Reference number(s)
2194-A

STANDARD MEDICARE PART B MANAGEMENT

RUCONEST (C1 esterase inhibitor [recombinant])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Ruconest is indicated for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE).

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. For initial authorization:
   1. C1 inhibitor functional and antigenic protein levels
   2. F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation testing, if applicable
   3. Chart notes confirming family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy, if applicable
B. For continuation of therapy, chart notes demonstrating a reduction in severity and/or duration of attacks

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a prescriber who specializes in the management of HAE.

IV. CRITERIA FOR INITIAL APPROVAL

Hereditary angioedema (HAE)
Authorization of 6 months may be granted for treatment of acute HAE attacks when either of the following criteria are met at the time of diagnosis:

A. Member has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing and meets one of the following criteria:
1. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or
2. Normal C1-INH antigenic level and a low C1-INH functional level (functional C1-INH less than 50% or C1-INH functional level below the lower limit of normal as defined by the laboratory performing the test).

B. Member has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
1. Member has an F12, angiopoietin-1, plasminogen, kininogen-1 (KNG1), heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing, or
2. Member has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine therapy (i.e., cetirizine at 40 mg per day or the equivalent) for at least one month.

V. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted for continued treatment of acute HAE attacks when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication.
B. The member is receiving benefit from therapy. Benefit is defined as a reduction in severity and/or duration of acute attacks.

VI. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Ruconest.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema.
4. Hereditary Angioedema International Working Group. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group.
5. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema.
6. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel.
7. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update.
8. International consensus on hereditary and acquired angioedema.
9. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group.

10. Hereditary angioedema: beyond international consensus – The Canadian Society of Allergy and Clinical Immunology.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Ruconest are covered.

VII. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the above diagnostic criteria can be found in the US HAEA Medical Advisory Board Guidelines for the Management of Hereditary Angioedema. When HAE is suspected based on the clinical presentation, the provider should test serum C4, C1INH antigenic level, and C1INH functional level. Low C4 and low C1INH antigenic or functional levels are consistent with a diagnosis of HAE with an abnormal C1INH.
When a diagnosis of HAE with normal C1INH is suspected, additional genetic tests for factor XII, plasminogen, angiopoietin-1, and kininogen mutations should be performed. If the genetic testing is unable to be performed or a known mutation is not found, the US HAEA guidelines indicate a positive family history of recurrent angioedema and a documented lack of efficacy of high-dose antihistamine therapy for at least 1 month or an interval expected to be associated with three or more attacks of angioedema, whichever is longer, can be used as clinical criteria to support the diagnosis. The understanding of the genetic mutations associated with HAE is evolving. Veronez et al have identified additional genetic mutations not mentioned in the US HAEA guidelines. There are five new genes associated with HAE and a normal C1-INH: ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-O-sulfotransferase 6).

VIII. REFERENCES

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2. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010;6(1):24.
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4. Busse PJ, Christiansen, SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol: In Practice.* 2021 Jan;9(1):132-150.e3.
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6. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update. *Allergy*. 2022 Jan 10. doi: 10.1111/all. 15214. Online ahead of print.
7. Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol*. 2012;109:395-202.
8. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69:602-616.
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12. Veronez CL, Csuka D, Sheik FR, et al. The expanding spectrum of mutations in hereditary angioedema. *J Allergy Clin Immunol Pract.* 2021;S2213-2198(21)00312-3.