PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

HAEGARDA™

C1 Esterase Inhibitor Subcutaneous (Human)

Powder and Diluent for Solution for Injection

For Subcutaneous Administration

2000 IU/vial, reconstituted with 4 mL of diluent

3000 IU/vial, reconstituted with 6 mL of diluent

CSL Behring Canada, Inc.

55 Metcalfe Street, Suite 1460

Ottawa, Ontario

K1P 6L5

Date of Revision: April 12, 2019 **Date of Approval:** August 13, 2019

Submission Control No: 226788

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
DESCRIPTION 3
INDICATIONS AND CLINICAL USE 4
CONTRAINDICATIONS 4
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 6
DRUG INTERACTIONS 7
DOSAGE AND ADMINISTRATION 7
OVERDOSAGE 12
ACTION AND CLINICAL PHARMACOLOGY 12
STORAGE AND STABILITY 13
DOSAGE FORMS, COMPOSITION AND PACKAGING 14
PART II: SCIENTIFIC INFORMATION 15
PHARMACEUTICAL INFORMATION 15
CLINICAL TRIALS 16
DETAILED PHARMACOLOGY 17
MICROBIOLOGY 17
TOXICOLOGY 17
REFERENCES 19
PART III: CONSUMER INFORMATION 20

HAEGARDA™

C1 Esterase Inhibitor Subcutaneous (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Summary Product Information

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous (SC)	Lyophilized powder for reconstitution and injection; 2000 IU[1]/vial, 3000 IU/vial	Glycine, sodium chloride, sodium citrate *For a complete listing see section **DOSAGE FORMS, COMPOSITION AND PACKAGING**.*

DESCRIPTION

HAEGARDA (C1 Esterase Inhibitor Subcutaneous (Human)) is a human plasma derived, purified, pasteurized, nanofiltered, lyophilized concentrate of C1 Esterase Inhibitor (C1-INH) to be reconstituted for subcutaneous (SC) administration. HAEGARDA is prepared from large pools of human plasma.

The manufacturing process for HAEGARDA includes multiple steps that reduce the risk of virus transmission. The virus inactivation/reduction capacity consists of three steps:

- Pasteurization in aqueous solution at 60°C for 10 hours
- Hydrophobic interaction chromatography
- Virus filtration (also called nanofiltration) by two filters, 20 nm and 15 nm, in series

(*See section **Viral Inactivation** for further details.*)

[1] The potency of C1-INH is expressed in International Units (IU), which is related to the current World Health Organization (WHO) standard for C1-INH products.

INDICATIONS AND CLINICAL USE

HAEGARDA (C1 Esterase Inhibitor Subcutaneous (Human)) is indicated for routine prevention of Hereditary Angioedema (HAE) attacks in adolescent and adult patients.

Geriatrics:

Clinical study has been performed in patients ≤72 years of age (S*ee section **WARNINGS AND PRECAUTIONS**, subsection Special Populations*).

Pediatrics:

No clinical study has been performed in children <12 years of age (*See section **WARNINGS AND PRECAUTIONS**, subsection Special Populations*).

CONTRAINDICATIONS

HAEGARDA (C1 Esterase Inhibitor Subcutaneous (Human)) is contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or to any ingredient in the formulation or component of the container.

For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

HAEGARDA should not be used to treat an acute HAE attack. In case of an acute HAE attack, individualized treatment should be initiated.

If severe allergic reactions occur, the administration of HAEGARDA must be stopped immediately (e.g. discontinue injection) and appropriate medical care must be initiated.

Thromboembolic events (TEE)

Thrombosis has occurred in treatment attempts with high doses of C1-INH intravenous (IV) for prophylaxis or therapy of capillary leak syndrome before, during or after cardiac surgery under extracorporeal circulation (unlicensed indication and dose). At the recommended SC doses, a causal relationship between TEEs and the use of C1-INH concentrate has not been established.

Virus safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/ removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. Products made from human plasma may contain infectious agents such as viruses and, theoretically, the agent responsible for the Creutzfeldt-Jakob disease (CJD). This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and for the non-enveloped viruses HAV and parvovirus B19.

Appropriate vaccination (hepatitis A and B) should be generally considered for patients in regular/repeated receipt of human plasma-derived products.

It is strongly recommended that every time HAEGARDA is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-613-783-1892. The physician should discuss the risks and benefits of this product with the patient.

Special Populations

Pregnant Women:

There are limited data that suggest no increased risk from the use of general C1 inhibitor products in pregnant women. C1 inhibitor is a physiological component of human plasma. No studies on reproduction and developmental toxicity have been performed with HAEGARDA in animals. No adverse effects on fertility, pre- and postnatal development are expected in humans. HAEGARDA should be given to a pregnant woman only if clearly needed.

Nursing Women:

It is unknown whether C1 inhibitor is present in human milk. HAEGARDA should be given to a nursing mother only if clearly needed.

