
HAEGARDA® (C1 Esterase Inhibitor Subcutaneous (Human), C1-INH) is indicated for routine prevention of hereditary angioedema (HAE) attacks in adolescent and adult patients.[1]

HAEGARDA®
C1 Esterase Inhibitor
Subcutaneous (Human)

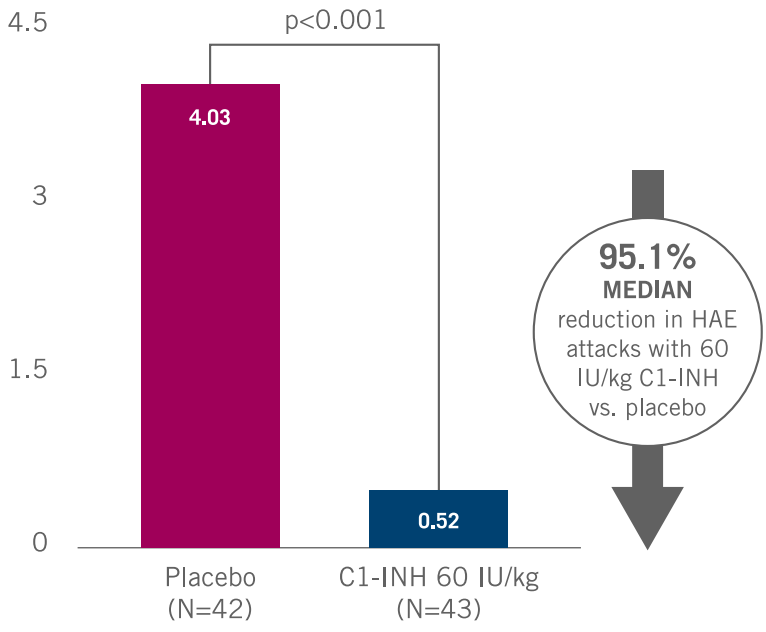
60 IU/KG HAEGARDA® DEMONSTRATED

# 95.1% REDUCTION

## in median HAE attacks vs. placebo[1,2*]

60 IU/kg HAEGARDA® twice weekly as routine preventive therapy was shown to reduce the median number of HAE attacks by 95.1% vs. placebo among subjects with evaluable data (25th, 75th percentile: 79.0-100, ITT population).[1*]

## NUMBER OF HAE ATTACKS PER MONTH (LS MEAN†)




LS = Least squares
† From a mixed model

* In a multicenter, randomized, double-blind, placebo-controlled, crossover study, patients 12-72 years of age with symptomatic HAE type I or II (N=90) were randomized to receive either 60 IU/kg or 40 IU/kg HAEGARDA® in one 16-week treatment period, and placebo in the other 16-week treatment period. Patients subcutaneously self-administered HAEGARDA® or placebo twice per week. Efficacy was evaluated for the last 14 weeks of each treatment period. Primary efficacy endpoint: Number of investigator-reported HAE attacks. Secondary efficacy endpoints: Percentage of patients who had a ≥50% reduction in number of HAE attacks vs. placebo, and the number of rescue medication uses.

**60 IU/KG HAEGARDA® DEMONSTRATED**

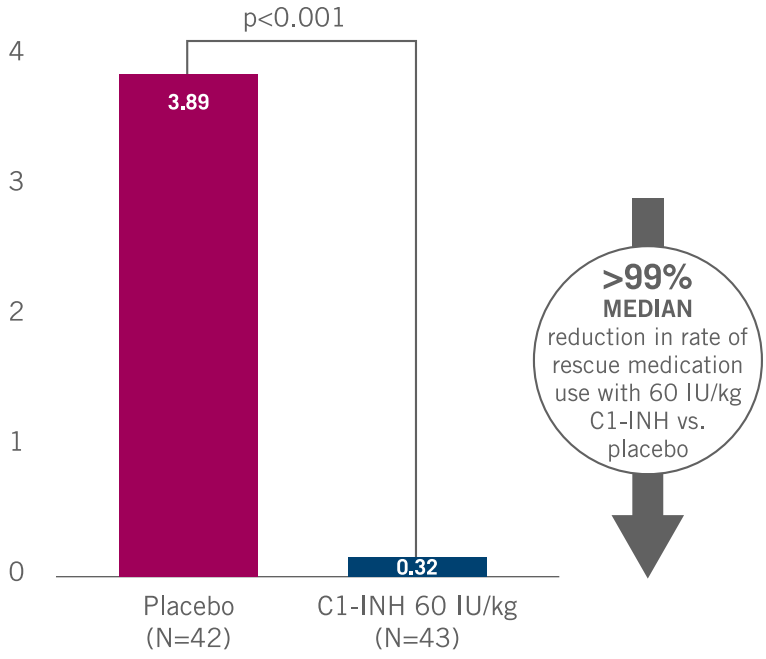
# >99%

# MEDIAN REDUCTION

## in use of rescue medication vs. placebo (0.32 vs. 3.89 mean uses per month)[1*]

The mean rate of rescue medication use was reduced from 3.89 uses/month on placebo to 0.32 uses/month on 60 IU/kg HAEGARDA® (p<0.001).[1,2*]

