhzyro (lanadelumab-flyo) are the most cost-effective guideline-recommended options.
- There is insufficient evidence on prophylactic treatment in patients with HAE-nl-C1-INH and acquired angioedema, as such use in these patient populations is considered investigational.

Diagnosis [1 2 11 12]

- HAE is diagnosed with clinical presentation, family history, and measurements of serum C1-INH function, levels of C1-INH protein, and levels of C4 protein.
- A comprehensive diagnostic evaluation is also based on a suggestive HAE clinical history including (but not limited to) recurrent episodes of angioedema without urticaria (wheals) or pruritus lasting 2-5 days without treatment, unexplained recurrent painful abdominal symptoms, unexplained upper airway edema, onset of angioedema episodes in childhood and adolescence, a positive family history of angioedema, and an exclusion of other causes of angioedema (i.e., mast-cell mediated angioedema, idiopathic angioedema, allergic reactions/anaphylaxis, drug-induced angioedema, allergic contact dermatitis, autoimmune conditions).
- The most straightforward parameter is the assessment of C1-INH *function*, which is low in both HAE types I and II (usually <50% of normal function). The C4 protein level is low in both HAE types I and II. The C1-INH protein *level* is low in HAE type I, and normal or elevated in HAE type II.
- HAE with normal C1-INH levels (HAE-nl-C1-INH, formerly called HAE type III) is a subset of rare HAE that largely resembles type 1 or 2 HAE and may be caused by multiple mutations. However, in many patients with HAE-nl-C1-INH, no gene mutation can be found, and the diagnosis is based on family history, normal levels of C4, C-1 INH protein (or "antigen") and function, normal levels of C1q protein, and an exclusion of other causes of angioedema (such as mast-cell mediated angioedema). Mast-cell mediated angioedema is ruled out with a failed response to antihistamines, glucocorticoids, omalizumab or epinephrine.
- If acquired angioedema (AAE) is suspected due to lack of family history or late onset of symptoms (age over 40 years), C1q antigenic protein testing is used to rule out AAE. Serum C1q level is low in patients with AAE but normal in patients with HAE. Patients with acquired angioedema demonstrate the following: low C4 protein levels, low or normal C1-INH protein levels, low C1-INH function (usually < 50% of normal), and low C1q (usually <50% of normal) levels.

Clinical Efficacy – Acute Treatments [1 5 8 13]

- Berinert, Ekterly, Ruconest, icatibant (generic, Firazyr, Sajazir), and Kalbitor (ecallantide) have all demonstrated efficacy in the treatment of acute attacks of HAE. While the body of evidence is generally considered low quality evidence, the products have demonstrated an overall improvement in symptoms following an HAE attack.
- The evidence for efficacy of Ekterly (sebetralstat) contains several notable limitations:
    * The efficacy of Ekterly (sebetralstat) for the treatment of severe laryngeal attacks (swelling that compromises breathing and/or swallowing) is unknown as this attack type was excluded from sebetralstat treatment in the pivotal trial. While rare, laryngeal attacks are the highest mortality attack type. Patients who experienced severe laryngeal attacks in the pivotal trial were treated with well-established, effective, standard of care options including C1-INH concentrate, icatibant or ecallantide.

    * Forty percent of patients treated with sebetralstat in the pivotal trial required a second dose due to a lack of response and persistent symptoms. Other standard of care options (C1-INH concentrate, ecallantide and icatibant) have demonstrated substantially lower rates (3-7%) of repeat dose administration for persistent symptoms in their respective pivotal trials.
    * About 50% of sebetralstat-treated patients in the pivotal trial did not have a reduction in the severity of attack symptoms within 12 hours nor relief (complete symptom resolution) within 24 hours of treatment.
- There are no head-to-head studies comparing treatments for acute HAE attacks.
- The treatment effect of on-demand therapies in HAE-nl-C1-INH, (formerly type III HAE) is uncertain; available evidence is limited to small, uncontrolled trials and case reports for specific agents only (Kalbitor [ecallantide], icatibant [generic, Firazyr, Sajazir) and C1-INH concentrate). There is currently no available evidence to support the use of Ekterly (sebetralstat) in the treatment of HAE-nl-C1-INH.
- Concurrent use of more than one acute HAE treatment (as listed in *Table 1*), meaning use of more than one product for the same attack, has not been shown to be safe or effective and is considered investigational.

