Pharmacy Policy Bulletin: J-0424 Hereditary Angioedema - Commercial and Healthcare Reform	
Number: J-0424	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1. or 2.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization (Ekterly, Orladeyo) **2.** Miscellaneous Specialty Drugs Injectable = Yes w/ Prior Authorization (Andembry, Berinert, Cinryze, Firazyr, Sajazir, Haegarda, Ruconest, Takhzyro) **Quantity Limits (1., 2., 3., or 4.):** **1.** Rx Mgmt Quantity Limits = Safety/Specialty **2.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt **3.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt + Watchful **4.** Rx Mgmt Performance = MRxC = Yes **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0424-020	**Original Date:** 03/04/2015
Effective Date: 10/08/2025	**Review Date:** 09/17/2025

Drugs Product(s):	• Andembry (garadacimab-gxii) • Berinert [C1 Esterase Inhibitor (Human)] • Cinryze [C1 Esterase Inhibitor (Human)] • Ekterly (sebetralstat) • Firazyr, Sajazir (icatibant) • Haegarda [C1 Esterase Inhibitor (Human)] • Orladeyo (berotralstat) • Ruconest [C1 Esterase Inhibitor (Recombinant)] • Takhzyro (lanadelumab-flyo)
FDA-Approved Indication(s):	• **Andembry**: Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 12 years and older.

	• **Berinert**: Treatment of acute abdominal, facial, or laryngeal HAE attacks in adult and pediatric patients. • **Cinryze**: Routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6 years of age and older) with HAE. • **Ekterly**: Treatment of acute attacks of HAE in adult and pediatric patients aged 12 years and older. • **Firazyr, Sajazir**: Treatment of acute attacks of HAE in adults 18 years of age and older. • **Haegarda**: Routine prophylaxis to prevent HAE attacks in patients 6 years of age or older. • **Orladeyo**: Prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years of age and older. • **Ruconest**: Treatment of acute attacks in adult and adolescent patients with HAE. • **Takhzyro**: Prophylaxis to prevent attacks of HAE in adult and pediatric patients 2 years of age and older.

Background:	• HAE is a rare autosomal dominant disease that presents with episodes of unpredictable, non-allergic swelling. HAE can be divided into two main types: HAE due to C1 inhibitor (HAE-C1INH) deficiency or HAE with normal C1NH (HAE-nl-C1NH, previously referred to as HAE type 3). HAE-C1INH is further divided into Type 1 HAE (deficient levels of C1INH protein and function) and Type 2 HAE (normal level of C1INH protein that is dysfunctional). The estimated prevalence of Type 1 and 2 HAE is 1 per 50,000, so there are approximately 6,000 affected patients in the United States. • HAE is a disease that presents with episodes of non-allergic angioedema. Patients experience swelling episodes that resolve within 2 to 5 days without treatment; however laryngeal swelling can be fatal. The swelling occurs without hives or itching. Bradykinin is a vasodilator that results in the swelling that is associated with angioedema. Since the angioedema is non-allergic, histamines are not involved and antihistamines are not effective. HAE can also occur because of a deficiency or malfunction of the C1 inhibitor in the body which regulates the coagulation pathway. • ICD-10 Code Information: ○ D84.1 “Defects in the complement system” may apply to hereditary angioedema; however, the prescriber must specify diagnosis. • **Andembry**: Inhibitor of activated Factor XII (FXIIa) that binds to the catalytic domain of activated Factor XII (FXIIa and βFXIIa) and inhibits its catalytic activity. FXIIa is a key component in the contact activation pathway, which triggers the kallikrein-kinin system. By inhibiting FXIIa, Andembry reduces the production of kallikrein and bradykinin. Bradykinin is a mediator of inflammation and swelling, and its reduction helps to prevent HAE attacks. • **Berinert, Cinryze, Haegarda, Ruconest:** C1 esterase inhibitors, belonging to the group of serine protease inhibitors, and have an important inhibiting potential on the complement system and coagulation cascade. HAE patients have low levels of endogenous or functional C1 esterase inhibitor. • **Ekterly:** Reversible inhibitor of plasma kallikrein that reduces bradykinin production by blocking the cleavage of high molecular weight kininogen, thereby decreasing vascular permeability and edema associated with acute HAE attacks. Additionally, Ekterly inhibits the kallikrein-kinin system's positive feedback loop by reducing factor XIIa and further kallikrein generation. • **Icatibant:** Competitive antagonist selective for the bradykinin B2 receptor, with an affinity similar to bradykinin. Bradykinin inhibition counteracts vasodilation which is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain.

