Hereditary Angioedema (HAE) Therapies

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the hereditary angioedema (HAE) therapies drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies while steering utilization to the most cost-effective medication within the therapeutic class.

The HAE therapies in this policy include the following: Andembry (garadacimab-gxii) FXIIa inhibitor; Berinert (C1 inhibitor), Cinryze (C1 inhibitor), and Haegarda (C1 inhibitor) C1 esterase inhibitors; Dawnzera (donidalorsen) prekallikrein inhibitor; Firazyr/Sajazir (icatibant) selective bradykinin B2 receptor antagonists; Ekterly (sebetralstat), Kalbitor (ecallantide), Orladeyo (berotralstat) and Takhzyro (lanadelumab) kallikrein inhibitors; and Ruconest (conestat alfa) a recombinant C1 esterase inhibitor. All HAE therapies inhibit either the formation or the activity of bradykinin, whose overproduction in the setting of C1 esterase inhibitor (C1INH) deficiency leads to capillary leakage and fluid accumulation in body tissues resulting in HAE symptoms. HAE therapies are administered by either oral (Ekterly, Orladeyo), intravenous (Ruconest, Berinert and Cinryze) or subcutaneous (Andembry, Dawnzera, Firazyr/Sajazir, Haegarda Kalbitor, Takhzyro) injection.

FDA-Approved Indication

- Andembry: prophylaxis to prevent attacks of HAE in adult and pediatric patients 12 years of age and older
- Berinert: treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and pediatric patients
- Cinryze: routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years of age or older) with HAE
- Dawnzera: prophylaxis to prevent attacks of HAE in adult and pediatric patients 12 years of age and older

- Ekterly: treatment of acute attacks of HAE in adult and pediatric patients 12 years of age and older
- Firazyr/Sajazir/icatibant: 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 and older
- Kalbitor: treatment of acute attacks of HAE in patients 12 years of age and older
- Orladeyo: prophylaxis to prevent attacks of HAE in adults and pediatric patients 2 years of age and older. *Note: should not be used for treatment of acute HAE attacks.*
- Ruconest: treatment of acute attacks in adults and adolescent patients with HAE. *Note: effectiveness was not established in HAE patients with laryngeal attacks.*
- Takhzyro: prophylaxis to prevent attacks of HAE in patients 2 years of age and older

Compendial Use

- Berinert: Short-term preprocedural prophylaxis for HAE attacks

POLICY

Required Documentation

Submission of the following information is necessary to initiate the prior authorization review:

- For initial authorization, the following should be documented:
    - C1 inhibitor functional and antigenic protein levels
    - F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
    - Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
- For continuation of therapy, chart notes demonstrating a reduction in frequency (Andembry, Cinryze, Dawnzera, Haegarda, Orladeyo, Takhzyro) or a reduction in the severity and/or duration (Berinert, Ekterly, Firazyr/Sajazir/icatibant, Kalbitor, Ruconest) of attacks

Prescriber Specialties

The medication must be prescribed by or in consultation with a prescriber who specializes in the management of HAE.

Criteria for Initial Approval

I. Andembry may be considered **medically necessary** for the prevention of HAE attacks when the requested medication will not be used in combination with any other medication used for the prophylaxis of HAE attacks and either of the following criteria is met at the time of diagnosis:
    - Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
        - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
        - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

      OR
    - Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
        - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
        - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

II. Berinert may be considered **medically necessary** for the treatment of HAE attacks when the requested medication will not be used with Ekterly, Firazyr/Sajazir, Kalbitor, or Ruconest and either of the following criteria is met at the time of diagnosis:
- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
    - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
    - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

  OR
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
    - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

III. Berinert may be considered **medically necessary** for short-term preprocedural prophylaxis (i.e., prior to surgical or major dental procedures) when either of the following criteria is met at the time of diagnosis:
- Member C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
    - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
    - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

  OR
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
    - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **30 days.**

IV. Cinryze may be considered **medically necessary** for the prevention of HAE attacks when the requested medication will not be used in combination with any other medication used for the prophylaxis of HAE attacks and either of the following criteria is met at the time of diagnosis:

- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
    - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
    - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

  OR
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
    - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

V. Dawnzera may be considered **medically necessary** for the prevention of HAE attacks when the requested medication will not be used in combination with any other medication used for the prophylaxis of HAE attacks and either of the following criteria is met at the time of diagnosis:
- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
    - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
    - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

  OR
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
    - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

VI. Ekterly may be considered **medically necessary** for the treatment of HAE attacks when the requested medication will not be used with Berinert, Firazyr/Sajazir, Kalbitor, or Ruconest and either of the following criteria is met at the time of diagnosis:
- Member must meet at least one of the following exception criteria:
    - Member is currently receiving treatment with Ekterly through health insurance, (not obtained as samples or via manufacturer's patient assistance programs)
    - Member has tried and experienced an inadequate response to Firazyr/Sajazir (icatibant)
    - Member has tried and experienced an intolerable adverse event to Firazyr/Sajazir (icatibant)

- Member has a contraindication to Firazyr/Sajazir (icatibant)
- Member is less than 18 years of age

AND

- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
  - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
  - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

OR

- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
  - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
  - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

VII. Brand and generic Firazyr/Sajazir (icatibant) may be considered **medically necessary** for the treatment of acute HAE attacks when the requested medication will not be used in combination with Berinert, Ekterly, Kalbitor, or Ruconest and either of the following criteria is met at the time of diagnosis:

- Member has a C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
  - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
  - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

OR

- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
  - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
  - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

VIII. Haegarda may be considered **medically necessary** for the prevention of HAE attacks when the requested medication will not be used in combination with any other medication used for prophylaxis of HAE attacks and either of the following criteria is met at the time of diagnosis:

- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:

- C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
- Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

OR

- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
  - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
  - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

IX. Kalbitor may be considered **medically necessary** for the treatment of acute HAE attacks when the requested medication will not be used in combination with Berinert, Ekterly, Firazyr/Sajazir, and Ruconest and either of the following criteria is met at the time of diagnosis:

- Member has a C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
  - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
  - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

OR

- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
  - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
  - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

X. Orladeyo may be considered **medically necessary** for prevention of hereditary angioedema attacks when the requested medication will not be used in combination with any other medication used for the prophylaxis of HAE attacks and either of the following criteria is met at the time of diagnosis:

- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
  - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
  - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).

OR

- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
    - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

XI. Ruconest may be considered **medically necessary** for the treatment of acute HAE attacks when the requested medication will not be used in combination with Berinert, Ekterly, Firazyr/Sajazir, or Kalbitor and either of the following criteria is met at the time of diagnosis:

- Member has a C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
    - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
    - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

  OR
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
    - Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

XII. Takhzyro may be considered **medically necessary** for the prevention of HAE attacks when the requested medication will not be used in combination with any other medication used for the prophylaxis of HAE attacks and either of the following criteria is met at the time of diagnosis:

- Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
    - C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test; or
    - Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test)

  OR
- Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
    - Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or

- Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (i.e., cetirizine at 40 mg per day or equivalent) for at least one month.

Approval will be for **12 months.**

XIII. Andembry, Berinert, Cinryze, Dawnzera, Ekterly, Brand and generic Firazyr/Sajazir, Haegarda, Kalbitor, Orladeyo, Ruconest, and Takhzyro are considered **not medically necessary** for patients who do not meet the criteria set forth above.

Continuation of Therapy

I. Authorization of 12 months may be granted for continuation of therapy of Berinert, Ekterly, Kalbitor, Firazyr/Sajazir, and Ruconest for the treatment of acute HAE attacks when all of the following criteria are met:
   - Member meets the criteria for initial approval.
   - Member has experienced reduction in severity and/or duration of acute attacks.
   - Prophylaxis should be considered based on the attack frequency, attack severity, comorbid conditions, and member's quality of life.

II. Authorization may be granted for continuation of therapy of Berinert for short-term preprocedural prophylaxis (i.e., prior to surgical or major dental procedures) when all initial authorization criteria are met.

