MEDICAL MUTUAL®

MedicalPolicy

Policy:	**201006**	**Initial Effective Date: 12/21/2010**
Code(s):	**HCPCS J0598, J0599**	**Annual Review Date: 03/15/2018**
SUBJECT:	**Cinryze® (C1 esterase inhibitor)** **Haegarda® (C1 esterase inhibitor)**	**Last Revised Date: 12/26/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Medical.

OVERVIEW:

Cinryze and Haegarda are human plasma-derived C1-INH indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE). The safety and efficacy of Cinryze or Haegarda for the treatment of acute attacks have not been established.

Hereditary angioedema is a rare, debilitating, potentially life-threatening genetic disorder caused by a deficiency in C1-INH, a plasma protein involved in the regulation of the complement and intrinsic coagulation pathways. Hereditary angioedema is caused by mutations in the C1-INH gene located on chromosome 11q and inherited as an autosomal dominant trait. Two main types of hereditary angioedema exist: mutations causing Type I hereditary angioedema are associated with decreased production of C1-INH leading to decreased functional levels; Type II hereditary angioedema mutations are associated with a dysfunctional C1 inhibitor but the inhibitor level is normal.

HAE is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema associated with pain syndrome, nausea, vomiting, diarrhea, and/or life-threatening airway swelling. Airway obstruction due to swelling is life-threatening if left untreated. There is a wide variation in the frequency and severity of attacks. Clinical experience suggests that minor trauma and/or stress, among other triggers, may precipitate attacks. Untreated attacks typically last over 48 to 96 hours. Short-term prophylaxis with a C1-INH - is recommended if more than minor manipulation (e.g., mild dental work) is needed, and prior to intubation or major procedures. The dose for short-term prophylaxis with C1-INH varies from 10 U/kg to 20 U/kg or 1,000 units, 1 to 6 hours before procedure. Long-term prophylaxis should be considered in all severely symptomatic patients, taking into consideration the severity of disease, frequency of attacks, patient's quality of life, availability of resources, and failure to achieve adequate control by on-demand therapy.

The Site of Care Medical Necessity Criteria applies to initial therapy and reauthorizations.

Medical Necessity: The Company considers Cinryze **and** Haegarda **medically necessary** and eligible for reimbursement providing that ***all*** of the following medical criteria are met:

1. **Hereditary Angioedema (HAE) Type 1 and 2 Prophylaxis, Initial Therapy.** Approve Cinryze or Haegarda if the patient meets the following criteria (a, b, c, d, e, f, g, h, and i):
   - **a)** The patient has HAE as confirmed by following criteria (i or ii)
     i) Patient has low levels of functional C1-INH protein (< 67% of normal) as defined by the laboratory reference values [documentation required]; OR
     ii) Patient has lower than normal serum C4 levels (< 14 mg/dL), as defined by the laboratory reference values AND lower than normal C1-INH level (< 19.9 mg/dL) [documentation required]; AND
   - **b)** The medication is prescribed by or in consultation with an allergist, immunologist, hematologist or a physician that specializes in the treatment of HAE or related disorders; AND
   - **c)** Failure of, intolerance to or unable to receive treatment with attenuated androgens (e.g, danazol, stanozolol); AND
   - **d)** All other causes of acquired angioedema (e.g., medications, auto-immune diseases) have been excluded; AND
   - **e)** Patient has at least ONE of the following criteria (i, ii, or iii)
     i.) 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
     ii.) Disabling symptoms for at least 5 days per month; OR
     iii.) Laryngeal edema; AND
   - **f)** Patient has at least ONE of the following criteria (i, ii, or iii); AND
     i.) Patient must have history of self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, which is recurrent and lasts >12 hours; OR
     ii.) Self-limiting, recurrent abdominal pain without a clear organic cause lasting >6 hours; OR
     iii.) A history of laryngeal edema; AND
   - **g)** Cinryze and Haegarda are not used in combination with other approved treatments for HAE (e.g. Firazyr, Berinert, Kalbitor, or Ruconest); AND
   - **h)** If the requested drug is Cinryze, the patient is 6 years of age or older; if the requested drug is Haegarda, the patient is an adolescent or adult; AND
   - **i)** Site of care medical necessity is met*.