	• **Orladeyo:** Plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity and decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.
	• **Takhzyro:** Fully human monoclonal antibody (IgG1/κ-light chain) that binds plasma kallikrein and inhibits its proteolytic activity. Takhzyro decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.
	• Prescribing Considerations:
	  ○ The safety and efficacy of Berinert for prophylactic therapy has not been established.
	  ○ Orladeyo should not be used for the treatment of acute HAE attacks.
	  ○ The recommended starting dose for Takhzyro is 300 mg (≥ 12 years of age) or 150 mg (6 to < 12 years of age) subcutaneously (SC) every 2 weeks; or 150 mg SC every 4 weeks (2 to < 6 years of age). A dosing interval of 300 mg (≥ 12 years of age) or 150 mg (6 to < 12 years of age) every 4 weeks is also effective and may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months.
	  ○ Appropriately trained patients may administer Berinert or icatibant upon recognition of an HAE attack. Patients or caregivers may self-administer Andembry, Takhzyro, or Cinryze after training.
	  ○ The effectiveness of Ruconest has not been established in HAE patients with laryngeal attacks. Ruconest is contraindicated in patients with known or suspected allergy to rabbits and rabbit-derived products.
	  ○ Serious arterial and venous thromboembolic events have been reported at the recommended dose of plasma-derived C1 esterase inhibitor products in patients with risk factors.

Approval Criteria

I. Initial Authorization

A. Andembry, Cinryze, Haegarda, Orladeyo, Takhzyro

1. HAE due to a deficiency of C1INH (Type I & II) (no ICD-10 code)

When a benefit, initiation of Andembry, Cinryze, Haegarda, Orladeyo, or Takhzyro may be approved when all of the following criteria are met **(a. through h.):**

a. The member meets one (1) of the following **(i., ii., or iii.):**
- **i.** If the request is for Takhzyro, the member is 2 years of age or older.
- **ii.** If the request is for Cinryze or Haegarda, the member is 6 years of age or older.
- **iii.** If the request is for Andembry or Orladeyo, the member is 12 years of age or older.

b. The medication is being used for prophylaxis management against angioedema attacks of HAE.

c. The medication is prescribed by or in consultation with an allergist, immunologist, or a provider who specializes in the treatment of hereditary angioedema.

d. The member has low C4 level less than or equal to 14mg/dL or a C4 below the lower limit of the laboratory's reference range and one (1) of the following criteria **(i. or ii.):**
- **i.** C1 inhibitor (C1INH) antigenic level less than or equal to 19 mg/dL (normal range: 19 to 37 mg/dL) or below the lower limit of the laboratory's reference range.
- **ii.** A normal C1INH antigenic level (C1INH greater than or equal to 19 mg/dL) and a low C1INH functional level (functional C1INH less than 50% or below the laboratory's reference range).

e. The member has a history of at least one (1) symptom of moderate or severe angioedema attack (for example, airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion) in absence of concomitant hives or use of medication to cause angioedema.

f. The member's medications known to cause angioedema (for example, ACE-inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.
g. The member should not be on two (2) prophylactic therapies simultaneously (for example, Andembry, Cinryze, Haegarda, Orladeyo, or Takhzyro).
h. If the request is for Haegarda, the prescriber submits the member's weight.