## RESCUE MEDICATION USES PER MONTH (LS MEAN†)




LS = Least squares
† From a mixed model

**ON 60 IU/KG HAEGARDA®**

## 90% of subjects demonstrated a ≥50% HAE attack rate reduction (95% CI: 77.0-96.0%)[1,2*]

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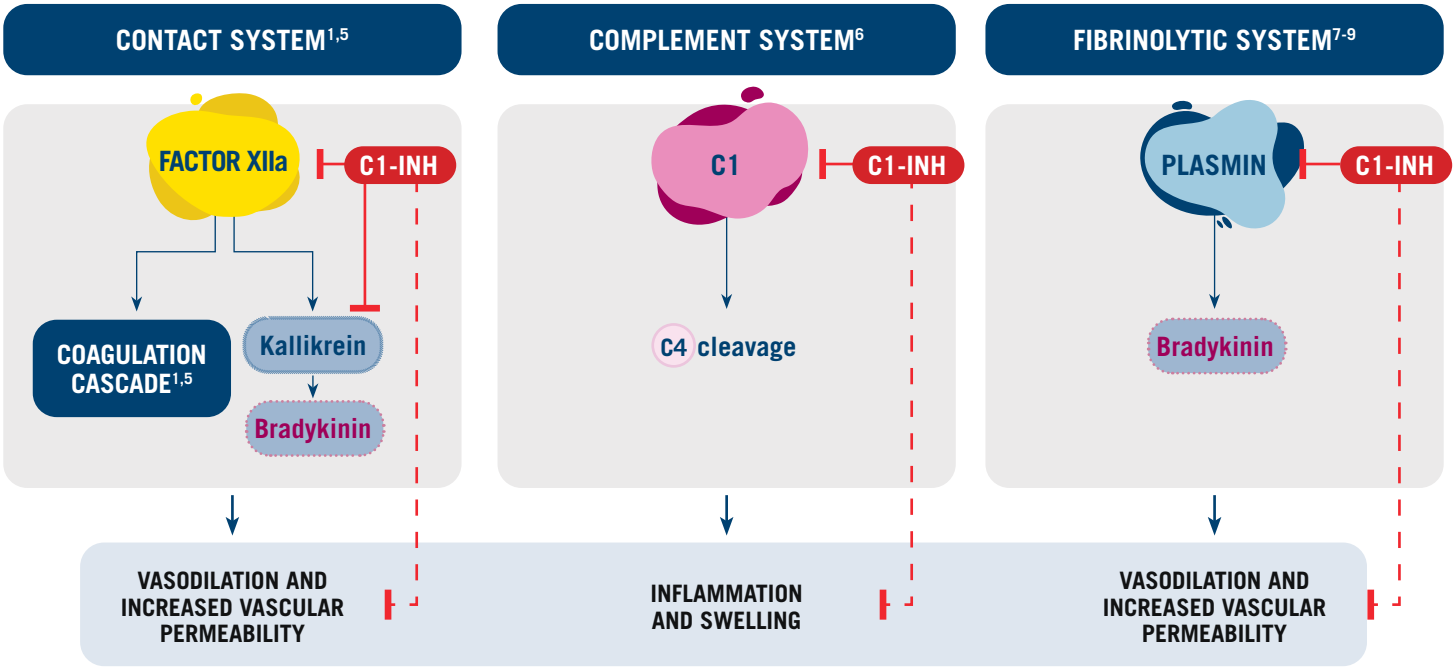
# Missing or malfunctioning C1-INH contributes to HAE[1†]

## C1-INH regulates multiple pathways involved in HAE[1]

C1-INH, normally present in human plasma, is the only known inhibitor for the subcomponents of complement component 1 (C1), coagulation factor XIIa, and plasma kallikrein.[1]

**C1-INH IS THOUGHT TO HAVE AN INHIBITORY ROLE IN AT LEAST FOUR CASCADE SYSTEMS IN THE HUMAN BODY:[3-9*]**




This is a simplified schematic for illustrative purposes only.

