I. Medication Description

Hereditary Angioedema (HAE) is an autosomal dominant disease caused by mutation of the C1 inhibitor gene (SERPING1), resulting in low levels of C1 inhibitor protein, or loss of functionality of this protein. Although multiple mutations have been identified, the exact cause of HAE is still unclear. C1 inhibitor protein plays a role in four enzymatic cascades in the body, all of which are interrelated to eventually cause the production of the peptide bradykinin. Deficiency in C1 inhibitor protein results in lack of inhibition of these cascades and increased levels of bradykinin. This uninhibited production of bradykinin causes angioedema in patients with HAE. Laboratory measurement of C1-INH, C1-INH activity and serum C4 levels are performed for diagnosis.

II. Position Statement

Coverage is provided through a prior authorization process with supporting clinical documentation for every request.

- Medical benefit drugs:
  - Cinryze (when administered by a healthcare professional)
  - Berinert (when administered by a healthcare professional)
  - Ruconest (when administered by a healthcare professional)
  - Kalbitor

- Pharmacy benefit drugs:
  - Cinryze (when self-administered)
  - Berinert (when self-administered)
  - Ruconest (when self-administered)
  - Firazyr

III. Policy

- In all cases, the diagnosis of Hereditary Angioedema (HAE) must have (at some time) been confirmed by an allergist, immunologist, or hematologist.
- Coverage of the prophylactic use of Cinryze is provided for the following:
  - For long-term prophylaxis against angioedema attacks when:
    - The disease is severely symptomatic AND
    - The member is at least 12 years of age AND
• The member has had an inadequate response to one plan-preferred medication such as attenuated androgen (i.e. Danazol) or antifibrinolytic (i.e. tranexamic acid) OR the following criteria have been met:
  • When requesting coverage of a brand medication for which an A/B rated generic is available, there is sufficient evidence that the use of the A/B rated generic equivalent has resulted in inadequate results AND
  • At least one of the following is met:
    o The plan-preferred medications are contraindicated or will likely cause an adverse reaction by or physical or mental harm to the member.
    o The plan-preferred medications are expected to be ineffective based on the known clinical history and conditions of the member and the member’s prescription drug regimen.
    o The member has tried the plan-preferred medications or another prescription drug in the same pharmacologic class or with the same mechanism of action and such prescription drug was discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event.
    o The member is stable on the medication selected by their healthcare professional for the medical condition under consideration (where “stable” is defined as receiving the medication for an adequate period of time, have achieved optimal response, and continued favorable outcomes are expected UNLESS the medication was initially selected due to the availability of a drug sample or a coupon card).
    o The plan-preferred medication is not in the best interest of the member because it will likely cause a significant barrier to the member’s adherence or to compliance with the member’s plan of care, will likely worsen a comorbid condition of the member, or will likely decrease the member’s ability to achieve or maintain reasonable functional ability in performing daily activities.
      o For short-term prophylaxis against angioedema attacks:
        ▪ Before surgeries, where endotracheal intubation is required, where upper airway or pharynx is manipulated, or before bronchoscopy or endoscopy AND
        ▪ When the member is at least 12 years of age
  • Coverage of the following is provided for acute treatment of HAE attacks:
    o Cinryze or Kalbitor when the member is at least 12 years of age
    o Ruconest when the member is at least 13 years of age
    o Firazyr when the member is at least 18 years of age
    o Berinert when the member is at least 6 years of age

IV. Quantity Limitations

• Cinryze
  o Medical benefit: 1000 billable units/30 days
  o Pharmacy benefit: 20 vials/30 days
• Berinert
  o Medical benefit: 800 billable units/30 days
  o Pharmacy benefit: 16 vials/30 days
• Kalbitor – Medical benefit: 240 billable units/30 days
• Firazyr – Pharmacy benefit: 4 syringes/30 days
• Ruconest
  o Medical benefit: 1680 billable units/30 days
  o Pharmacy benefit: 8 vials/30 days
• Additional quantities of each medication may be available through coverage review of supporting documentation (i.e., body weight, frequency of attacks, etc.).

V. Coverage Duration

• Coverage is provided for 6 months and may be renewed.
• Coverage of short-term prophylaxis is limited to 1 month.

VI. Coverage Renewal Criteria

Coverage can be renewed based upon the following criteria:
• Prophylaxis of hereditary angioedema attacks:
  o Documentation must be provided of a decrease in frequency of HAE attacks versus baseline and/or significant improvement in the severity or duration of attacks AND
  o Absence of significant adverse reaction or toxicity to medication is shown
• Acute treatment of hereditary angioedema attacks:
  o Subsequent requests will be authorized based on documentation that member has responded to prior treatments AND
  o Absence of significant adverse reaction or toxicity to medication is shown

VII. Billing/Coding Information

• Cinryze:
  o Medical when administered by a healthcare professional
  o Pharmacy when self-administered
  o Medical – J0598 (1 billable unit = 10 units of drug)
  o Pharmacy - 500 units of drug per each single-use vial
• Berinert:
  o Medical when administered by a healthcare professional
  o Pharmacy when self-administered
  o Medical- J0597 (1 billable unit = 10 units of drug)
  o Pharmacy- 500 units of drug per each single-use vial
• Kalbitor:
  o Medical benefit only
  o J1290 (1 billable unit = 1mg of drug; 10mg/ml single use vials containing 10mg each, 3 vials per carton)
Drug Therapy Guidelines

Hereditary Angioedema (HAE) Agents

Last Review Date: 5/2017

- **Firazyr:**
  - Pharmacy benefit only
  - 3ml prefilled syringe (10mg/ml)

- **Ruconest:**
  - Medical when administered by a healthcare professional
  - Pharmacy when self-administered
  - Medical—J0596 (1 billable unit = 10 units of drug)
  - Pharmacy—2100 IU of drug per each single use vial

- **Related diagnosis:**
  - Other deficiencies of circulating enzymes: D84.1

### VIII. Summary of Policy Changes

- **9/1/11:**
  - Removed requirement of trial of C-1 esterase inhibitor prior to Kalbitor
  - Renewal criteria defined

- **6/15/12:** Firazyr added to policy

- **6/2012:** Cinryze and Berinert made available under the pharmacy benefit

- **3/15/13:** no changes

- **3/15/14:**
  - Allowed Berinert for prophylaxis if requested
  - Simplified acute attack coverage criteria
  - Expanded short-term prophylaxis coverage situations

- **10/22/14:** Ruconest added to policy

- **3/15/15:** change in age requirement for coverage of Kalbitor

- **7/1/15:** formulary distinctions made

- **9/15/15:** change in age requirement for Cinryze and Berinert (from 13 years to 12 years)

- **1/1/16:** drug code updated for Ruconest

- **7/19/16:** no policy changes

- **5/1/17:** step therapy criteria added

- **6/21/17:** updated age limitations and Berinert use

### IX. References

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6. UpToDate, retrieved May 2015

The Plan fully expects that only appropriate and medically necessary services will be rendered. The Plan reserves the right to conduct pre-payment and post-payment reviews to assess the medical appropriateness of the above-referenced therapies.

The preceding policy applies only to members for whom the above named pharmacy benefit medications are included on their covered formulary. Members with closed formulary benefits are subject to trying all appropriate formulary alternatives before a coverage exception for a non-formulary medication will be considered.

The preceding policy is a guideline to allow for coverage of the pertinent medication/product, and is not meant to serve as a clinical practice guideline.