Pediatrics (<18 years):

The safety and effectiveness of HAEGARDA were evaluated in a subgroup of six pediatric patients 12 to <17 years of age in the randomized, double-blind, placebo-controlled, crossover, routine prophylaxis trial. Results of subgroup analysis by age were consistent with overall study results (See Clinical Trial Section).

Geriatrics:

The safety and effectiveness of HAEGARDA were evaluated in a subgroup of seven geriatric patients 65 to 72 years of age in the randomized, double-blind, placebo-controlled, crossover, routine prophylaxis trial. Results of subgroup analysis by age were consistent with overall study results (see Clinical Trial Section).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions occurring in more than 4% of subjects treated with HAEGARDA were: injection site reaction, hypersensitivity, nasopharyngitis and dizziness.

Clinical Trial Adverse Drug Reactions

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 the double-blind, placebo-controlled, cross-over study (*see Section CLINICAL TRIALS*), 86 subjects received at least 1 dose of HAEGARDA and 86 subjects received at least 1 dose of placebo (**Table 2**). 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).

Table 2: Adverse Reactions in >4% of Subjects Treated with HAEGARDA

MedDRA System Organ Class	Adverse Reaction	HAEGARDA 60 IU/kg (N=43) n (%)	HAEGARDA 40 IU/kg (N=43) n (%)	HAEGARDA Overall* (N=86) n (%)	Placebo (N=86) n (%)
General Disorders and Administration Site Conditions	Injection Site Reaction†	15 (34.9)	12 (27.9)	27 (31.4)	21 (24.4)
Immune System Disorders	Hypersensitivity‡	3 (7.0)	2 (4.7)	5 (5.8)	1 (1.2)
Infections and Infestations	Nasopharyngitis	8 (18.6)	1 (2.3)	9 (10.5)	6 (7.0)
Nervous System Disorders	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.

Of the injection site reactions occurring after treatment with HAEGARDA, 95.0% were of mild intensity and 82.5% resolved within 1 day after onset.

DRUG INTERACTIONS

No drug interaction studies have been conducted with HAEGARDA.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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. HAEGARDA is administered subcutaneously in the abdominal area or other subcutaneous injection sites.

The maximum tolerated dose used in patients in clinical studies was 10,000 IU, corresponding to a volume of 20 mL, twice weekly by subcutaneous injection.

Administration

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

General Instructions:

- The reconstituted solution for HAEGARDA should be colourless and clear to slightly opalescent.
- After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that have particles or deposits in them.
- Reconstitution and withdrawal must be carried out using aseptic techniques.
- In the absence of compatibility studies HAEGARDA must not be mixed with other medicinal products and diluents.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
- The suggested infusion site for the injection of HAEGARDA is the abdominal area, however other subcutaneous injection areas can be used. In the clinical trials, HAEGARDA was injected into a single site each administration and subsequent injection sites were rotated.
- The reconstituted preparation should be administered by subcutaneous injection at a rate tolerated by the patient.
- If the reconstituted product is not administered immediately, storage shall not exceed 8 hours at room temperature. The reconstituted product should only be stored in the vial.

Reconstitution

Follow the steps below and use aseptic technique to reconstitute and administer HAEGARDA:

Use the Mix2Vial® filter transfer set, syringe and either the SC infusion set or the hypodermic needle provided with HAEGARDA (see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section).

HAEGARDA 2000 IU should be reconstituted with the provided 4 mL of Sterile Water for Injection (Diluent).

HAEGARDA 3000 IU should be reconstituted with the provided 6 mL of Sterile Water for Injection (Diluent).

Step 1: Assemble supplies

- HAEGARDA and diluent vials
  (**Ensure that the HAEGARDA and the diluent are at room temperature)**
- Mix2Vial®
- SC infusion set or hypodermic needle
- Sterile syringe
- Alcohol or disinfectant wipes

Step 2: Clean surface

- Thoroughly clean a table or other flat surface using alcohol or disinfectant wipes.

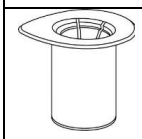
Step 3: Wash hands

- Thoroughly wash and dry your hands.

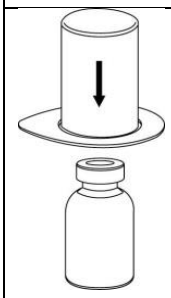
Reconstitution:

Step 4: Clean Stoppers

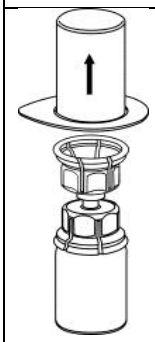
Remove the flip caps from both vials (HAEGARDA and diluent). Wipe rubber stoppers with an antiseptic wipe and allow the rubber stopper to dry.



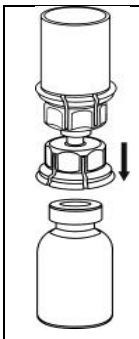
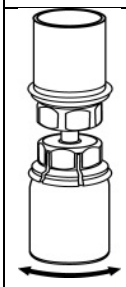
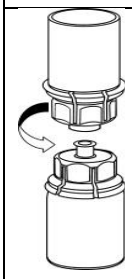
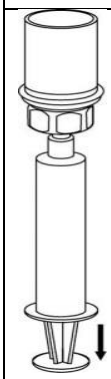
Step 5: Open the Mix2Vial® package by peeling off the lid. Do not remove the Mix2Vial® from the blister package!

