

C1 esterase inhibitor [recombinant] (Ruconest[®])

Policy # 00427

Original Effective Date: 11/21/2014

Current Effective Date: 12/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the C1 esterase inhibitor (C1INH) [recombinant] product, Ruconest[®], to be **eligible for coverage**.** when the patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for the C1 esterase inhibitor (C1INH) [recombinant] product, Ruconest, will be considered when the following criteria are met:

- Patient has a diagnosis of hereditary angioedema (HAE) as confirmed by appropriate lab test(s); AND
- Ruconest is being used for the treatment of acute attacks of hereditary angioedema (HAE); AND
- Ruconest is NOT being used to treat laryngeal attacks of hereditary angioedema (HAE); AND
- Patient is 13 years of age or older.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of the C1 esterase inhibitor (C1INH) [recombinant] product, Ruconest, when patient selection criteria are not met to be **investigational**.*

Background/Overview

Ruconest is a recombinant version of C1INH. It is purified from the milk of transgenic rabbits. C1INH is a normal constituent of human blood, and it regulates the activation of the complement and contact system pathways. C1INH exerts its inhibitory effect by irreversibly binding several proteases (target proteases) of the contact and complement systems. The effect of Ruconest on the

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following target proteases was assessed in vitro: activated C1s, kallikrein, factor XIIa and factor XIa. Inhibition kinetics were found to be comparable with those observed for plasma-derived human C1INH. HAE patients have low levels of endogenous or functional C1INH. Although the events that induce attacks of angioedema in HAE patients are not well defined, it is thought that contact system activation, and resulting increased vascular permeability lead to the clinical manifestation of HAE attacks. Suppression of contact system activation by C1INH through the inactivation of plasma kallikrein and factor XIIa is thought to modulate vascular permeability by preventing the generation of bradykinin. The recommended dose of Ruconest is 50 IU (international units) per kg, with a max dose of 4,200 IU (for patients weighing ≥ 84 kg). If symptoms persist, a second dose can be given at the recommended dose level. No more than 2 doses should be given within a 24 hour period.

Hereditary Angioedema (HAE)

HAE is a rare, autosomal dominant disease caused by a deficiency or dysfunction of the C1 inhibitor, which is involved in regulating how certain immune system and blood clotting pathways function. The disease is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema typically involving the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue or larynx. Its prevalence is not known but it is estimated to occur in approximately 1 case in 50,000 patients. Typically symptoms commence in childhood (often as early as 2 or 3 years of age) and worsen in adolescence and persist throughout life. There is a wide variation in the frequency and severity of attacks. Untreated patients typically experience attacks once weekly to twice weekly. However, some patients can have attacks approximately every 3 days and others may virtually never experience additional attacks. Clinical experience suggests that minor trauma and/or stress may precipitate attacks. Attacks usually are predictable, although different on an individual basis. A prodrome, such as a tingling sensation, may occur prior to an attack and approximately one-third of patients experience a nonpruritic, serpentine erythematous rash. The swelling typically slowly worsens over the first 24 hours to 36 hours and then gradually subsides over the next 48 hours to 72 hours. The most common sites of swelling are the arms, legs, hands, feet, and abdomen. Attacks that impact the skin may cause patients to experience a sensation of uncomfortable stretching, tightness, or numbness. Oropharyngeal swelling is less frequent but can be life-threatening when it occurs. Abdominal attacks may also happen, which can lead to severe abdominal pain, nausea and vomiting.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Ruconest was approved in 2014 for the treatment of acute attacks of HAE in patients 13 years of age or older. The efficacy of Ruconest was not established in HAE patients with laryngeal attacks.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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The safety and efficacy of Ruconest was established in three, phase 3 randomized, double-blind, placebo-controlled, multicenter studies in patients with HAE. Study 1 included 75 subjects and the primary outcome studied was the time to onset of sustained relief at the primary attack location based on the Treatment Effect Questionnaire (TEQ). The time to onset for subjects taking Ruconest was significantly shorter (90 minutes vs. 152 minutes, $p=0.031$) than those receiving placebo. In Study 2, which included 70 subjects, the median times to the beginning of relief of symptoms (as measured by a decrease in the visual analog scale (VAS) score of ≥ 20 mm for two consecutive readings) were 66 minutes ($p<0.001$), 122 minutes ($p=0.013$), and 495 minutes respectively, for Ruconest 100U/kg, 50U/kg, and placebo. The results from Study 2 were pooled results from two different studies. In an open label extension, the efficacy of Ruconest was maintained over multiple HAE attacks with sustained relief of symptoms achieved in $\geq 87\%$ of treated patients in 4 hours.

References

1. Ruconest. [package insert]. Salix Pharmaceuticals. Raleigh, NC. July 2014.
2. Ruconest. ExpressScripts Drug Evaluation. Updated August 2014.

Policy History

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11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. New policy.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. No change to coverage.
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. No change to coverage.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. No change to coverage.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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11/07/2024 Medical Policy Committee review

11/13/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

11/06/2025 Medical Policy Committee review

11/12/2025 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 11/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.