Hereditary Angioedema (HAE) Agents

**Covered Medications**

- C1 Inhibitor [Human] (Cinryze®)

### What they do and how they are used

- Cinryze® is a C1 esterase inhibitors.
- Cinryze® is indicated for routine prophylaxis against angioedema attacks in adolescents and adults with hereditary angioedema (HAE). Cinryze® has also been studied as treatment in acute attacks of HAE.
- 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.
- Other types of angioedema exist, including allergic and drug-induced angioedema. Cinryze® is not indicated for use in any type of angioedema other than HAE.
- 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.
- Patients with HAE have recurrent episodes of angioedema, characterized by swelling of the face, abdomen, extremities or airway. Abdominal attacks cause severe pain, cramping, nausea, vomiting, and diarrhea. Laryngeal edema can result in fatal asphyxiation, and has been estimated to be the cause of death for up to 30% of patients with this disease. Severity of attacks is often variable and unpredictable.
- Attacks of angioedema are self-limiting, and most subside in 2 to 5 days. The frequency of attacks is variable, ranging from rare attacks to one every three days. Minor trauma or stress may precipitate exacerbations but often there is no known trigger.
- The estimated frequency of HAE is about 1 in 50,000 people.
- Symptoms of HAE generally present in childhood, as young as 2-3 years old, worsen at puberty, and persist throughout life.
- The most common drug for prophylaxis of HAE is danazol, an androgen with excellent efficacy but many side effects including masculinization of females, weight gain, amenorrhea, myalgia, headaches, and depression. In a retrospective evaluation of danazol use in 118 patients, 30 (25.4%) discontinued due to adverse events.
- Attacks of angioedema are self-limiting, and most subside in 2 to 5 days. The frequency of attacks is variable, ranging from rare attacks to one every three days. Minor trauma or stress may precipitate exacerbations but often there is no known trigger.
- The estimated frequency of HAE is about 1 in 50,000 people.
- Symptoms of HAE generally present in childhood, as young as 2-3 years old, worsen at puberty, and persist throughout life.
- The most common drug for prophylaxis of HAE is danazol, an androgen with excellent efficacy but many side effects including masculinization of females, weight gain, amenorrhea, myalgia, headaches, and depression. In a retrospective evaluation of danazol use in 118 patients, 30 (25.4%) discontinued due to adverse events.
- The most common adverse event was weight gain.
- In most countries, C1 inhibitor protein replacement is the mainstay of therapy, and has been shown to be effective and safe. In the United States, fresh frozen plasma (FFP) is sometimes used because it contains C1 inhibitor protein, but use is controversial because FFP also contains enzymes that can increase bradykinin, thereby worsening angioedema. Drugs commonly used for other types of bodily swelling (epinephrine, corticosteroids, antihistamines, etc.) have shown little or no benefit. Currently, treatment is mostly symptomatic control.
- Cinryze® is a human C1 inhibitor protein, which decreases incidence, severity, and duration of angioedema attacks in patients with HAE when used regularly as prophylaxis.
- Cinryze® is given as a 1,000 unit intravenous infusion every 3 or 4 days for prophylaxis.

### Rationale for coverage authorization

To reduce costs associated with the use of Cinryze® or Berinert® for conditions other than hereditary angioedema and to provide coverage for an amount sufficient to treat the majority of patients requiring both acute and/or routine prophylaxis.

### Benefit design

Coverage for Cinryze® and Berinert® is determined through prior authorization for every claim.

### Coverage authorization criteria

Coverage is provided for Cinryze® in the following situations:

- Coverage is provided in patient’s 13 years of age or older for the routine prophylaxis against angioedema attacks in patients with Hereditary Angioedema (HAE)

AND

- In situations where the patient’s diagnosis of Hereditary Angioedema (HAE) has been established by an allergist, immunologist, or hematologist.

AND

- In situations where the patient has a history of one or more severe attack(s) per month (defined as an attack that significantly interrupts daily activities despite short-term treatment) OR disabling symptoms for at least 5 days per month OR laryngeal edema.
AND

- In situations where the patient has at least ONE of the following: a history of recurrent, self-limiting, non-inflammatory, subcutaneous angioedema, without urticaria that lasts >12 hours OR a history of recurrent, self-limiting, abdominal pain without clear organic cause that lasts > 6 hours.

AND

- In situations where the patient’s C1 inhibitor level/activity is shown to be less than 50% of the lower level of normal on two separate lab determinations at least one month apart.

AND

- In situations where all other causes of acquired angioedema (for example, medications, autoimmune diseases) have been excluded.

AND

- In situations where the patient had an inadequate response, experienced intolerance to, or is unable to receive treatment with attenuated androgens (for example, danazol).

Coverage duration:

- Routine prophylaxis against angioedema attacks: 24 months

References