2. **Patient has been started on Cinryze or Haegarda**. Approve for, an indication or condition addressed as an approval in the Recommended Authorization Criteria (FDA-Approved Indications), continuation of therapy if the patient meets the following criteria (a, b, c, d, e, f, g, h, i, and j)

   - **a)** The patient has HAE as confirmed by following criteria (i or ii):
     i) Patient has low levels of functional C1-INH protein (< 67% of normal) as definedby the laboratory reference values [documentation required]; OR

ii) Patient has lower than normal serum C4 levels (< 14 mg/dL or as defined by the laboratory reference values) AND lower than normal C1-INH level (< 19.9 mg/dL or as defined by the laboratory reference values) [documentation required]; AND**b)** The medication is prescribed by or in consultation with an allergist, immunologist, hematologist or a physician that specializes in the treatment of HAE or related disorders; AND

c) Failure of, intolerance to or unable to receive treatment with attenuated androgens (e.g, danazol, stanozolol); AND

d) All other causes of acquired angioedema (e.g., medications, auto-immune diseases) have been excluded; AND

e) Patient has at least ONE of the following criteria (i, ii, or iii)
i.) 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
ii.) Disabling symptoms for at least 5 days per month; OR
iii.) Laryngeal edema; AND

f) Patient has at least ONE of the following criteria (i, ii, or iii)
i.) Patient must have history of self-limiting, non-inflammatory subcutaneous angioedema, without urticaria, which is recurrent and lasts >12 hours; OR
ii.) Self-limiting, recurrent abdominal pain without a clear organic cause lasting >6 hours; OR
iii.) A history of laryngeal edema; AND

g) Cinryze and Haegarda are not used in combination with other approved treatments for HAE (e.g. Firazyr, Berinert, Kalbitor, or Ruconest); AND

h) Patient has at least 1 annual assessment by an HAE specialist; AND

i) If the requested drug is Cinryze, the patient is 6 years of age or older; if the requested drug is Haegarda, the patient is an adolescent or adult; AND

j) Site of care medical necessity is met*.

Approval Duration: 365 days (1 year)

Dosing in Hereditary Angioedema (HAE).

Cinryze: IV:
12 years of age and older: 1,000 units every 3 to 4 days; doses ≤2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
Children 6 to 11 years: IV: 500 units every 3 to 4 days; adjust dose based on individual patient response, up to 1,000 units every 3 to 4 days

Haegarda: SubQ: 60 units/kg every 3 or 4 days.

The Company considers Cinryze or Haegarda for acute treatment of hereditary angioedema attacks **investigational** and **not** eligible for reimbursement.

*MMO Site of Care Medical Necessity Criteria:

- Medications in this policy will be administered in a place of service that is a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met[†]:

    1. Age less than 18* years; or
    2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
    3. History of a severe adverse event from previous administration of the prescribed medication; or
    4. Requested medication is being administered as follows:
        - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
        - administered with dialysis; or
    5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
    6. Up to 1 dose of medication or re-initiation after at least 12 months; or
    7. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

* Effective 01/01/2019, age criterion applies to 18 years of older. Age at original effective date (03/01/2016) was 21 years or older.
[†]This criterion does not apply to Medicare or Medicare Advantage members.

Documentation Requirements:

The Company reserves the right to request additional documentation and to deny reimbursement when it has determined that the services performed were not medically necessary, investigational and/or a pattern of practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

Sources of Information:

- Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol. 2004;114(3 Suppl):S51-S131.
- American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma & Immunology and Joint Council of Allergy, Asthma & Immunology. Joint Taskforce on practice parameters. Diagnosis and management of urticaria: a practice parameter. Part 1: acute urticaria/angioedema. 2000. Available at URL: http://www.allergyparameters.org/file_depot/0-10000000/30000-40000/30326/folder/73825/2000AcuteUrticaria.pdf. Accessed December 09, 2010.
- American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma & Immunology and Joint Council of Allergy, Asthma & Immunology. Joint Taskforce on practice parameters. Diagnosis and management of urticaria: a practice parameter. Part II: chronic urticaria/angioedema. 2000. Available at URL: http://www.allergyparameters.org/file_depot/0-10000000/30000-40000/30326/folder/73825/2000ChronicUrticaria.pdf. Accessed December 09, 2010.
- Bowen T, Cicardi M (on behalf of PREHAEAT), Farkas H, et al. Canadian 2003 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. J Allergy Clin Immunol. 2004;114(3):629-637.
- Centers for Medicare & Medicaid Services: C1 esterase inhibitor (human) (Cinryze™). No national or local coverage determination found in the coverage database. December 09, 2010.
    - Cinryze® [prescribing information]. New York, NY: ViroPharma Biologics; February 23, 2017
- Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol. 2009;124(4):801-808.
- Craig T, Riedl M, Dykewicz MS, et al. When is prophylaxis for hereditary angioedema necessary? Ann Allergy Asthma Immunol. 2009;102(5):366-372.
- Dagen C, Craig TJ. Treatment of hereditary angioedema: items that need to be addressed in practice parameter. Allergy Asthma Clin Immunol. 2010;6(1):2-7.
- Farkas H, Jakab L, Temesszentandrási G, et al. Hereditary angioedema: a decade of human C1-inhibitor concentrate therapy. J Allergy Clin Immunol. 2007;120(4):941-947.
- Frank MM, Haixiang J. New therapies for hereditary angioedema: disease outlook changes dramatically. J Allergy Clin Immunol. 2008;121(1):272-280.
- Frank MM. Hereditary angioedema. J Allergy Clin Immunol. 2008;121(2):S398-S401.
- Frank MM. Hereditary angioedema: the clinical syndrome and its management in the United States. Immunol Allergy Clin N Am. 2006;26:653-668.
- Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005;139(3):379-394.
- Morgan BP. Hereditary angioedema – therapies old and new. NEJM. 2010; 363(6):581-583.
- US Hereditary Angioedema Association. Angioedema types. Revised October 02, 2009. Available at URL: http://www.haea.org/what-is-hae/angioedema-table/. Accessed December 09, 2010.
- US Hereditary Angioedema Association. HAE expert's approach to diagnosing HAE: clinical criteria and laboratory evaluation. Available at URL: http://www.haea.org/treating-hae/. Accessed December 09, 2010.

- Weiler CR, van Dellen RG. Genetic test indications and interpretations in patients with hereditary angioedema. Mayo Clin Proc. 2006;81(7):958-972.
- Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. NEJM. 2010;363(6):513-522.
- Zuraw BL. Current and future therapy for hereditary angioedema. Clinical Immunology. 2005;114(1):10-16.
- Zuraw BL. Hereditary angioedema. NEJM. 2008;359(10):1027-1036.
- Zuraw BL. Novel therapies for hereditary angioedema. Immunol Allergy Clin N Am. 2006;26:691-708.
- Bernstein JA, Riedl M, Zacek L, Shapiro RS. Facilitating home-based treatment of hereditary angioedema. Allergy Asthma Proc 36:92–99, 2015
- Riedl MA, Banerji A, Gower R. Current medical management of hereditary angioedema: follow-up survey of US physicians. J Allergy Clin Immunol Pract. 2015 Mar-Apr;3(2):220-7.
- Longhurst HJ, Farkas H, Craig T, et al. HAE international home therapy consensus document. Allergy, Asthma, and Clinical Immunology □:
- Petraroli A, Squeglia V, Di Paola N, Barbarino A, Bova M, Spanò R, Marone G, Triggiani M. Home Therapy with Plasma-Derived C1 Inhibitor: A Strategy to Improve Clinical Outcomes and Costs in Hereditary Angioedema. Int Arch Allergy Immunol. 2015;166(4):259-66.

HCPCS Code(s):	
J0598	Injection, C-1 esterase inhibitor (human), Cinryze, 10 units
J0599	Injection, c-1 esterase inhibitor (human), Haegarda, 10 units