III. Authorization of 12 months may be granted for continuation of therapy of Andembry, Cinryze, Haegarda, and Orladeyo when all of the following criteria are met:
   - Member meets the criteria for initial approval.
   - Member has experienced a significant reduction in frequency of attacks (e.g., ≥ 50%) since starting prophylactic treatment.
   - Member has reduced the use of medications to treat acute attacks since starting prophylactic treatment.

IV. Authorization of 12 months may be granted for continuation of therapy of Dawnzera when all of the following criteria are met:
   - Member meets the criteria for initial approval.
   - Member has experienced a significant reduction in frequency of attacks (e.g., ≥ 50%) since starting treatment.
   - Member has reduced the use of medications to treat acute attacks.
   - The requested drug is being dosed every 8 weeks or dosing every 8 weeks has been considered if the member is well-controlled on therapy for 6 months.

V. Authorization of 12 months may be granted for continuation of therapy of Takhzyro when all of the following criteria are met:
   - Member meets the criteria for initial approval.
   - Member has experienced a significant reduction in frequency of attacks (e.g., ≥ 50%) since starting treatment.
   - Member has reduced the use of medications to treat acute attacks.
   - The requested drug is being dosed every 4 weeks or dosing every 4 weeks has been considered if the member is well-controlled on therapy for 6 months.

Requests for the continuation of therapy of Andembry, Berinert, Cinryze, Dawnzera, Ekterly, Brand and generic Firazyr/Sajazir, Haegarda, Kalbitor, Orladeyo, Ruconest, and Takhzyro are considered **not medically necessary** for patients who do not meet the criteria set forth above.

Other

Other causes of angioedema have been ruled out (e.g., angiotensin-converting enzyme inhibitor [ACE-I] induced angioedema, angioedema related to an estrogen-containing drug, allergic angioedema).

Non-Formulary Exception Criteria

Non-Formulary Exception criteria applies to formularies which do not include the requested product(s) on the formulary drug list. Meeting the criteria above may satisfy some, or all, portions of the Non-Formulary Exception Criteria. A medication that is non-formulary may be covered when the Criteria for Approval AND the following criteria are met:

1. The requested drug must be used for an FDA-approved indication, or an indication supported in the compendia of current literature (examples: AHFS, Micromedex, current accepted guidelines). Diagnostic testing/lab results required when applicable.
2. The prescribed dose/quantity must fall within the FDA-approved labeling or dosing guidelines found in the compendia of current literature.
3. All covered formulary alternative drugs on any tier will be ineffective, have been ineffective, would not be as effective as the non-formulary drug, or would have adverse effects. Documentation is required and must include chart note(s) or other documentation indicating prior treatment failure, severity of the adverse event (if any), and dosage and duration of the prior treatment, or contraindication to formulary alternatives.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits

Andembry 200mg/1.2mL prefilled syringe/auto-injector – 1 syringe per 30 days
Dawnzera 80mg/0.8mL prefilled auto-injector – 1 syringe per 28 days
Ekterly 300mg tablet – 8 tablets per 30 days
Haegarda 2000 IU vial – 20 vials per 30 days
Haegarda 3000 IU vial – 20 vials per 30 days
Orladeyo – 1 capsule or pellet pack per day
Takhzyro 300 mg/2mL prefilled syringe/vial – 2 pens/vials (4 mL) per 28 days
Takhzyro 150 mg/1 mL prefilled syringe – 2 pens (2 mL) per 28 days

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J0593: Injection, lanadelumab-flyo, Takhzyro, 1 mg
- J0596: Injection, C-1 esterase inhibitor (recombinant), Ruconest, 10 units
- J0597: Injection, C-1 esterase inhibitor (human), Berinert, 10 units
- J0598: Injection, C-1 esterase inhibitor (human), Cinryze, 10 units
- J0599: Injection, C-1 esterase inhibitor (human), Haegarda, 10 units
- J1290: Injection, ecallantide, Kalbitor, 1 mg
- J1744: Injection, icatibant, 1 mg

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