HAE type I or type II patients have absent or low levels of endogenous or functional C1-INH, which have been suggested to lead to impaired contact system inhibition and **unregulated bradykinin production.**[1,10†]

**LEGEND**

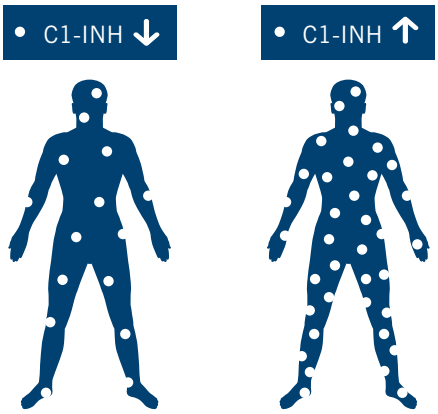
Direct Inhibition | Symptom Suppression | Activation

* Clinical significance not established.
† Missing and malfunctioning C1-INH characterize HAE types I and II, respectively.[10]

# HAEGARDA® replaces the missing or malfunctioning C1-INH protein[1]

## HAEGARDA® increases C1-INH and complement component 4 (C4) levels[1]

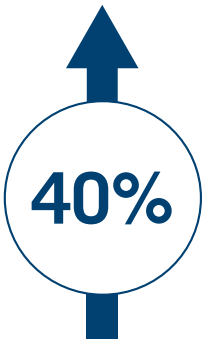
| | | | |
|---|---|---|---|
| **Untreated HAE[1]** | ↓ Functional C1-INH or C1-INH protein | → | ↓C4 |
| **With HAEGARDA®[1]** | ↑ Functional C1-INH | → | ↑C4 |




Untreated HAE | With HAEGARDA®

The administration of HAEGARDA® increases plasma levels of C1-INH in a dose dependent manner, and subsequently increases plasma concentrations of C4.[1]

**THE C4 PLASMA CONCENTRATIONS AFTER SUBCUTANEOUS ADMINISTRATION OF 60 IU/KG HAEGARDA® WERE IN THE NORMAL RANGE (16-38 MG/DL).[1]**




## Subcutaneous HAEGARDA® administration builds and maintains C1-INH functional activity levels above 40%[1]

The mean relative bioavailability of C1-INH was approximately 43% after subcutaneous administration with HAEGARDA® (95% CI, 35.2-50.2%).[1]

HAEGARDA® is expected to maintain a mean steady-state trough functional C1-INH level of 48% after twice weekly subcutaneous administration of the recommended dose (95% CI, 25.1-102%).[1*]

**HELP RESTORE C1-INH WITH HAEGARDA®**

* Functional C1-INH activity based on pharmacokinetic prediction model.[2]

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# An individualized approach for each patient through weight-based dosing[1]

The recommended dose of HAEGARDA® is 60 IU/kg body weight twice weekly (every 3-4 days) administered after reconstitution by subcutaneous injection at a rate tolerated by the patient.[1]

HAEGARDA® is supplied as a white lyophilized powder in either:

- **2000 IU/vial** accompanied with 4 mL of Sterile Water for Injection
- **3000 IU/vial** accompanied with 6 mL of Sterile Water for Injection

Reconstituted concentration is 500 IU/mL.


| HAEGARDA® DOSING CHART | | | | |
|---|---|---|---|---|
| Example weight | | Dose per infusion (60 IU/kg) | 2000 IU vials required per infusion | 3000 IU vials required per infusion |
| kg | lbs | | | |
| 50 | 110 | 3000 | | 1 |
| 67 | 148 | 4000 | 2 | |
| 83 | 183 | 5000 | 1 + | 1 |
| 100 | 220 | 6000 | | 2 |

HAEGARDA® is intended for self-administration by subcutaneous injection only. The patient or caregiver should be trained on how to administer HAEGARDA® as needed.[1]

**ADMINISTER HAEGARDA® SUBCUTANEOUSLY IN THE ABDOMINAL AREA OR OTHER SUBCUTANEOUS INJECTION SITES.[1]**

# Safety and Tolerability Profile

## Adverse reactions

Most common adverse reactions occurring in >4% of subjects were injection site reaction, hypersensitivity, nasopharyngitis, and dizziness.[1]

| ADVERSE REACTIONS IN >4% OF SUBJECTS TREATED WITH HAEGARDA® | | | | |
|---|---|---|---|---|
| Adverse Reaction | HAEGARDA® | | | Placebo (N=86) n (%) |
| | 60 IU/kg (N=43) n (%) | 40 IU/kg (N=43) n (%) | Overall* (N=86) n (%) | |
| Injection site reaction† | 15 (34.9) | 12 (27.9) | 27 (31.4) | 21 (24.4) |
| Hypersensitivity‡ | 3 (7.0) | 2 (4.7) | 5 (5.8) | 1 (1.2) |
| Nasopharyngitis | 8 (18.6) | 1 (2.3) | 9 (10.5) | 6 (7.0) |
| Dizziness | 0 (0.0) | 4 (9.3) | 4 (4.7) | 1 (1.2) |

N = number of subjects receiving the treatment; n = number of subjects experiencing ≥1 event.

