Effective date: 7/1/2019
Reviewed Date: 6/2019, 9/2020, 2/2021, 2/2022, 3/2023, 12/2023, 01/2024, 07/2025 Pharmacy Scope: Medicaid Medical Scope: Medicaid, Commercial, Medicare

SPECIALTY GUIDELINE MANAGEMENT

HAEGARDA (C1 Esterase Inhibitor Subcutaneous [Human])

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
Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older.

All other indications are considered experimental/investigational and are not a covered benefit.

II. SUMMARY OF EVIDENCE

Haegarda is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1-INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older. HAE is a genetic disorder resulting from C1-INH deficiency, leading to excessive bradykinin-mediated swelling.
Approval of Haegarda is based on a randomized, double-blind, placebo-controlled, crossover trial in 90 patients aged 12 to 72 years with ≥4 attacks over a 2-month period. Patients were randomized to receive subcutaneous Haegarda at 40 IU/kg or 60 IU/kg twice weekly for 16 weeks, alternating with placebo. At the 60 IU/kg dose, Haegarda reduced the median number of attacks per month by 95% compared to baseline (0.5 vs. 4.0; $p<0.001$), and by 83% versus placebo. The 40 IU/kg dose yielded a 72.8% reduction from baseline and 58% reduction versus placebo. Attack severity and duration were also reduced, and fewer patients required rescue medication during treatment. The most common adverse reactions (≥4%) were injection site reactions, hypersensitivity (urticaria, pruritus), dizziness, and abdominal pain. No thromboembolic events, anaphylaxis, or viral transmissions were reported in clinical trials.

III. CRITERIA FOR APPROVAL

Authorization for 6 months may be granted for prevention of hereditary angioedema attacks when all of the following criteria is met:

A. Patient is ≥ 6 years of age.
B. Medication is prescribed by, or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
C. Patient has documented diagnosis of HAE type I or type II and meets one of the following (a or b):
    a. Documentation that the patient has C1 inhibitor deficiency or dysfunction as confirmed by laboratory testing; and meets one of the following criteria:
        i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by the laboratory performing the test, or

ii. 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); OR

b. Documentation that the patient has normal C1 inhibitor as confirmed by laboratory testing and meets one of the following criteria:
   i. Patient has an F12, angiopoietin-1, plasminogen, or kininogen-1 (KNG1) gene, heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6), or myoferlin (MYOF) gene mutation as confirmed by genetic testing mutation as confirmed by genetic testing, or
   ii. Patient has a documented family history of angioedema and the angioedema was refractory to a trial of high-dose antihistamine (e.g., cetirizine) for at least one month.

D. Other causes of angioedema have been ruled out (e.g., angiotensin-converting enzyme inhibitor [ACE-I] induced an angioedema, angioedema related to an estrogen containing drug, allergic angioedema).

E. The patient is receiving treatment for one of the following:
   a. Short-term HAE prophylaxis prior to a procedure (i.e., dental, or medical procedure)
   b. Long term HAE prophylaxis because treatment with "on demand" therapy (i.e., Ekterly, Kalbitor, Icatibant, Ruconest or Berinert) did not provide satisfactory control or access to on demand therapy is limited, AND the patient has a history of one of the following criteria for long term HAE prophylaxis:
      i. History of at least one severe HAE attack per month (i.e., airway swelling, debilitating cutaneous or gastrointestinal episodes)
      ii. Patient is disabled more than 5 days per month by HAE
      iii. History of at least one laryngeal attack caused by HAE

F. Patient will not use Haegarda concomitantly with Andembry, Cinryze, Orladeyo, or Takhzyro.

G. Dose does not exceed FDA approved labeling.

H. Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements

IV. CONTINUATION OF THERAPY

Authorization of 6 months may be granted for continuation of therapy when all of the following criteria are met:

A. Patient meets all criteria for initial approval; AND

B. Patient has documentation of a favorable clinical response (i.e., decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks) since initiating Haegarda prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy).

C. Patient has documentation of reduced the use of medications to treat acute attacks since starting treatment.

V. QUANTITY LIMIT

Haegarda 2000 units or 3000 units: 20 vials per 30 days (daily dose of 0.667)

Per §§ 42 CFR 422.101, this clinical medical policy only applies to Medicare in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD).

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Policy Rationale:
Haegarda was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Haegarda according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For Medicare members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.

VII. DOSING AND ADMINISTRATION

Indication	Dose	Maximum dose (1 billable unit = 10 IU)
Prophylaxis of Hereditary Angioedema (HAE) attacks	60 IU/kg body weight injected subcutaneously twice weekly (every 3 or 4 days)	5,600 billable units per 28 days

The following HCPCS/CPT code is:

HCPCS/CPT Code	Description
J0599	Injection, c-1 esterase

VIII. REFERENCES

1. Haegarda [package insert]. Kankakee, IL: CSL Behring LLC; February 2022. Accessed June 2025.
2. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy*. 2018;00:1-22.
3. Cicardi M, Bork K, Caballero T, et al. 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. *Allergy*. 2012;67:147-157.
4. 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.
5. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol: In Practice*. 2013; 1(5): 458-467.
6. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc*. 2012; 33(6):S145-S156.
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.
9. Bowen T. Hereditary angioedema: beyond international consensus – circa December 2010 – The Canadian Society of Allergy and Clinical Immunology Dr. David McCourtie Lecture. *Allergy Asthma Clin Immunol*. 2011;7(1):1.

10. Bernstein J. Update on angioedema: Evaluation, diagnosis, and treatment. *Allergy and Asthma Proceedings.* 2011;32(6):408-412.
11. Longhurst H, Cicardi M. Hereditary angio-edema. *Lancet.* 2012;379:474-481.
12. Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. *Allergy*. 2017;72(2):300-313.