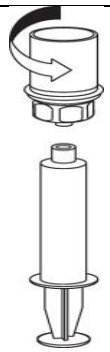


Step 6: Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial® together with the blister package and push the spike of the blue adapter end straight down through the diluent vial stopper.



Step 7: Carefully remove the blister package from the Mix2Vial® set by holding at the rim, and pulling vertically upwards. Make sure that you only pull away the blister package and not the Mix2Vial® set.

	**Step 8:** Place the HAEGARDA vial on an even and firm surface. Invert the diluent vial with the Mix2Vial® set attached and push the spike of the transparent adapter end straight down through the HAEGARDA vial stopper. The diluent will automatically flow into the HAEGARDA vial.
	**Step 9:** With the diluent and HAEGARDA vial still attached to the Mix2Vial® transfer set, gently swirl the HAEGARDA vial to ensure that the powder is fully dissolved. Do not shake the vial.
	**Step 10:** With one hand grasp the HAEGARDA-side of the Mix2Vial® set and with the other hand grasp the diluent-side and unscrew the set carefully counter-clockwise into two pieces. Discard the diluent vial with the blue Mix2Vial® adapter attached.
	**Step 11:** Draw air into an empty, sterile syringe. While the HAEGARDA vial is upright, connect the syringe to the Mix2Vial®'s Luer Lock fitting by screwing clockwise. Inject air into the HAEGARDA vial.
	**Step 12:** While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.



Step 13: Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial® adapter from the syringe by unscrewing counter-clockwise. The reconstituted solution should be colorless, clear and free from visible particles. Do not use if particulate matter or discoloration is observed.

Administration:

Step 14: Prepare injection site

- Select an area on the abdomen (stomach; Figure 1) or another subcutaneous area for the injection as discussed with a healthcare professional.
- Use a different place from last injection.
- New injection sites should be at least 5 centimeters (2 inches) away from the place where injection was given previously.
- Never give injection in areas where the skin is itchy, swollen, painful, bruised, or red.
- Avoid giving injections in places with scars or stretch marks.
- Clean the skin at the injection site with an alcohol swab and let the skin dry (Figure 2).

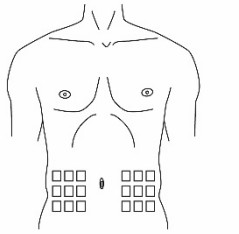


Figure 1

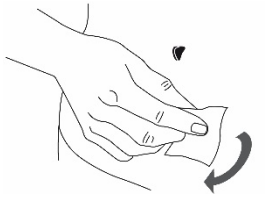


Figure 2

Step 15: Injection in the abdominal area or other subcutaneous injection area

As instructed by a healthcare provider:

- Attach a hypodermic needle or SC infusion set. Prime the needle or tubing as required and instructed.

Injection with Hypodermic Needle:

- Insert the needle into the fold of skin (Figure 3).

Injection by SC Infusion Set:

- Insert the needle into the fold of skin (Figure 4).

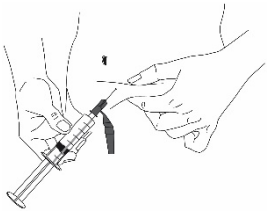


Figure 3

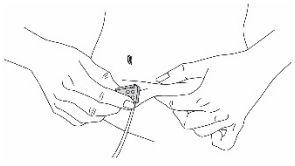


Figure 4

Step 16: Clean up

- After injecting the entire amount of HAEGARDA, remove the needle.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Step 17: Record treatment
Record the lot number from the HAEGARDA vial label in the patient's treatment diary or log book with the date and time of infusion every time HAEGARDA is used**.**

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No case of overdose has been reported. Doses corresponding to up to 117 IU/kg SC have been administered twice weekly in a fixed-dose clinical study and were well tolerated.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

C1-INH is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, alpha1-protease inhibitor, alpha2-antiplasmin, and heparin cofactor II. As with the other inhibitors in this group, C1-INH has an important inhibiting potential on several of the major cascade systems of the human body including the complement, fibrinolytic and coagulation systems. Regulation of these systems is performed through the formation of complexes between the protease and the inhibitor, resulting in inactivation of both and consumption of the C1-INH.

C1-INH, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1-INH is the only known inhibitor for the C1r and C1s subcomponents of complement component 1 (C1), coagulation factor XIIa, and plasma kallikrein. Additionally, C1-INH is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade.