2. HAE with normal C1INH (formerly referred to as Type III) (no ICD-10 code)
When a benefit, initiation of Andembry, Cinryze, Haegarda, Orladeyo, or Takhzyro may be approved when all of the following criteria are met **(a. through i.):**
a. The member meets one (1) of the following **(i., ii., or iii.):**
i. If the request is for Takhzyro, the member is 2 years of age or older.
ii. If the request is for Cinryze or Haegarda, the member is 6 years of age or older.
iii. If the request is for Andembry or Orladeyo, the member is 12 years of age or older.
b. The medication is being used for prophylaxis management against angioedema attacks of HAE.
c. The medication is prescribed by or in consultation with an allergist, immunologist, or a provider who specializes in the treatment of hereditary angioedema.
d. The member meets at least one (1) of the following **(i., ii., or iii.):**
i. C4 within normal limits (normal range: 14 to 40 mg/dL) OR C4 within normal limits of the laboratory's normal reference range.
ii. C1INH antigen within normal limits (normal range: 19 to 37 mg/dL) OR C1INH antigenic level within normal limits of the laboratory's normal reference range.
iii. C1INH functional within normal limits of the laboratory's normal reference range.
e. The member meets at least one (1) of the following **(i. through vii.):**
i. Family history of HAE
ii. FXII mutation
iii. Angiopoietin-1mutation
iv. Plasminogen mutation
v. Kininogen-1 mutation
vi. Myoferlin mutation
vii. Heparin sulfate-glucosamine 3-O-sulfotransferase 6 mutation
f. The member has a history of at least one (1) symptom of moderate or severe angioedema attack (for example, airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion) in absence of concomitant hives or use of medication to cause angioedema.
g. The member's medications known to cause angioedema (for example, ACE-inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.
h. The member should not be on two (2) prophylactic therapies simultaneously (for example, Andembry, Cinryze, Haegarda, Orladeyo, or Takhzyro).
i. If the request is for Haegarda, the prescriber submits the member's weight.

3. Quantity Limitations (Andembry)
When prior authorization is approved, Andembry may be authorized in quantities as follows:

Induction Therapy	Maintenance Therapy
Two (2) syringes/autoinjectors within the first four (4) weeks of therapy.	One (1) syringe/autoinjector every four (4) weeks.

B. Berinert, Ekterly, Firazyr/Sajazir (icatibant), Ruconest
4. HAE due to a deficiency of C1INH (Type I & II) (no ICD-10 code)

When a benefit, initiation of Berinert, Ekterly, Firazyr/Sajazir (icatibant), or Ruconest may be approved when all of the following criteria are met **(a. through j.)**:

- **a.** The member meets one (1) of the following **(i. through iv.):**
  - **i.** If the request is for Berinert, the member is 5 years of age or older.
  - **ii.** If the request is for Ekterly, the member is 12 years of age or older.
  - **iii.** If the request is for Firazyr/Sajazir (icatibant), the member is 18 years of age or older.
  - **iv.** If the request is for Ruconest, the member is 13 years of age or older.
- **b.** The medication is being used for the treatment of acute HAE attacks and not for prophylactic treatment of HAE.
- **c.** The medication is prescribed by or in consultation with an allergist, immunologist, or a provider who specializes in the treatment of hereditary angioedema.
- **d.** The member has low C4 level less than or equal to 14mg/dL or a C4 below the lower limit of the laboratory's reference range and one (1) of the following criteria **(i. or ii.):**
  - **i.** C1 inhibitor (C1INH) antigenic level less than or equal to 19 mg/dL (normal range: 19 to 37 mg/dL) or below the lower limit of the laboratory's reference range.
  - **ii.** A normal C1INH antigenic level (C1INH greater than or equal to 19 mg/dL) and a low C1INH functional level (functional C1INH less than 50% or below the laboratory's reference range).
- **e.** The member has a history of at least one (1) symptom of moderate or severe angioedema attack (for example, airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion) in absence of concomitant hives or use of medication to cause angioedema.
- **f.** The member's medications known to cause angioedema (for example, ACE-inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.
- **g.** The member should not be on two (2) acute therapies simultaneously (for example, Berinert, Ekterly, Firazyr, Kalbitor, or Ruconest).
- **h.** If the request is for Berinert or Ruconest, the member meets all of the following criteria **(i. and ii.)**:
  - **i.** If the member is 18 years of age or older, the member has experienced therapeutic failure, contraindication, or intolerance to plan-preferred generic icatibant.
  - **ii.** The prescriber submits the member's weight.
- **i.** If the request is for Ekterly and the member is 18 years or age or older, the member meets one (1) of the following criteria **(i. or ii.)**:
  - **i.** The member has experienced therapeutic failure, contraindication, or intolerance to plan-preferred generic icatibant.
  - **ii.** The prescriber submits clinical documentation the member is unable to use a self-administered injection confirmed by one (1) of the following **(A) or B))**:
    - **A)** Diagnosis of needle phobia confirmed by psychiatric evaluation.
    - **B)** Physical or cognitive impairment which places them at high risk of inappropriate administration with generic icatibant injection.
- **j.** If the request is for brand Firazyr, the member has experienced therapeutic failure or intolerance to generic icatibant.

