

## Drug and Biologic Coverage Policy



Effective Date ..... 1/15/2025

Coverage Policy Number.....IP0316

# Hereditary Angioedema – C1 Esterase Inhibitors (SC)

## Table of Contents

Overview .....	1
Medical Necessity Criteria .....	2
Reauthorization Criteria .....	2
Authorization Duration .....	3
Conditions Not Covered .....	3
Coding Information .....	3
References.....	3
Revision Details.....	4

## Related Coverage Resources

### 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. 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

### 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  $\geq 6$  years of age.<sup>1</sup>

### 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.<sup>2</sup> 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.<sup>3</sup> 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.

## Medical Necessity Criteria

**Haegarda is considered medically necessary when the following are met:**

**Hereditary Angioedema (HAE) – Prophylaxis.** Individual meets **ALL** of the following criteria:

- A. Diagnosis of HAE confirmed by documentation of **ONE** of the following:
  - i. Confirmed pathogenic variant in the *SERPING1*, *F12*, *ANGPT1*, *PLG* or *KNG1* gene.
  - ii. One C4 level below the lower limit of normal as defined by the laboratory performing the test and **ONE** of the following:
    - a. Has low levels of functional C1-INH protein (less than 50% of normal) at baseline, as documented by laboratory reference values
    - b. Has low C1-INH antigenic levels (less than 50% of normal) at baseline, as documented by laboratory reference values
- B. Haegarda will not be concomitantly administered with other FDA-approved prophylactic treatments for HAE (for example, Cinryze, Takhzyro®, or Orladeyo®)
- C. Medication is prescribed by, or in consultation with, an allergist/immunologist

**Dosing.** 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.

---

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

## Reauthorization Criteria

Continuation of Haegarda is considered medically necessary for hereditary angioedema prophylaxis when **ALL** of the following are met:

1. The above medical necessity criteria have been met prior to the start of Haegarda therapy
2. There is documentation of beneficial response since initiating Haegarda prophylactic therapy compared with baseline (for example, decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks)
3. Medication continues to be prescribed by, or in consultation with, an allergist/immunologist

## Authorization Duration

Initial approval duration: up to 12 months

Reauthorization approval duration: up to 12 months

## Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

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).
2. **C1-Inhibitor normal (levels and function) episodes of angioedema not related to a documented pathogenic variant mutation in the *F12*, *ANGPT1*, *PLG*, or *KNG1* gene.**

## Coding Information

**Note:** 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:**

HCPSC 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	<p><b>Updated</b> review date, disclaimer, refreshed background and references, and addition of change history.</p> <p><b>Updated Coding Added:</b> J0599</p>	1/15/2025

---

“Cigna Companies” refers to operating subsidiaries of The Cigna Group. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Evernorth Behavioral Health, Inc., Cigna Health Management, Inc., and HMO or service company subsidiaries of The Cigna Group. © 2025 The Cigna Group.