HAE patients have absent or low levels of endogenous or functional C1-INH.Although the events that induce 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.[1] Administration of HAEGARDA replaces the missing or malfunctioning C1-INH protein in patients with HAE.[2]

Pharmacodynamics

In untreated patients, insufficient levels of functional C1-INH lead to increased activation of C1, which results in decreased levels of complement component 4 (C4). The administration of HAEGARDA increases plasma levels of C1-INH in a dose-dependent manner and subsequently increases plasma concentrations of C4. The C4 plasma concentrations after SC administration of 60 IU/kg HAEGARDA were in the normal range (16 to 38 mg/dL).

Pharmacokinetics[3,4,5]

The pharmacokinetic (PK) characteristics of C1-INH were primarily described using population PK methods on pooled data from 3 clinical trials in healthy subjects and HAE subjects.

Following twice weekly SC dosing, C1-INH is slowly absorbed, with a median (95% CI) time to peak concentration (t_{max}) of approximately 59 hours (23, 134 hours). Based on a median (95% CI) apparent plasma half-life of 69 hours [2.9 days] (24, 250 hours [1, 10.4 days]), steady state for C1-INH is expected within 3 weeks of dosing. A mean (95% CI) steady-state trough functional C1-INH of 48% (25.1-102%) is expected after twice weekly SC administration of 60 IU/kg HAEGARDA. The mean (95% CI) relative bioavailability (F) of C1-INH after SC administration was approximately 43% (35.2, 50.2%).

The population mean (95% CI) clearance and apparent volume of distribution of C1-INH were estimated to be approximately 83 mL/hr (72.7, 94.2 mL/hr) and 4.33 L (3.51, 5.15 L). C1-INH clearance was found to be positively correlated with total body weight. The steady state PK of SC of C1-INH was found to be independent of dose between 20-80 IU/kg in HAE subjects.

Studies have not been conducted to evaluate the PK of C1-INH in specific patient populations stratified by gender, race, age, or the presence of renal or hepatic impairment. The population analysis, evaluating age (12 to 72 years), was found not to influence the PK of C1-INH.

STORAGE AND STABILITY

The shelf life of HAEGARDA (C1 Esterase Inhibitor Subcutaneous (Human)) is 36 months. When stored in the refrigerator or at room temperature (at +2°C to +30°C), HAEGARDA is stable for the period indicated by the expiration date on the carton and vial label.
Keep HAEGARDA in its original carton until ready to use. Do not freeze. Protect from light.
After reconstitution the physico-chemical stability has been demonstrated for 48 hours at room temperature (max. +30°C). From a microbiological point of view and as HAEGARDA contains no preservative, the reconstituted product should be used immediately. If it is not administered immediately, storage shall not exceed 8 hours at room temperature. The reconstituted product should only be stored in the **vial**.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HAEGARDA (C1 Esterase Inhibitor Subcutaneous (Human)) is supplied as a white lyophilized powder in the following two formats:

- 2000 IU; which contains 2000 IU of C1-INH per injection vial accompanied with 4 mL of Sterile Water for Injection for reconstitution. After reconstitution, the concentration is 500 IU/mL.
- 3000 IU; which contains 3000 IU of C1-INH per injection vial accompanied with 6 mL of Sterile Water for Injection for reconstitution. After reconstitution, the concentration is 500 IU/mL.

The potency of C1-esterase inhibitor is expressed in International Units (IU), which is related to the current WHO Standard for C1-esterase inhibitor products.

Each vial of reconstituted HAEGARDA contains 500 IU/mL of C1-INH, 65 mg total protein, 10 mg glycine, 8.5 mg sodium chloride and 2.5 mg sodium citrate.

Excipients with known effect:

- Sodium up to 486 mg (approximately 21 mmol) per 100 mL solution.

The product package includes:

- 1 vial with HAEGARDA powder
- 1 vial of diluent (Sterile Water for Injection)
- 1 Mix2Vial® transfer device for reconstitution
- 1 inner carton

The inner carton contains:

- 1 syringe (10 mL) for withdrawal
- 1 SC infusion set
- 1 hypodermic needle

The components used in the packaging for HAEGARDA are latex-free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: C1 Esterase Inhibitor (Human).

Chemical name: NA

Molecular formula and molecular mass: 105 KDa

Structural formula: C1-INH is a soluble, single-chain glycoprotein containing 478 amino acid residues organized into three beta-sheets and eight or nine alpha-helices. The molecular weight of the heavily glycosylated molecule is 105 kD, of which the carbohydrate chains comprise at least 26 % - 35 %.

Physicochemical properties: Colourless, clear to slightly opalescent solution.

Product Characteristics

HAEGARDA (C1 Esterase Inhibitor Subcutaneous (Human)) is a human plasma-derived, purified, pasteurized, nanofiltered white lyophilized concentrate of C1-INH to be reconstituted for SC administration. Each vial of reconstituted HAEGARDA contains 500 IU/mL of C1-INH, 65 mg total protein, 10 mg glycine, 8.5 mg sodium chloride and 2.5 mg sodium citrate.