2. **HAE with normal C1INH (formerly referred to as Type III) (no ICD-10 code)**
   When a benefit, initiation of Berinert, Ekterly, Firazyr/Sajazir (icatibant), or Ruconest may be approved when all of the following criteria are met **(a. through k.)**:
   - **a.** The member meets one (1) of the following **(i. through iv.):**
     - **i.** If the request is for Berinert, the member is 5 years of age or older.
     - **ii.** If the request is for Ekterly, the member is 12 years of age or older.
     - **iii.** If the request is for Firazyr/Sajazir (icatibant), the member is 18 years of age or older.
     - **iv.** If the request is for Ruconest, the member is 13 years of age or older.

b. The medication is being used for the treatment of acute HAE attacks and not for prophylactic treatment of HAE.
c. The medication is prescribed by or in consultation with an allergist, immunologist, or a provider who specializes in the treatment of hereditary angioedema.
d. The member meets at least one (1) of the following **(i., ii., or iii.)**:
  a. C4 within normal limits (normal range: 14 to 40 mg/dL) or C4 within normal limits of the laboratory's normal reference range.
  b. C1INH antigen within normal limits (normal range: 19 to 37 mg/dL) or C1INH antigenic level within normal limits of the laboratory's normal reference range.
  c. C1INH functional within normal limits of the laboratory's normal reference range.
e. The member meets at least one (1) of the following **(i. through vii.)**:
  i. Family history of HAE
  ii. FXII mutation
  iii. Angiopoietin-1mutation
  iv. Plasminogen mutation
  v. Kininogen-1 mutation
  vi. Myoferlin mutation
  vii. Heparin sulfate-glucosamine 3-O-sulfotransferase 6 mutation
f. The member has a history of at least one (1) symptom of moderate or severe angioedema attack (for example, airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion) in absence of concomitant hives or use of medication to cause angioedema.
g. The member's medications known to cause angioedema (for example, ACE-inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.
h. The member should not be on two (2) acute therapies simultaneously (for example, Berinert, Ekterly, Firazyr, Kalbitor, or Ruconest).
i. If the request is for Berinert or Ruconest, the member meets all of the following criteria **(i. and ii.)**:
  i. If the member is 18 years of age or older, the member has experienced therapeutic failure, contraindication, or intolerance to plan-preferred generic icatibant.
  ii. The prescriber submits the member's weight.
j. If the request is for Ekterly and the member is 18 years of age or older, the member meets one (1) of the following criteria **(i. or ii.)**:
  i. The member has experienced therapeutic failure, contraindication, or intolerance to plan-preferred generic icatibant.
  ii. The prescriber submits clinical documentation the member is unable to use a self-administered injection confirmed by one (1) of the following **(A) or B))**:
    A) Diagnosis of needle phobia confirmed by psychiatric evaluation.
    B) Physical or cognitive impairment which places them at high risk of inappropriate administration with generic icatibant injection.
k. If the request is for brand Firazyr, the member has experienced therapeutic failure or intolerance to generic icatibant.