Clinical Efficacy – Prophylactic Treatments

Clinical Efficacy – Andembry (garadacimab-gxii)[20 21]

- FDA approval of garadacimab was based on a single phase 3 multicenter, randomized, double-blind, placebo-controlled trial (VANGUARD).
    * Patients had type I or type II HAE and a history of at least two HAE attacks in the 2-month trial run-in period.
    * Patients were not allowed to continue current prophylactic medications for HAE.
    * Treatment with garadacimab significantly reduced the monthly number of attacks versus placebo (0.22 attacks vs. 2.07, respectively), resulting in an 89% reduction in monthly attacks compared to placebo ($p<0.0001$).
    * The garadacimab treatment group had less rescue medication use and lessened attack severity, compared to the placebo group.
- No direct comparative studies have been performed between attenuated androgens, C1-INH, lanadelumab, berotralstat and garadacimab.
- Maintenance doses higher than 200mg monthly were not studied in clinical trials.

Clinical Efficacy – Cinryze [15]

- FDA approval for Cinryze was based on one clinical trial in HAE attack prevention. The study was a prospective, randomized, double-blind, placebo-controlled multi-center crossover study with 22 HAE patients aged ≥ 6 years of age (range 9 to 73 years) for a 24-week period (12-week placebo and 12-week C1-INH).
    * Patients received twice weekly injections of either placebo or 1,000 units of C1-INH.

    * Patients included in the study had a history of at least two HAE attacks per month. Inclusion was not dependent on the severity of attack.
    * Patients were permitted to continue current medications, but dose changes to androgen or aminocaproic acid were not allowed during the study or 30-days prior to the study.
    * Cinryze (pdC1-INH) reduced the number of HAE attacks by 52% (primary endpoint), the severity of HAE attacks by 32% and duration of swelling by 66% (secondary endpoints). All values were statistically significant.
    * Only half of the study patients responded with a 50% or greater reduction in frequency of HAE attacks.
- No comparative studies have been performed between attenuated androgens and Cinryze (pdC1-INH).

Clinical Efficacy – Dawnzera (donidalorsen) [22]

- FDA approval of donidalorsen was based on a single phase 3 multicenter, randomized, double-blind, placebo-controlled trial (OASIS-HAE).
    * Patients had type I or type II HAE and a history of at least two HAE attacks in the 2-month trial run-in period.
    * Patients received donidalorsen 80mg every 4 weeks, 80mg every 8 weeks, or placebo for 24 weeks.
    * Measured from week 1 through week 24, donidalorsen demonstrated a substantial reduction versus placebo in mean monthly HAE attacks (81% reduction in the 4-week group and 55% in the 8-week group, $p<0.004$), at the end of week 24.
    * Measured from week 5 through week 24 (at steady state donidalorsen levels), an 87% and 60% reduction versus placebo ($p<0.004$) in mean monthly HAE attacks was demonstrated in the 4-week and 8-week donidalorsen groups, respectively, at the end of week 24.
    * A greater than 70% reduction in mean monthly attacks occurred in 82%, 65% and 18% of patients treated with donidalorsen 80mg every 4 weeks, every 8 weeks, or placebo, respectively.
    * Maintenance doses higher than 80mg every 4 weeks were not studied in the clinical trial.
- No direct comparative studies have been performed between attenuated androgens, C1-INH, lanadelumab, berotralstat, garadacimab, or donidalorsen.

Clinical Efficacy – Haegarda [14]

- Approval for Haegarda (pdC1-INH) was based on the COMPACT study, which was a phase 3 randomized, double-blind, placebo-controlled, cross-over study. The study evaluated two doses of Haegarda, but the FDA approved dose is 60 IU/kg.

    * Patients received twice weekly injections of either placebo or weight-based Haegarda (pdC1-INH).
    * Patients included in the study had a history of at least four HAE attacks over a 2-month period within 3 months of screening. Attacks must have required immediate treatment, medical attention, or caused significant functional impairment.
    * Patients were permitted to continue oral prophylaxis, but dose changes were not allowed during the study period.
    * Haegarda (pdC1-INH) 60 IU/kg reduced the median number of HAE attacks by 95% compared to placebo. The mean number of attacks per month was 0.52 in the Haegarda (pdC1-INH) period compared to 4.03 during the placebo period. Use of rescue medication was also significantly lower while patients received Haegarda (pdC1-INH).
    * A lower dose of 30 IU/kg was also found to be effective versus placebo but was less effective than the 60 IU/kg dose.
- There are no studies to date evaluating the efficacy of Haegarda (pdC1-INH) compared to other standard treatments for prevention of HAE attacks; however, the COMPACT study included patients who received concomitant attenuated androgens.
- No comparative studies have been performed between attenuated androgens and either Haegarda (pdC1-INH) or Cinryze (pdC1-INH).
- Concurrent use of more than one prophylactic HAE treatment (as listed in *Table* 4), meaning the use of more than one product for attack prevention, has not been shown to be safe or effective and is considered investigational.