Viral Inactivation

All plasma used in the manufacturing of C1-INH is obtained from US donors and is tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV. Additionally, the plasma is tested with Nucleic Acid Testing (NAT) for HBV, HCV, HIV-1 and HAV and found to be non-reactive (negative). The plasma is also tested by NAT for Human Parvovirus B19. Only plasma that has passed virus screening is used for production, and the limit for Parvovirus B19 in the fractionation pool is set not to exceed 10^4 IU of Parvovirus B19 DNA per mL.

The manufacturing process for HAEGARDA includes multiple steps that reduce the risk of virus transmission. The virus inactivation/reduction capacity consists of three steps:

- Pasteurization in aqueous solution at 60°C for 10 hours
- Hydrophobic interaction chromatography
- Virus filtration (also called nanofiltration) by two filters, 20 nm and 15 nm, in series.

CLINICAL TRIALS[5]

The efficacy and safety of HAEGARDA for routine prophylaxis to prevent HAE attacks were demonstrated in a multicenter, randomized, double-blind, placebo-controlled, crossover study. The study assessed 90 adult and adolescent subjects with symptomatic HAE type I or II. The median (range) age of subjects was 40 (12 to 72) years old; 60 subjects were female and 30 subjects were male. Subjects 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 2 times per week. Efficacy was evaluated for the last 14 weeks of each treatment period.

Twice per week SC doses of 60 IU/kg or 40 IU/kg HAEGARDA significantly reduced the time-normalized number of HAE attacks (the rate of attacks) relative to placebo (Table 3). 60 IU/kg reduced the mean rate of attacks to 0.52 attacks per month from 4.03 attacks per month on placebo ($p < 0.001$). 40 IU/kg reduced the mean rate of attacks to 1.19 attacks per month from 3.61 attacks per month on placebo ($p < 0.001$).

Table 3: Time-normalized Number of HAE Attacks (Number/Month) (ITT Population)

	60 IU/kg HAEGARDA Treatment Sequences (N = 45)		**40 IU/kg HAEGARDA Treatment Sequences (N = 45)**	
	HAEGARDA	**Placebo**	**HAEGARDA**	**Placebo**
n	43	42	43	44
Mean (SD)	0.53 (0.771)	4.02 (2.308)	1.22 (2.310)	3.61 (2.088)
Min, Max	0.0, 3.1	0.6, 11.3	0.0, 12.5	0.0, 8.9
Median	0.29	3.75	0.29	3.81
LS Mean (SE)*	0.52 (0.261)	4.03 (0.263)	1.19 (0.327)	3.61 (0.327)
95% CI for LS Mean*	(0.00, 1.04)	(3.51, 4.55)	(0.54, 1.85)	(2.96, 4.26)
Treatment difference (within-subjects)	**60 IU/kg HAEGARDA – Placebo**		**40 IU/kg HAEGARDA – Placebo**	
LS Mean* (95% CI)	-3.51 (-4.21, -2.81)		-2.42 (-3.38, -1.46)	
p-value*	< 0.001		< 0.001	

CI = confidence interval; HAE = hereditary angioedema; ITT = Intent-to-treat; N = number of subjects; n = number of subjects with data; LS = Least squares.
* From a mixed model.

The median (25th, 75th percentile) percentage reduction in the time-normalized number of HAE attacks relative to placebo was 95.1% (79.0, 100.0) on 60 IU/kg HAEGARDA and 88.6% (69.6, 100.0) on 40 IU/kg HAEGARDA among subjects with evaluable data in both treatment periods.

The percentage of responders (95% CI) with a ≥50% reduction in the time-normalized number of HAE attacks on HAEGARDA relative to placebo was 82.9% (73.4%, 89.5%). 90% of subjects on 60 IU/kg responded to treatment and 76.2% of subjects on 40 IU/kg responded to treatment.

The percentages of subjects (95% CI) with ≥70% and ≥90% reductions in the time-normalized number of HAE attacks on HAEGARDA relative to placebo were 74.4% (64.0%, 82.6%) and 50.0% (39.4%, 60.6%), respectively. The percentages of subjects with ≥70% and ≥90% reductions were 82.5% and 57.5% on 60 IU/kg and 66.7% and 42.9% on 40 IU/kg. 71.1% of subjects on 60 IU/kg and 53.3% of subjects on 40 IU/kg had ≥1 HAE attack per 4 week period on placebo and <1 HAE attack per 4 week period on HAEGARDA.

Forty percent (40.0%) of subjects on 60 IU/kg and 37.8% of subjects on 40 IU/kg were attack-free, and the median rate of HAE attacks per month was 0.29 on both doses. The maximum rate of HAE attacks per month was 3.1 on 60 IU/kg and 12.5 on 40 IU/kg.

HAEGARDA reduced the time-normalized number of uses of rescue medication (the rate of rescue medication use) relative to placebo. 60 IU/kg reduced the mean rate of rescue medication use to 0.32 uses per month from 3.89 uses per month on placebo. 40 IU/kg reduced the mean rate of rescue medication use to 1.13 uses per month from 5.55 uses per month on placebo.

DETAILED PHARMACOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeat dose toxicity and local tolerability.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeat dose toxicity and local tolerability.

