C1 Esterase Inhibitor (recombinant) (Ruconest®)

NDC CODE(S) 68012-0350-XX RUCONEST 2100UNIT Solution Reconstituted (PHARMING HEALTHCARE INC.)
71274-0350-XX RUCONEST 2100UNIT Solution Reconstituted (PHARMING HEALTHCARE INC.)

DESCRIPTION

C1 esterase inhibitor (C1-INH) is a normal constituent of human blood and is a serine proteinase inhibitor or serpin. C1-INH's primary function is to regulate the activation of the complement and intrinsic coagulation pathway. It also has a role in regulation of the fibrinolytic system.

Individuals with an inherited deficiency of C1-INH suffer from sudden, recurrent edematous swellings of the subcutaneous or submucosal tissues. This condition is known as hereditary angioedema (HAE).

Commercially, C1-INH is available in two forms, those derived from purified human plasma which has undergone multiple viral reduction steps and a recombinant analogue purified from the milk of transgenic rabbits. Ruconest® is a recombinant product formulated for treatment of attacks.

POLICY

- C1 Esterase Inhibitor - Ruconest® for the treatment of acute abdominal, peripheral or facial attacks of Hereditary Angioedema (HAE) is considered ***medically necessary*** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**
- C1 Esterase Inhibitor - Ruconest® for the treatment of other conditions/diseases is considered investigational.

MEDICAL APPROPRIATENESS

INITIAL APPROVAL

- C1 Esterase Inhibitor - Ruconest® is considered **medically appropriate** if **ALL** of the following criteria are met:
  - Individual is 13 years of age or older
  - Confirmation the individual is avoiding the following possible triggers for HAE attacks:
    - Estrogen-containing oral contraceptive agents AND hormone replacement therapy
    - Antihypertensive agents containing ACE inhibitors
    - Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin)
    - Neprilysin inhibitors (e.g., sacubitril)
  - Individual has a history of **ANY ONE** of the following:
    - Moderate to severe cutaneous attacks (without concomitant hives)
    - Abdominal attacks
    - Mild to severe airway swelling attacks of HAE (i.e. debilitating cutaneous/gastrointestinal symptoms OR laryngeal/pharyngeal/tongue swelling)
  - Individual has one of the following clinical presentations consistent with a HAE subtype, which must be confirmed by repeat blood testing (treatment for acute attack should not be delayed for confirmatory testing):
    - **HAE I (C1-Inhibitor deficiency)** if **ALL** of the following:
      - Low C1 inhibitor (C1-INH) antigenic level (C1-INH antigenic level below the lower limit of normal as defined by the performing lab)

- Low C4 level (C4 below the lower limit of normal as defined by the performing lab)
- Low C1-INH functional level (C1-INH functional level below the lower limit of normal as defined by the performing lab) and **ANY ONE** of the following:
  - Individual has a positive family history of HAE
  - Acquired angioedema has been ruled out (i.e., onset of symptoms occur prior to 30 years old, normal C1q levels, individual does not have underlying disease such as lymphoma or benign monoclonal gammopathy [MGUS], etc.)

▪ **HAE II (C1-Inhibitor dysfunction)** if **ALL** of the following:
- Normal to elevated C1-INH antigenic level
- Low C4 (C4 below the lower limit of normal as defined by the performing lab)
- Low C1-INH functional level (C1-INH below the lower limit of normal as defined by the performing lab)

▪ **HAE with normal C1INH (formerly known as HAE III)** if **ALL** of the following:
- Normal C1-INH antigenic level
- Normal C4 level
- Normal C1-INH functional level
- Repeat blood testing during an attack has confirmed the individual does not have abnormal lab values indicative of HAE I or HAE II
- Individual has **ANY ONE** of the following:
  - Individual has a known HAE-causing mutation (e.g., mutation of coagulation factor XII gene [F12 mutation], mutation in the angiopoietin-1 gene, mutation in the plasminogen gene, etc.)
  - Individual has a family history of HAE and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (e.g. cetirizine standard dosing at up to four times daily or an alternative equivalent, given for at least one month or an interval long enough to expect three or more angioedema attacks) AND corticosteroids with or without omalizumab

RENEWAL CRITERIA

- C1 Esterase Inhibitor Ruconest ® is considered **medically appropriate** for renewal if **ALL** of the following criteria are met:
  - Individual continues to meet initial approval criteria
  - Significant improvement in severity and duration of attacks have been achieved and sustained
  - Absence of unacceptable toxicity from the drug, Examples of unacceptable toxicity include the following: hypersensitivity reactions, serious thromboembolic events (arterial or venous), etc.
  - The cumulative amount of medication(s) the patient has on-hand, indicated for the acute treatment of HAE, will be taken into account when authorizing. The authorization will provide a sufficient quantity in order for the patient to have a cumulative amount of HAE medication(s) on-hand in order to treat up to 4 acute attacks per 4 weeks for the duration of the authorization (unless otherwise specified).

INDICATION(S)	DOSAGE & ADMINISTRATION
Acute Hereditary Angioedema (HAE) attack	Body weight < 84 kg: 50 International Units (IU) per kg body weight by intravenous injection Body weight ≥ 84 kg: 4200 IU (2 vials) by intravenous injection *If the attack symptoms persist, an additional (second) dose can be administered at the recommended dose level. Do not exceed 4200 IU per dose. No more than two doses should be administered within a 24 hour period.*

LENGTH OF AUTHORIZATION

Coverage will be provided for 12 weeks and is eligible for renewal (unless otherwise specified).

The cumulative amount of medication(s) the patient has on-hand, indicated for the acute treatment of HAE, will be taken into account when authorizing. The authorization will provide a sufficient quantity in order for the patient to have a cumulative amount of HAE medication(s) on-hand in order to treat up to 4 acute attacks per 4 weeks for the duration of the authorization (unless otherwise specified).

Refer to **DOSAGE LIMITS** below

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

Betschel, S., Badiou, J., Binkley, K., Borici-Mazi, R., Hébert, J., Kanani, A., et al. (2019). The International/Canadian Hereditary Angioedema Guideline. *Allergy, Asthma & Clinical Immunology*. 2019. 15:72. Published online 2019 Nov 25. doi: 10.1186/s13223-019-0376-8.

Bowen, T., Cicardi, M., Farkas, H., Bork, K., Longhurst, H. J., Zuraw, B., et al. (2010). International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma & Clinical Immunology*, 6 (1), 24.

Lexi-Comp Online. (2020, March). AHFS DI. *C1 Esterase Inhibitor*. Retrieved November 19, 2020 from Lexi-Comp Online with AHFS.

Maurer, M., Magerl, M., Ansotegui, I., Ayg€oren-P€urs€un, E., Betschel, S., Bork, K., et al. (2018). The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. *Allergy,* 73 (8), 1575–1596.

MICROMEDEX Healthcare Series. Drugdex Evaluations. (2020, September). *C1 Esterase Inhibitor*. Retrieved November 9, 2020 from MICROMEDEX Healthcare Series.

U. S. Food and Drug Administration. (2014, July). Center for Biologics Evaluation and Research. *Ruconest® C1 Esterase Inhibitor (Recombinant) label.* Retrieved November 9, 2020 from http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM405634.pdf.

EFFECTIVE DATE 4/2/21

ID_MRx