Clinical Efficacy – Orladeyo (berotralstat) [19]

- FDA approval for berotralstat was based a single phase 3, multicenter, randomized, double-blind, placebo-controlled trial; the APEX-2 trial. The study evaluated two doses of berotralstat.
    * Patients included in the study had a history of at least one HAE attack per 4 weeks (≥2 investigator confirmed HAE attacks in the 56-day run-in period).
    * Patients were not permitted to continue current prophylactic medications
    * Treatment with berotralstat 110 mg by mouth every day significantly reduced the monthly rate of attacks versus placebo (1.65 attacks vs. 2.35, respectively; $p = 0.024$).
    * Treatment with berotralstat 150 mg by mouth every day significantly reduced the monthly rate of attacks versus placebo (1.31 attacks vs. 2.35, respectively; $p < 0.001$).
    * Additionally, the berotralstat groups had less rescue medication use compared to the placebo-group.
- No comparative studies have been performed between attenuated androgens, C1-INH, lanadelumab and berotralstat.

- Doses higher than 150 mg every day were not studied during clinical trials.

Clinical Efficacy – Takhzyro (lanadelumab) [16-18]

- FDA approval for lanadelumab was based on one randomized phase 3, double-blind, placebo-controlled trial; the HELP trial. The study evaluated various dosing regimens of lanadelumab. The FDA approved dose of 300 mg every 2 weeks was evaluated for prophylaxis of HAE attacks.
    * Patients included in the study had a history of at least one HAE attack per 4 weeks.
    * Patients were not permitted to continue current prophylactic medications
    * Treatment with lanadelumab 300 mg subcutaneously every 2 weeks significantly reduced the number of attacks versus placebo (0.257 attacks vs. 1.967, respectively; $p < 0.001$).
    * Treatment with lanadelumab 300 mg subcutaneously every 4 weeks significantly reduced the number of attacks versus placebo (0.526 attacks vs. 1.967, respectively; $p < 0.001$).
    * Treatment with lanadelumab 150 mg subcutaneously every 4 weeks significantly reduced the number of attacks versus placebo (0.480 attacks vs. 1.967, respectively; $p < 0.001$).
    * Additionally, the lanadelumab group had less rescue medication use and a lower number of moderate to severe HAE attacks compared to the placebo-group.
- In patients with no HAE attacks in the past 6 months while on lanadelumab, a dose reduction to 300mg every 4 weeks has been shown to be safe and effective.
- No comparative studies have been performed between attenuated androgens, C1-INH, and lanadelumab.
- Doses higher than 300 mg every 2 weeks were not studied during clinical trials.
- There are no trials of Takhzyro (lanadelumab) used in combination with Haegarda (C1-INH) or any other HAE prophylactic agent; therefore, use of Takhzyro (lanadelumab) in combination with any other HAE prophylactic agent is considered investigational.

Not Medically Necessary Uses

- The efficacy of Ekterly (sebetralstat) for the treatment of severe laryngeal attacks (swelling that compromises breathing and/or swallowing) is unknown as this attack type was excluded from sebetralstat treatment in the pivotal trial. For this reason, the use of Ekterly (sebetralstat) for the treatment of severe laryngeal attacks is considered not medically necessary. While rare, laryngeal attacks are associated with the highest mortality among HAE attack types. Patients who experienced severe laryngeal attacks in the pivotal trial were treated with well-established, effective, standard of care options including C1-INH concentrate formulations, icatibant or ecallantide.

Investigational Uses

- C1-INH is currently being studied in a variety of other conditions including angioedema due to causes other than HAE, myocardial infarction, and sepsis; however, due to lack of published data, it is considered investigational in these conditions.
- There are no well-designed, published trials that evaluate the efficacy of medications for HAE for the treatment of mast-cell mediated angioedema. Mast-cell mediated angioedema is often treated with high-dose (double or quadruple the usual dose) antihistamines alone or in combination with montelukast and/or a trial of omalizumab. Therefore, the use of medications for HAE for this condition is considered investigational. [23]
- Icatibant (generic, Firazyr, Sajazir) is currently being studied in a variety of other conditions including angioedema due to causes other than HAE, prevention of HAE attacks, osteoarthritis, and ischemic heart disease; however, due to lack of published data, it is considered investigational in these conditions.
- Prophylactic therapy for HAE-nl-C1-INH, (formerly type III HAE): Due to normal levels of C1-INH, the use of C1-INH replacement therapy for long term prophylaxis is controversial, not recommended by guidelines, and evidence of efficacy is anecdotal. Data is limited to a few small case reports and a single retrospective study; there are no well-designed, published clinical trials that evaluate the treatment efficacy of prophylactic medications for HAE in patients with HAE-nl-C1-INH. The prophylactic use of these agents in this setting is considered investigational.[24-26]
- There is no evidence to support the use of Ekterly (sebetralstat) for the treatment of HAE-nl-C1-INH and its use for this indication is considered investigational.