In a local tolerability study in rabbits, a single subcutaneous administration of C1-INH at dose levels up to approximately 670 IU/kg did not result in adverse findings. Accordingly, a NOAEL of 670 IU/kg was obtained for single subcutaneous administration.

In vivo thrombogenicity tests in rabbits indicate that there was no prothrombotic risk associated with the IV administration of C1-INH up to 800 IU/kg.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been completed to evaluate the effects of C1-INH on carcinogenesis, mutagenesis, and impairment of fertility.

REFERENCES

1. Davis AE, The pathophysiology of hereditary angioedema. *Clin Immunol.* 2005;114:3-9.
2. Nuijens JH, Eerenberg-Belmer AJM, Huijbregts CCM, et al. Proteolytic inactivation of plasma C1 inhibitor in sepsis. *J Clin Invest*. 1989;84:443-450.
3. Study 1001: A randomized, double-blind, single-center, cross-over study to evaluate the safety, bioavailability and pharmacokinetics of two formulations of C1-esterase inhibitor administered intravenously
4. Study 2001: An Open-label, Cross-over, Dose-ranging Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of the Subcutaneous Administration of a Human Plasma-derived C1-esterase Inhibitor in Subjects with Hereditary Angioedema.
5. Study 3001: A double-blind, randomized, placebo-controlled, crossover study to evaluate the clinical efficacy and safety of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema.

PART III: CONSUMER INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

HAEGARDA™
C1 Esterase Inhibitor Subcutaneous (Human)

Read this carefully before you start taking HAEGARDA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about HAEGARDA.

ABOUT THIS MEDICATION

What is HAEGARDA used for?

HAEGARDA is an injectable medicine used to prevent swelling and/or painful attacks in adults and adolescents with Hereditary Angioedema (HAE). HAEGARDA should not be used to treat an acute HAE attack. In the event of an acute attack, seek medical attention.

How does HAEGARDA work?

HAE is caused by the poor functioning or lack of a protein called C1 that is present in your blood and helps control inflammation (swelling) and parts of the immune system. HAEGARDA contains C1 esterase inhibitor (C1 INH), a protein that helps control C1.

What are the ingredients in HAEGARDA?

Medicinal ingredients:

- C1 Esterase Inhibitor (Human)

Non-medicinal ingredients:

- Glycine
- Sodium chloride
- Sodium citrate

HAEGARDA comes in the following dosage forms:

HAEGARDA is supplied as a white lyophilized powder in the following two formats:

- 2000 IU; which contains 2000 IU of C1-INH per injection vial accompanied with 4 mL diluent (Sterile Water for Injection) for reconstitution. After reconstitution, the concentration is 500 IU/mL.
- 3000 IU; which contains 3000 IU of C1-INH per injection vial accompanied with 6 mL diluent (Sterile Water for Injection) for reconstitution. After reconstitution, the concentration is 500 IU/mL.

The product package includes:

- 1 vial with HAEGARDA powder
- 1 vial of diluent (Sterile Water for Injection)
- 1 Mix2Vial® transfer device for reconstitution
- 1 inner carton

The inner carton contains:

- 1 syringe (10 mL) for withdrawal
- 1 SC infusion set
- 1 hypodermic needle

The components used in the packaging for HAEGARDA are latex-free.

WARNINGS AND PRECAUTIONS

Do not use HAEGARDA if:

You have experienced life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take HAEGARDA. Talk about any concerns, health conditions or problems you may have, including the following:

- You are pregnant or planning to become pregnant. . The effect of HAEGARDA on your unborn baby is not known.
- You are breastfeeding or plan to breastfeed. It is not known if HAEGARDA passes into your breast milk or if it can affect your baby.
- You have a history of blood clotting problems. Blood clots have occurred in patients receiving HAEGARDA. Very high doses of C1-INH could increase the risk of blood clots. Tell your healthcare professional if you have a history of heart or blood vessel disease, stroke, blood clots, or have thick blood, an indwelling catheter/access device in one of your veins, or have been immobile for some time. These factors may increase your risk of having a blood clot after using HAEGARDA. Also, tell your healthcare professional what drugs you are using, as some drugs, such as birth control pills or certain androgens, may increase your risk of developing a blood clot.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Products made from human plasma may contain infectious agents such as viruses and, theoretically, the agent responsible for the Creutzfeldt-Jakob disease (CJD).

Appropriate vaccination (hepatitis A and B) should be generally considered for subjects in regular/repeated receipt of human plasma-derived products.

INTERACTIONS WITH THIS MEDICATION

The following may interact with HAEGARDA:

No formal drug interaction studies have been conducted with HAEGARDA. To date, no relevant interactions are known.

PROPER USE OF THIS MEDICATION

Usual Dose:

The recommended usual dose is 60 IU per kg of body weight twice weekly (every 3 or 4 days) administered after reconstitution by subcutaneous injection at a rate tolerated by the patient. HAEGARDA is administered subcutaneously in the abdominal area or other subcutaneous injection sites.

