Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) For Subcutaneous Injection

Policy Number: MC/PC 017
Effective Date: June 1, 2025

Instructions for Use

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Related Policies

- N/A

Coverage Rationale

This policy is applicable to Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) for subcutaneous injection, freeze-dried powder for reconstitution only.

Prophylaxis of Hereditary Angioedema (HAE)

For initial coverage of Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) for subcutaneous injection for prophylaxis of hereditary angioedema (HAE), the following will be required:

- Diagnosis of hereditary angioedema (HAE) **and**
- One of the following:
  - Diagnosis has been confirmed by both of the following:
    - C4 level below the lower limit of normal **and**
    - C1 inhibitor (C1-INH) deficiency or dysfunction (Type I or II HAE) as documented by ONE of the following:
      - C1-INH antigenic level below the lower limit of normal
      - C1-INH functional level below the lower limit of normal **or**
  - Diagnosis has been confirmed by both of the following:
    - Normal C4 level and
    - Normal C1-INH levels (HAE-n1-C1INH previously referred to as HAE Type 3) **and**
    - One of the following:
      - Confirmed presence of a FXII, plasminogen, angiopoietin-1 or kininogen-1, myoferlin or heparan sulfate-glucosamine 3-0-sulfotransferase 6 gene mutation.
      - Patient has recurrent angioedema attacks that are refractory to high-dose antihistamines (e.g., cetirizine) with a confirmed family history of recurrent angioedema **and**

- For prophylaxis against HAE attacks **and**
- Not used in combination with other approved treatments **nd**
- Patient is 6 years of age or older **and**
- Prescribed by or in consultation with one of the following:
    - Immunologist
    - Allergist

For reauthorization coverage of Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]) for subcutaneous injection for prophylaxis of hereditary angioedema (HAE), the following will be required:

- Patient demonstrates positive clinical response to therapy (e.g., reduction in the number or rate of HAE attacks while on therapy) **and**
- Not used in combination with other approved treatments for prophylaxis against HAE attacks.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0599	Injection, C1 esterase inhibitor (human), HAEGARDA, 10 units

ICD-10 Code	Description
D84.1	Defects in the complement system

Background

Hereditary angioedema (HAE) is a rare disease which affects 1 in 10,000 to 50,000 people worldwide and approximately 6,000 to 10,000 patients in the United States (U.S.). It is characterized by recurrent episodes of localized subcutaneous or submucosal edema lasting for 2 to 5 days that can be disabling and, in the case of laryngeal attacks, life-threatening (Busse et al 2021, Craig et al 2018, Zuraw 2025, Zuraw and Christiansen 2016). HAE is an autosomal dominant disease, and most patients with HAE have a positive family history of angioedema. However, approximately 25% of cases result from de novo mutations (Zuraw 2025). For the majority of patients, HAE first presents in childhood between 8 to 12 years of age, worsens around puberty, and persists throughout life with fluctuating severity of disease over time (Busse et al 2021, Farkas et al 2017, Zuraw and Christiansen 2016).

HAE is predominantly facilitated by an excessive production of bradykinin, a potent vasodilatory peptide which mediates swelling in HAE through vasodilation and vascular leakage and is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Component 1 esterase inhibitor (C1-INH) controls bradykinin production through inhibition of key steps in the coagulation system (Banerji et al 2017, Busse et al 2021, Lumry 2018, Zuraw 2025). HAE due to C1-INH deficiency (HAE-C1INH) accounts for the majority of HAE cases and includes 2 subtypes that are clinically indistinguishable: type I HAE (85% of HAE cases) with low C1-INH antigenic and functional levels, and type II HAE (15% of HAE cases) with normal C1-INH antigenic levels but decreased C1-INH functional levels (Busse et al

2021, Farkas et al 2017, Maurer et al 2018, Zuraw 2025, Zuraw et al 2013a). Th cks are highly variable and unpredictable but attacks typically follow a predictable y and continuously for 24 hours and then gradually subsides over the next 48 to 72 hours (Craig et al 2018, Zuraw 2025, Zuraw and Christiansen 2016).

Although the events that cause attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1-INH through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin. Administration of Haegarda replaces the missing or malfunctioning C1-INH protein in patients with HAE. The recommended dose for all patients is 60 IU per kg body weight by subcutaneous injection twice weekly (every 3 or 4 days) (Haegarda Prescribing Information 2022).

Clinical Evidence

The efficacy of Haegarda for prophylaxis of HAE attacks was evaluated in COMPACT, a 32-week Phase 3, double-blind, placebo-controlled, crossover randomized trial in 90 patients with HAE (Longhurst et al 2017). Treatment with Haegarda 60 IU/kg subcutaneous (SC) injection twice weekly reduced the rate of attacks by 84%, with a mean difference of -3.51 attacks per month vs placebo (95% CI, -4.21 to -2.81; $p < 0.001$). Treatment with Haegarda also significantly reduced the severity and duration of HAE attacks compared with placebo. Haegarda was also assessed in an open-label, parallel-arm extension of COMPACT, including patients ≥ 6 years of age who had either completed the trial or who were study treatment-naïve (Craig et al 2019). The incidence of adverse events was similar in both Haegarda dose groups (11.3 and 8.5 events per patient-year for 40 and 60 IU/kg, respectively). Median annualized attack rates were 1.3 and 1.0, respectively, and median rescue medication use was 0.2 and 0.0 times per year, for 40 and 60 IU/kg groups.

Clinical Guidelines

Short-term (or pre-procedural) prophylaxis is indicated when patients are at increased risk of having an HAE attack associated with known triggers such as invasive dental or medical procedures or stressful life events. C1-INH and anabolic androgens are appropriate therapy options for short-term prophylaxis (Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a). The 2020 HAEA guidelines specify the C1-INHs, Cinryze and Haegarda, and Takhzyro as preferred prophylactic therapy options in most circumstances (Busse et al 2021). Decisions regarding the use of long-term prophylactic treatment should be individualized, based on the patient's quality of life and treatment preferences in the context of attack frequency, attack severity, comorbid conditions, and access to emergent treatment (Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a). Long-term prophylaxis with androgen therapy (i.e. danazol) is not preferred, due to numerous safety concerns including androgenic, anabolic, and hepatic adverse events (Busse et al 2021, Farkas et al 2017, Maurer et al 2018).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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.

References

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Policy History/Revision Information

Date	Summary of Changes
02/15/2024	Approved by OptumRx P&T Committee
05/15/2025	Annual review. Updated references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).