* Includes subjects who were treated with 40 IU/kg or 60 IU/kg HAEGARDA®.

† Includes the MedDRA Preferred Terms: Injection site bruising, Injection site coldness, Injection site discharge, Injection site erythema, Injection site hematoma, Injection site hemorrhage, Injection site induration, Injection site edema, Injection site pain, Injection site pruritus, Injection site rash, Injection site reaction, Injection site scar, Injection site swelling, Injection site urticaria, Injection site warmth.

‡ Includes the MedDRA Preferred Terms: Hypersensitivity, Pruritus, Rash, and Urticaria.

95.0% of injection site reactions occurring during the clinical trial treatment period were of mild intensity, and 82.5% resolved within 1 day after onset.[1§¶]

§ Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

¶ Of the 90 subjects randomized in a double-blind, placebo-controlled, cross-over study, 86 subjects received at least 1 dose of HAEGARDA® and 86 subjects received at least 1 dose of placebo. A total of 5081 injections of HAEGARDA® and placebo were administered over a range of 3 to 19 weeks (median of 16.6 weeks for HAEGARDA®; median of 16.3 weeks for placebo).

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# Offer your patients routine prevention for HAE attacks with HAEGARDA® [1]

## HAEGARDA® 60 IU/kg demonstrated favourable efficacy results

**95.1% reduction**
**in median HAE attacks vs. placebo (primary endpoint)**

**>99% median reduction**
**in use of rescue medication vs. placebo**
**(0.32 vs. 3.89 mean uses per month; secondary endpoint)**

## Help restore C1-INH levels with HAEGARDA®[1]

HAEGARDA® replaces missing or malfunctioning C1-INH, bringing functional activity to levels above 40% and increasing plasma concentrations of C4

**Relevant warnings and precautions:**

- Should not to be used to treat an acute HAE attack, in which case individualized treatment should be initiated.
- If severe allergic reactions occur, administration must be stopped immediately (e.g. discontinue injection) and appropriate medical care must be initiated.
- Thrombosis has occurred in treatment attempts with high doses of C1-INH intravenous for prophylaxis or therapy of capillary leak syndrome before, during or after cardiac surgery under extracorporeal circulation (unlicensed indication and dose).
- When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. Appropriate vaccination for hepatitis A and B should be considered.
- There are limited data that suggest no increased risk from the use of general C1 inhibitor products in pregnant women. Use in pregnant women should occur only if clearly needed.
- It is unknown whether C1 inhibitor is present in human milk. Use in nursing mothers should occur only if clearly needed.

**For more information:**

Please consult the Product Monograph at http://labeling.cslbehring.ca/PM/CA/HAEGARDA/EN/HAEGARDA-Product-Monograph.pdf for important information relating to contraindications, adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.
The Product Monograph is also available by calling CSL Behring Medical Information at 1-866-773-7721.

**1.** HAEGARDA® Product Monograph. CSL Behring Canada, Inc. August 13, 2019. **2.** Longhurst H, Cicardi M, Craig T, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med. 2017;376(12):1131-1140. **3.** Bernstein JA, Coleman S, Bonnin AJ. Successful C1 inhibitor short-term prophylaxis during redo mitral valve replacement in a patient with hereditary angioedema. J Cardiothorac Surg. 2010;5(86):1-4. **4.** Davis AE, 3rd, Lu F, Mejia P. C1 inhibitor, a multi-functional serine protease inhibitor. Thromb Haemost. 2010;104(5):886-893. **5.** Bender L, Weidmann H, Rose-John S, Renné T, Long AT. Factor XII-Driven Inflammatory Reactions with Implications for Anaphylaxis. Front Immunol. 2017;8:1-11. **6.** Janeway CA Jr, Travers P, Walport M, et al. Immunobiology: The Immune System in Health and Disease. 5th edition. New York: Garland Science; 2001. The complement system and innate immunity. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27100/. **7.** Brown EW, Ravindran S, Patston PA. The reaction between plasmin and C1-inhibitor results in plasmin inhibition by the serpin mechanism. Blood Coagul Fibrinolysis. 2002;13(8):711-714. **8.** Maas C. Plasminflammation-An Emerging Pathway to Bradykinin Production. Front Immunol. 2019;10:2046. **9.** Levy J, Rivard GE, Wagner E, et al. Examination of genetic variants involved in generation and biodisposition of kinins in patients with angioedema. Allergy Asthma Clin Immunol. 2014;10(1):60. **10.** Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol. 2019;15:72.

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CSL Behring
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**More than 40 years of experience worldwide with C1-INH replacement therapy**



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