Drug Coverage Policy

Effective Date……01/01/2026
Coverage Policy Number……IP0316
Policy Title…..C1 Esterase Inhibitors (Subcutaneous)

Hereditary Angioedema – C1 Esterase Inhibitors (Subcutaneous)

- Haegarda® (C1 esterase inhibitor [human] subcutaneous injection - CSL Behring)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Haegarda, a human plasma-derived C1 esterase inhibitor (C1-INH), is indicated for **routine prophylaxis to prevent hereditary angioedema (HAE) attacks** in adults and pediatric patients ≥ 6 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1-INH antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient. First-line medications for HAE I/II include intravenous C1-INH, Haegarda, or Takhzyro® (lanadelumab-flyo subcutaneous injection). The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[3] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the intravenous route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

An international consensus paper was published on the diagnosis, pathophysiology, and treatment of HAE-nl-C1INH.[4] The paper notes there is a paucity of high-level evidence in HAE-nC1INH and that all recommendations are based on expert opinion. Mutations in six different genes have been linked to HAE-nC1INH; however, the paper also specifies that many patients still lack an identified pathogenic variant for HAE-nC1INH.

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POLICY STATEMENT

Prior Authorization is required for benefit coverage of Haegarda. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Haegarda as well as the monitoring required for adverse events and long-term efficacy, approval requires Haegarda to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Haegarda for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Haegarda). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Haegarda, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records. All documentation must include patient-specific identifying information.

Haegarda is considered medically necessary when the following are met:

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis.** Approve Haegarda for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **B)** Patient is currently receiving Haegarda prophylaxis. Approve if the patient meets ALL of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Haegarda for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Haegarda prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
       Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

   Dosing. Approve up to a maximum dose of 60 IU/kg per injection, administered subcutaneously no more frequently than twice weekly with doses separated by at least 3 days.

Conditions Not Covered

Haegarda for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concomitant Use with Other Hereditary Angioedema (HAE) Prophylactic Therapies.** Haegarda has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use

other medications, including Cinryze (C1 esterase inhibitor [human] intravenous infusion), for treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.
Note: Examples of other HAE prophylactic therapies include Cinryze (C1 esterase inhibitor [human] intravenous infusion), Orladeyo (berotralstat capsules), and Takhzyro (lanadelumab-flyo subcutaneous injection).

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0599	Injection, C1 esterase inhibitor (human), (Haegarda), 10 units

References

1. Haegarda® subcutaneous injection [prescribing information]. Kankakee, IL: CSL Behring; January 2022.
2. 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 Pract*. 2021;9(1):132-150.e3.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** review date, disclaimer, refreshed background and references, and addition of change history. **Updated Coding** **Added:** J0599	01/15/2025
Annual Revision	**Policy Title.** **Updated** from "Hereditary Angioedema – C1 Esterase Inhibitors (SC)" **to** "Hereditary Angioedema – C1 Esterase Inhibitors (Subcutaneous)" **Updated** documentation requirements throughout the policy where required. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis.**	01/01/2026

	Added "Due to C1 Inhibitor (C1-INH) Deficiency" to indication name **Added** "Patient has HAE type I or type II as confirmed by the following diagnostic criteria and **added** "Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement." **Removed** "Confirmed pathogenic variant in the *SERPING1, F12, ANGPT1*, *PLG* or *KNG1* gene" **Removed** "Haegarda will not be concomitantly administered with other FDA-approved prophylactic treatments for HAE (for example, Cinryze, Takhzyro, or Orladeyo)". This was duplicative and already present in "Conditions Not Covered". **Added** "a physician who specializes in the treatment of HAE or related disorders" to specialist requirement. **Added** criteria for "Patient is currently receiving Haegarda prophylaxis" **Conditions Not Covered** **Removed** C1-Inhibitor normal (levels and function) episodes of angioedema not related to a documented pathogenic variant in the *F12, ANGPT1, PLG,* or *KNG1* gene.	

The policy effective date is in force until updated or retired.