

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
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Medication Policy Manual

Policy No: dru172

Topic: Cinryze™, C1 Inhibitor (human)

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Next Review Date: March, 2010

IMPORTANT REMINDER

This Medical 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 medical policy is to provide a guide to coverage. Medical 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

Cinryze™ is a C1 inhibitor that may be helpful in preventing swelling in people diagnosed with hereditary angioedema (HAE). It is made from pooled blood proteins from donors in the United States.

Policy/Criteria

- I.** Most contracts require prior authorization approval of C1 inhibitor prior to coverage. C1 inhibitor may be considered medically necessary for the prevention of hereditary angioedema (HAE) attacks when all criteria A through D below are met.

A. The diagnosis of hereditary angioedema has been established.

1. The diagnosis of HAE has been established by, or in consultation with, an allergist, immunologist or a hematologist.

AND

2. The diagnosis of HAE is confirmed by genetic testing or normal C1q laboratory levels with levels below the limits of the laboratory's normal reference range for both C4 and C1INH (antigenic or functional level).

AND

B. The patient has been evaluated for potentially treatable triggers of HAE attacks and is maximally managed with respect to avoiding triggers.

AND

C. A 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.

AND

D. Previous preventive treatment with the medications indicated has been ineffective, contraindicated or not tolerated due to serious adverse effects for either of the following indications:

1. Long-term preventive treatment with attenuated androgens, such as danazol and stanozolol, for frequent and severe HAE attacks

OR

2. Short-term preventive treatment with attenuated androgens, such as danazol and stanozolol, for severe HAE attacks in triggering situations including but not limited to substantial dental work, invasive medical procedures, and surgical procedures. See Appendix 1 for common oral medication dosing information.

II. Administration, Quantity Limitations, and Authorization Period

- A. Regence does not consider C1 inhibitor to be a self-administered medication.
- B. When prior authorization is approved, C1 inhibitor may be authorized in quantities as follows:
 1. **Long-term prevention:** 8,000 units (16 of the 500-unit vials) per month.

OR

2. **Short-term prevention:** 1,000 units (2 of the 500-unit vials) per procedure.
- C. Authorization shall be reviewed at least **every month** to confirm that current medical necessity criteria are met and that the medication is effective as defined by at least a 50% decrease in frequency of HAE attack, significant improvement in severity and duration of attacks, and clinical documentation of functional improvement.

III. C1 inhibitor is considered not medically necessary when used in doses exceeding 2,000 units per week.

IV. C1 inhibitor is considered investigational when used for all other conditions, including, but not limited to:

- A. Angioedema due to causes other than HAE, include but not limited to drug-induced angioedema, acquired angioedema, allergic angioedema and idiopathic angioedema.
- B. Myocardial infarction.
- C. Sepsis.
- D. Acute treatment of HAE attacks.

Position Statement ^[1-9]

- Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic blood disease in which people have inadequate or non-functional C1 inhibitor proteins in their blood. C1 inhibitor protein is a normal component of the blood that helps regulate the inflammatory and clotting system.
- HAE is diagnosed thru clinical history, diagnostic test and exclusion of other causes of angioedema. The specific tests required to make the diagnosis include C4, C1q, and C1INH (antigenic or functional level). Genetic testing is not necessary to confirm the diagnosis of HAE.
- The symptoms of HAE attacks vary, from swelling in the extremities or gastrointestinal tract to cases involving the face and throat which is less frequent but could be life threatening.
 - * Attacks are commonly triggered by stress, hormonal changes, dental surgery, and trauma. In some cases, attacks can occur without an apparent trigger.
 - * Angiotensin-converting enzyme (ACE) inhibitors and estrogen containing medications may trigger life-threatening attacks in patients with HAE.
- Patients with frequent attacks or attacks involving swelling of the face, throat or incapacitating gastrointestinal attacks may benefit on long-term preventive medications.
- HAE patients, who are not on long-term preventive therapy, undergoing surgical or dental procedures may benefit from short-term preventive medications.
- Attenuated androgens have a long-standing track record as an established treatment to prevent HAE attacks. Regular monitoring for safety and dosage adjustments are recommended in patients receiving attenuated androgens.
- There is unreliable evidence that C1 inhibitor is effective in treating acute HAE attacks.