The maximum tolerated dose used in patients in clinical studies was 10,000 IU, corresponding to a volume of 20 mL, twice weekly by subcutaneous injection.

Overdose:

No cases of overdose have been reported.

If you think you have taken too much HAEGARDA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if you have no symptoms.

Missed Dose:

Proceed with your next dose immediately and continue at regular intervals as advised by your healthcare professional. Do not take a double dose to make up for a forgotten dose.

Home treatment / Self-administration:

You should prepare the prescribed dose of HAEGARDA for self-administration as directed by your healthcare professional.

- **Do not attempt to self-administer unless you have been taught how by your healthcare professional.**
- See the following step-by-step instructions for **reconstitution** and **administering** HAEGARDA**.** The steps listed below are general guidelines for using HAEGARDA. If you are unsure of the steps, please contact your healthcare professional before using.
- Your healthcare professional will prescribe the dose that you should administer, which is based on your body weight.
- Talk to your healthcare professional before traveling to make sure you have an adequate supply of HAEGARDA**.**
- Use a new needle for each HAEGARDA injection.

Reconstitution and Administration:

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

General Instructions:

- The reconstituted solution for HAEGARDA should be colourless and clear to slightly opalescent.
- After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that have particles or deposits in them.
- Reconstitution and withdrawal must be carried out using aseptic techniques.
- In the absence of compatibility studies HAEGARDA must not be mixed with other medicinal products and diluents.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
- The suggested infusion site for the injection of HAEGARDA is the abdominal area, however other subcutaneous injection areas can be used. In the clinical trials, HAEGARDA was injected into a single site each administration and subsequent injection sites were rotated.
- The reconstituted preparation should be administered by subcutaneous injection at a rate tolerated by the patient.
- If the reconstituted product is not administered immediately, storage shall not exceed 8 hours at room temperature. The reconstituted product should only be stored in the vial.

Follow the steps below and use aseptic technique to reconstitute and administer HAEGARDA:

Use the Mix2Vial® filter transfer set, syringe and either the SC infusion set or the hypodermic needle provided with HAEGARDA (see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section).

HAEGARDA 2000 IU should be reconstituted with the provided 4 mL of Sterile Water for Injection (Diluent).

HAEGARDA 3000 IU should be reconstituted with the provided 6 mL of Sterile Water for Injection (Diluent).

Step 1: Assemble supplies

- HAEGARDA and diluent vials
  (**Ensure that the HAEGARDA and the diluent are at room temperature)**
- Mix2Vial®
- SC infusion set or hypodermic needle
- Sterile syringe
- Alcohol or disinfectant wipes
- Sharp/biohazardous container
- Treatment diary / log book
- Gloves (if recommended by your healthcare professional)

Step 2: Clean surface

- Thoroughly clean a table or other flat surface using alcohol or disinfectant wipes.

Step 3: Wash hands

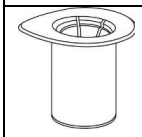
- Thoroughly wash and dry your hands.

- If you have been told to wear gloves when preparing your infusion, put the gloves on.

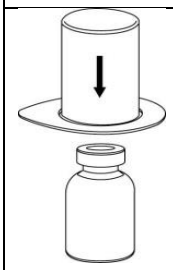
Reconstitution:

Step 4: Clean Stoppers

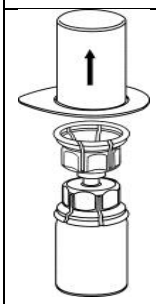
Remove the flip caps from both vials (HAEGARDA and diluent). Wipe rubber stoppers with an antiseptic wipe and allow the rubber stopper to dry.



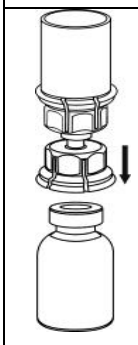
Step 5: Open the Mix2Vial® package by peeling off the lid. Do not remove the Mix2Vial® from the blister package!



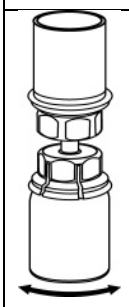
Step 6: Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial® together with the blister package and push the spike of the blue adapter end straight down through the diluent vial stopper.



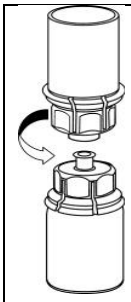
Step 7: Carefully remove the blister package from the Mix2Vial® set by holding at the rim, and pulling vertically upwards. Make sure that you only pull away the blister package and not the Mix2Vial® set.



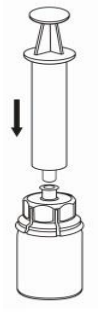
Step 8: Place the HAEGARDA vial on an even and firm surface. Invert the diluent vial with the Mix2Vial® set attached and push the spike of the transparent adapter end straight down through the HAEGARDA vial stopper. The diluent will automatically flow into the HAEGARDA vial.



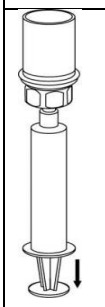
Step 9: With the diluent and HAEGARDA vial still attached to the Mix2Vial® transfer set, gently swirl the HAEGARDA vial to ensure that the powder is fully dissolved. Do not shake the vial.