3. Quantity Limitations (Ekterly)
When a benefit and prior authorization is approved, an additional quantity of 8 tablets at retail or 24 tablets at mail for Ekterly may be authorized if the following criterion is met **(a.)**:
a. The member requires additional doses of Ekterly to treat a subsequent attack of HAE.

Note: At retail, the approval quantity should be the number of Ekterly tablets the patient has received in the past 28 days plus 8 tablets. At mail, the approval quantity should be the number of

Ekterly tablets the patient has received in the past 84 days plus 24 tablets. One override may be approved ONCE every 28 days.

II. Reauthorization

When a benefit, reauthorization of may be approved when all of the following criteria are met **(A., B., and C.)**

A. The member meets one (1) of the following **(1. or 2.):**
  1. The member has experienced a decrease in frequency of HAE attacks from baseline.
  2. The member has experienced significant improvement from baseline in the severity or duration of attacks.

B. If the request is for Takhzyro, the prescriber has assessed the member for dose de-escalation and one (1) of the following criteria are met **(1., 2., or 3.):**
  1. Takhzyro is requested at a dosing interval of every 4 weeks.
  2. The member has had one (1) or more HAE attacks in the last 6 months and dose de-escalation to an every 4-week dosing interval would not be appropriate.
  3. An every 4-week dosing interval would not be appropriate.

C. If the request is for brand Firazyr, the member has experienced therapeutic failure or intolerance to generic icatibant.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drugs addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- **Commercial and HCR Plans:**
  - **For all medications listed (except Takhzyro):**
    - If approved, up to a 12 month authorization may be granted.
    - Andembry Note: For induction therapy authorization duration, refer to the Quantity Limitations tables.
  - **For Takhzyro:**
    - If approved for initiation therapy, up to a 6 month authorization may be granted.
    - If approved for maintenance therapy, up to a 12 month authorization may be granted

Automatic Approval Criteria

None

References:

1. Berinert [package insert]. Kankakee, IL: CSL Behring; September 2021.
2. Cinryze [package insert]. Lexington, MA: Shire ViroPharma, Inc.; November 2024.
3. Firazyr [package insert]. Lexington, MA: Takeda Pharmaceuticals America, Inc.; January 2024.

4. Haegarda [package insert]. Kankakee, IL: CSL Behring, LLC; January 2022.
5. Orladeyo [package insert]. Durham, NC: BioCryst Pharmaceuticals, Inc.; October 2024.
6. Ruconest [package insert]. Warren, NJ: Pharming Healthcare Inc.; April 2020.
7. Takhzyro [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; February 2023.
8. Andembry [package insert]. King of Prussia, PA: CSL Behring LLC; June 2025.
9. Ekterly [package insert]. Cambridge, MA: KalVista Pharmaceuticals, Inc.; July 2025.
10. Banerji A. Lanadelumab for prevention of attacks in hereditary angioedema: results from the phase 3 HELP study. American College of Allergy, Asthma and Immunology Meeting. 2017, 74: 1-18
11. Banerji et al. Inhibiting plasma kallikrein for hereditary angioedema prophylaxis. *N Engl J Med*. 2017; 376(8):717-728.
12. Zuraw BL, Banerji A, Bernstein JA, Busse PJ, 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*. 2013;1:458-67.
13. Gainer JV, Morrow JD, Loveland A, et al. Effect of Bradykinin-Receptor Blockade on the Response To Angiotensin-Converting-Enzyme Inhibitor In Normotensive And Hypertensive Subjects. *N Engl J Med*.1998; 339(18): 1285-1291.
14. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel. *Allergy Asthma Proc*. 2012;33 Suppl 1:S145-S156.
15. Bowen T, Cicardi M, Farkas H, et al. 2010. International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010;6:24.
16. 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.
17. 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*. 2020 Sep 6;S2213-2198(20)30878-3.