Other medications used to treat HAE

- The standard of treatment for prevention of HAE is attenuated androgens. Androgens increase the production of C1 inhibitor protein in the liver. Danazol and stanozolol are well recognized for the prevention of HAE attacks. Stanozolol is no longer available commercially at this time, but can be compounded by local pharmacies.

- Low-dose danazol for both long-term and short-term prevention has been shown to be safe and effective in pediatric patients. ^[10]
- Oxandrolone is FDA approved for weight gain in pediatric patients and may be considered as an alternative androgen for the prevention of HAE attacks in children based on case reports. ^[10, 11]
- Attenuated androgen is contraindicated in pregnant woman. Dosage above 200 mg/day should be avoided in prepubescent adolescent due to side effects on growth and development.
- Aminocaproic acid and tranexamic acid has been reported for use in prevention of HAE attacks based on low quality evidence. Rare but serious side effects have been associated with the use of these antifibrinolytic agents.
- C1 inhibitor is the only FDA approved medication to date for replacing C1 inhibitor protein in the blood.

Clinical Efficacy^[12]

- There is unreliable evidence that C1 inhibitor reduces the frequency, duration and severity of HAE attacks.
- There is one clinical U.S. trial to date that examines C1 inhibitor in HAE attack prevention. The study is a prospective, randomized, double-blinded, 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 inhibitor).
 - * Patients received twice weekly injections of either placebo or 1,000 units of C1 inhibitor.
 - * 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-day prior to the study.
 - * The study showed that C1 inhibitor significantly reduces the number of HAE attacks by 52% (primary endpoint), severity by 32% and duration of swelling by 66% (secondary endpoints). All values are statistically significant.

- * Only half of the study patients responded 50% or greater in reduction of frequency of HAE attacks.
- * The study evidence was rated unreliable due to several fatal flaws including:
 - More than 5% of patients dropped out from the study and was not included in the final analysis of HAE attack frequency.
 - C1 inhibitor was allowed during the entire duration of the study to treat acute HAE attacks. This can lead to uncertainty regarding the effectiveness of C1 inhibitor.
- There are no studies to date evaluating the efficacy of C1 inhibitor compared to other standard treatments.
- There is no evidence that C1 inhibitor is more effective than danazol or stanozolol in prevention of HAE attacks as there has not been a head-to-head comparison study done.

Safety^[12-14]

- The prescribing information includes warnings that:
 - * Thrombotic events have been reported in association with C1 inhibitor products when used off-label at high, repeated, doses.
 - * C1 inhibitor is made from human plasma and therapy may potentially transmit infectious agents.
- C1 Inhibitor replacement therapy has been used in Europe for over 30 years without evidence of drug interactions or immunogenicity. No cases of pathogen transmission have been reported.
- The main differences between European and US C1 inhibitor include the requirement that US C1 inhibitor be manufactured with only US donors. There is also an added step in the manufacturing process, called nanofiltration, to increase safety of the product. The US C1 inhibitor, manufactured in Holland, does not contain added hepatitis B immunoglobulin.

Appendix 1: Oral Drugs Commonly Used as Prophylaxis for Hereditary Angioedema^[1,2,4]

Long-Term Prophylaxis			
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
Short-Term Prophylaxis			
Drug	Dosage		
Danazol	2.5 to 10 mg/kg/day, with a maximum of 600 mg/day	5 days before and 2 days after the procedure.	
Stanozolol	2-6 mg/day		

References

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Cross References
Compounded Medications dru135

Codes	Description
C9251	Injection, C1 esterase inhibitor (human)