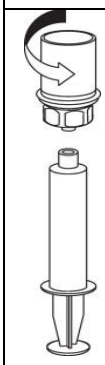
Step 10: With one hand grasp the HAEGARDA-side of the Mix2Vial® set and with the other hand grasp the diluent-side and unscrew the set carefully counter-clockwise into two pieces. Discard the diluent vial with the blue Mix2Vial® adapter attached.



Step 11: Draw air into an empty, sterile syringe. While the HAEGARDA vial is upright, connect the syringe to the Mix2Vial®'s Luer Lock fitting by screwing clockwise. Inject air into the HAEGARDA vial.



Step 12: While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.



Step 13: Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial® adapter from the syringe by unscrewing counter- clockwise. The reconstituted solution should be colorless, clear and free from visible particles. Do not use if particulate matter or discoloration is observed.

Administration:

Step 14: Prepare injection site

- Select an area on the abdomen (stomach; Figure 1) or another subcutaneous area for the injection as discussed with a healthcare professional.
- Use a different place from your last injection; you should rotate the places where you are injecting.
- New injection sites should be at least 5 centimeters (2 inches) away from the place where you gave yourself an injection before.

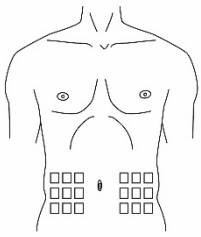


Figure 1

- Never give yourself an injection in areas where the skin is itchy, swollen, painful, bruised, or red.
- Avoid giving yourself injections in places where you have scars or stretch marks.
- Clean the skin at the injection site with an alcohol swab and let the skin dry (Figure 2).

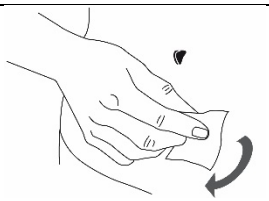


Figure 2

Step 15: Injection in the abdominal area or other subcutaneous injection area

As instructed by your healthcare provider:

- Attach a hypodermic needle or SC infusion set. Prime the needle or tubing as required and instructed.

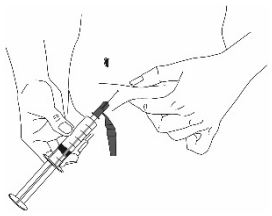


Figure 3

Injection with Hypodermic Needle:

- Insert the needle into the fold of skin (Figure 3).

Injection by SC Infusion Set:

- Insert the needle into the fold of skin (Figure 4).

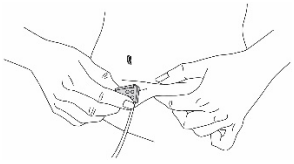


Figure 4

Step 16: Clean up

- After injecting the entire amount of HAEGARDA, remove the needle.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Step 17: Record treatment

Record the lot number from the HAEGARDA vial label in your treatment diary or log book with the date and time of infusion every time you use HAEGARDA**.**

HOW TO STORE IT

Keep the non-reconstituted HAEGARDA in its original carton to protect from light until ready to use. The shelf life of HAEGARDA is 36 months. When stored in the refrigerator or at room temperature (at +2°C to +30°C), HAEGARDA is stable for the period indicated by the expiration date on its label. Do not freeze.

Storage after reconstitution: If the reconstituted product is not administered immediately, storage shall not exceed 8 hours at room temperature. The reconstituted product should only be stored in the vial. Do not freeze the reconstituted solution.

Keep out of reach and sight of children.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What are possible side effects from using HAEGARDA?

These are not all the possible side effects you may feel when taking HAEGARDA. If you experience any side effects not listed here, contact your healthcare professional. *Please also see section WARNINGS AND PRECAUTIONS.*

Allergic reactions may occur with HAEGARDA. Talk to your healthcare professional right away if you have any of the following symptoms after using HAEGARDA:

- wheezing
- difficulty breathing
- chest tightness
- turning blue (look at lips and gums)
- fast heartbeat
- swelling of the face
- rash or hives

Signs of a blood clot include:

- pain and/or swelling of an arm or leg with warmth over the affected area
- discoloration of an arm or leg
- unexplained shortness of breath
- chest pain or discomfort that worsens on deep breathing
- unexplained rapid pulse
- numbness or weakness on one side of the body

The most common side effects with HAEGARDA are injection site reactions (pain, redness, swelling), hypersensitivity (itching and rash), nasopharyngitis (runny or stuffy nose, sneezing, watery eyes) and dizziness.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Address Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

We recommend that CSL Behring Canada, Inc. be copied when reporting suspected side effects, at the following address:

AdverseReporting@CSLBehring.com

MORE INFORMATION

If you want more information about HAEGARDA:

Talk to your healthcare professional

Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website at www.CSLBehring.ca, or by calling 1-866-773-7721.

This leaflet was prepared by CSL Behring Canada, Inc.

Date of Approval: August 13, 2019