Safety

- The most common adverse reactions with Berinert are injection site nausea, headache, dysgeusia, abdominal pain, and vomiting. Other rare but serious adverse events include hypersensitivity and thromboembolic events. There is also a risk of transmission of infectious agents (e.g., viruses) because Berinert is derived from human blood.[25]
- The most common adverse reactions with Ruconest are headache, nausea, and diarrhea. Other rare but serious adverse events include hypersensitivity and thromboembolic events.[26]
- The most common adverse reactions with icatibant (generic, Firazyr, Sajazir) are injection site reactions (97%), such as erythema (redness of skin) and swelling, most of which are transient, spontaneously resolving, and mild to moderate in severity. Slowing the injection time can mitigate injection site reactions. Other common adverse reactions (> 1%) included pyrexia, increased liver enzymes, dizziness, and rash.[27 28]
- Kalbitor (ecallantide) is given subcutaneously and carries a boxed warning for anaphylactic reactions (3.9%). Due to the risk of anaphylaxis Kalbitor (ecallantide) should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.[29]
- The most common adverse reactions with Kalbitor (ecallantide) are headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis.[29]

- The most common adverse events reported with plasma-derived Haegarda include injection site reactions, hypersensitivity, nasopharyngitis, and dizziness. Of the injections site reactions reported in clinical trials, 95% were of mild intensity and 83% resolved within one day of onset.[30]
- The most common side effects experienced during lanadelumab clinical trials included injection site reactions, rash, dizziness, upper respiratory infections, headache, diarrhea and myalgia.[18]
- The most common side effects experienced during berotralstat clinical trials included upper respiratory tract infection, abdominal pain, diarrhea, headache, and back pain.[31]
- The most common side effects experienced during garadacimab clinical trials included nasopharyngitis and abdominal pain, but long-term safety is lacking.[20]
- Plasma-derived C1-INH replacement therapy has a long history of use without evidence of drug interactions or immunogenicity. No cases of pathogen transmission have been reported.[2]

Appendices

Appendix 1: Oral Prophylactic Medications for Hereditary Angioedema[3 32 33]

Drug	Usual Adult Dose	Dosage Range	FDA Approved for HAE
danazol (Danocrine)	200 mg/day	100 mg every 3 days – 600 mg/day	Yes
stanozolol (Winstrol)	2 mg/day	1 mg every 3 days – 6 mg/day	Yes
oxandrolone (Oxandrin)	10 mg/day	2.5 mg every 3 days – 20 mg/day	No
epsilon aminocaproic acid (Amicar)	2 g three times/day	1 g twice/day – 4 g three times/day	No
tranexamic acid (Lysteda)	20-50 mg/kg/day	3-6 g/day maximum	No

Dosing

Appendix 2: FDA-Approved, HAE-specific Medications			
Drug	**Indication**	**Usual Dose and Route**	**Approved for Self-Administration**
Acute treatments			
Ekterly (sebetralstat[34])	Treatment of acute attacks of HAE	600mg (two 300mg tablets) by mouth; a repeat dose may be given *once* within 3 hours if symptoms persist/recur	Yes
Kalbitor (ecallantide)[29]	Treatment of acute attacks of HAE	30 mg injected subcutaneously (SC) in three 10 mg injections	No
icatibant (generic, Firazyr, Sajazir)[27 28]	Treatment of acute attacks of HAE	30 mg injected SC to the abdominal area	Yes
Berinert (pdC1-INH)[25]	Treatment of acute attacks of HAE	20 IU per kg injected intravenously (IV)	Yes
Ruconest (rhC1-INH)[26]	Treatment of acute attacks of HAE Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks	50 IU per kg injected IV; Max dose 4200 IU	Yes
Prophylactic treatments			
Andembry (garadacimab-gxii)[20]	Routine prophylaxis to prevent HAE attacks	400 mg SC as a single loading dose, then 200 mg SC monthly thereafter	Yes
Cinryze (IV plasma derived C1-INH)[15]	Routine prophylaxis to prevent HAE attacks	1000 U IV twice weekly (every 3 to 4 days)	Yes
Dawnzera (donidalorsen)[35]	Routine prophylaxis to prevent HAE attacks	80 mg SC every 4 weeks. 80 mg every 8 weeks may be considered.	Yes
Haegarda (SC plasma-derived C1-INH) [30]	Routine prophylaxis to prevent HAE attacks	60 IU/kg SC twice weekly (every 3 to 4 days)	Yes
Takhzyro (lanadelumab-flyo)[18]	Routine prophylaxis to prevent HAE attacks	300 mg SC every two weeks	Yes
Orladeyo (berotralstat) [31]	Routine prophylaxis to prevent HAE attacks	≥12 years of age: 150 mg orally daily 2 to <12 years: up to 132 mg orally daily (exact dose based on weight)	Yes

Codes	Number	Description
HCPCS	J1290	Injection, ecallantide (Kalbitor), 1 mg
HCPCS	J0597	Injection, c-1 esterase inhibitor (human), Berinert, 10 units
HCPCS	J0598	Injection, c-1 esterase inhibitor (human), Cinryze, 10 units
HCPCS	J0596	Injection, c1 esterase inhibitor (recombinant), Ruconest, 10 unit

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408

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Revision history

Revision Date	Revision Summary
1/22/2026	• Added Dawnzera (donidalorsen), a new prophylactic agent, to the policy as preferred. • Added Ekterly (sebetralstat), a new acute agent, to the policy. • Andembry (garadacimab-gxii) changed to preferred with step through non-preferred products removed. • Prophylactic product step therapy now allows step through one of the following products: Andembry, Dawnzera, Haegarda, or Takhzyro. Previously required Haegarda or Takhzyro. • Added pediatric dosing (ages 2 to less than 12 years of age) for new Orladeyo (berotralstat) oral pellets.
10/02/2025	• Added Andembry (garadacimab-gxii), a new prophylactic agent, to the policy. • Clarified COT criteria: **1.** Documentation of prior coverage instead of attestation. **2.** The requested treatment is not for indications listed under the Investigational Uses section in the policy. • Added that the use of prophylactic agents for HAE with normal C1-INH (HAE-nl-C1-INH), formerly type III HAE, is considered investigational.
12/12/2024	• Clarification of Continuation of therapy (COT) criteria for dose requests above the initial coverable Quantity Limit (no change to intent). • Clarification of diagnostic criteria wording, to ensure the diagnosis is established by a specialist and documentation of *full* assessment (no change to intent). Rewording for clarity and consistent administration. • Updated criteria for laboratory requirements for AAE and each specific HAE type. Clarification of reauthorization requirements, to explicitly require documentation of details of attacks, response to therapy, and justification of requested doses.
6/20/2024	Added Cinryze (plasma-derived C1-INH) to site of care (SOC) program (effective 10/1/2024).
12/7/2023	Updated reauthorization time frame to 12 months for all HAE medications in this policy.
12/9/2022	• Added Sajazir (icatibant), newly approved medication, to the policy. • Added step therapy requirement with Berinert (plasma-derived C1-INH) to Ruconest (recombinant human C1-INH) for acute HAE treatment.

Revision Date	Revision Summary
	• Removed step through attenuated androgens/antifibrinolytics for prophylactic HAE treatments. Clarified HAE-nl-C1-INH (formerly type III HAE) diagnosis and treatment, with prophylactic treatment considered investigational.
1/20/2021	• Added Orladeyo (berotralstat), a newly-approved medication, to the policy. • Added generic icatibant step therapy requirement for all acute HAE therapies. • Removed Haegarda step therapy requirement for Takhzyro (lanadelumab-flyo). Clarified reauthorization criteria and quantity limits for maintenance Takhzyro (lanadelumab-flyo) therapy.
1/22/2020	• Added step therapy requirement with generic icatibant to brand Firazyr (icatibant). • Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2019	No criteria changes with this annual update.
11/16/18	Added Takhzyro (lanadelumab-flyo), a newly-approved medication, to the policy (effective January 1, 2019).
2/19/2018	• New policy (effective July 1, 2018): All existing HAE policies have been combined into a single policy, with no overall change to the intent of coverage criteria. • Added a criterion clarifying that multiple treatments for acute attacks of HAE should not be used concurrently. Extended the authorization period to 6 months from 3 months for all medications.

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