HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HAEGARDA safely and effectively. See full prescribing information for HAEGARDA.

HAEGARDA® (C1 Esterase Inhibitor Subcutaneous [Human])
For Subcutaneous Injection, Freeze-Dried Powder for Reconstitution
Initial U.S. Approval: 2017

---------- **INDICATIONS AND USAGE** ----------
HAEGARDA is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1-INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients. (1)

---------- **DOSAGE AND ADMINISTRATION** ----------
For subcutaneous use after reconstitution only.
- Administer 60 International Units per kg body weight twice weekly (every 3 or 4 days). (2)
- Reconstitute HAEGARDA prior to use using Sterile Water for Injection, USP. (2.1)
- Use a silicone-free syringe for reconstitution and administration. (2.1)
- Administer at room temperature within 8 hours after reconstitution. (2.1)

---------- **DOSAGE FORMS AND STRENGTHS** ----------
HAEGARDA is available as a white lyophilized powder supplied in single-use vials containing 2000 or 3000 International Units (IU) of C1-INH. (3)

---------- **CONTRAINDICATIONS** ----------
Do not use in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis to C1-INH preparations or its excipients. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------
- Severe hypersensitivity reactions may occur. In case of severe hypersensitivity, discontinue HAEGARDA administration and institute appropriate treatment. Epinephrine should be immediately available for treatment of severe hypersensitivity reaction. (5.1)
- At the recommended subcutaneous (S.C.) dose, a causal relationship between thromboembolic events (TEEs) and the use of HAEGARDA has not been established. However, thrombosis has occurred in treatment attempts with high doses of C1-INH intravenous (I.V.) for prevention or therapy of capillary leak syndrome before, during or after cardiac surgery (unapproved indication and dose). (5.2)
- Because HAEGARDA is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.3)

---------- **ADVERSE REACTIONS** ----------
- Adverse reactions occurring in more than 4% of subjects treated with HAEGARDA were injection site reaction, hypersensitivity, nasopharyngitis and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Issued: 06/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HAEGARDA is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1-INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients.

2 DOSAGE AND ADMINISTRATION

After reconstitution, for subcutaneous use only.

HAEGARDA is intended for self-administration after reconstitution at a dose of 60 International Units (IU) per kg body weight by subcutaneous (S.C.) injection twice weekly (every 3 or 4 days). The patient or caregiver should be trained on how to administer HAEGARDA.

HAEGARDA is provided as a freeze-dried powder for reconstitution with Sterile Water for Injection, USP.

2.1 Preparation and Handling

- Check the expiration date on the product vial label. Do not use beyond the expiration date.
- Work on a clean surface and wash hands before performing the following procedures.
- Prepare and administer using aseptic techniques *[see Dosage and Administration (2.2)]*.
- Use a silicone-free syringe for reconstitution and administration.
- Each vial of HAEGARDA is for single-use only. Promptly use the reconstituted solution. The solution must be used within 8 hours. Discard partially used vials. HAEGARDA contains no preservative.
- Do not freeze the reconstituted solution.

2.2 Reconstitution and Administration

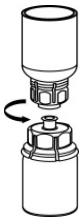
Use either the Mix2Vial® transfer set provided with HAEGARDA or a commercially available double-ended needle and vented filter spike *[see How Supplied/Storage and Handling (16)]*.

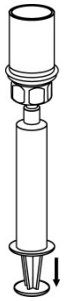
Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of HAEGARDA.

Table 1. HAEGARDA Reconstitution Instructions

1. Ensure that the HAEGARDA vial and Sterile Water for Injection (diluent) vial are at room temperature.	
2. Place the HAEGARDA vial, diluent vial and Mix2Vial transfer set on a flat surface.	
3. Remove flip caps from the HAEGARDA and diluent vials.	

4. Wipe the stoppers with an alcohol swab and allow to dry prior to opening the Mix2Vial transfer set package.	
5. Open the Mix2Vial transfer set package by peeling away the lid (Figure 1). Do not remove the device from the package.	 Figure 1
6. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial (Figure 2).	 Figure 2
7. Carefully remove the clear package from the Mix2Vial transfer set. Do not remove the Mix2Vial transfer set or touch the exposed end of the device (Figure 3).	 Figure 3
8. With the HAEGARDA vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the HAEGARDA vial (Figure 4). The diluent will automatically transfer into the HAEGARDA vial.	 Figure 4
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 (Figure 5). Do not shake the vial.	 Figure 5
10. With one hand, grasp the HAEGARDA side of the Mix2Vial transfer set and with the other hand grasp the blue diluent side of the Mix2Vial transfer set, and unscrew the set into two pieces (Figure 6).	 Figure 6
11. Draw air into an empty, sterile syringe. Use a silicone-free syringe. While the HAEGARDA vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the HAEGARDA vial.	

12. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Figure 7).	 Figure 7
13. Disconnect the filled syringe by unscrewing it from the Mix2Vial transfer set (Figure 8). The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if particles or discoloration are observed.	 Figure 8
14. Use immediately or within 8 hours of reconstitution. Store reconstituted solution at room temperature. Do not refrigerate.	
15. If the dose requires more than one vial, use a separate, unused Mix2Vial transfer set and diluent vial for each product vial. Repeat steps 10-12 to pool the contents of the vials into one syringe.	

Administration

For subcutaneous injection only.

- Train the patient or caregiver on how to self-administer HAEGARDA .
- Do not mix HAEGARDA with other medicinal products.
- Visually inspect the final solution for particles and discoloration prior to administration, and whenever solution and container permit. Do not use if particles or discoloration is observed.
- Attach the syringe containing the reconstituted HAEGARDA solution to a hypodermic needle or subcutaneous infusion set and administer by subcutaneous injection. Adapt the rate of administration to the comfort level of the patient.
- Inject in the abdominal area or other subcutaneous injection sites. Rotate injection sites so that the same site is not used repeatedly.
- Administer HAEGARDA at room temperature and within 8 hours after reconstitution. Following administration, discard any unused solution and all administration equipment in an appropriate manner as per local requirements.

3 DOSAGE FORMS AND STRENGTHS

HAEGARDA is available as a white lyophilized powder supplied in single-use vials containing 2000 or 3000 IU of C1-INH.

- The 2000 IU vial must be reconstituted with 4 mL of Sterile Water for Injection, USP.
- The 3000 IU vial must be reconstituted with 6 mL of Sterile Water for Injection, USP.

4 CONTRAINDICATIONS

HAEGARDA is contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or its excipients *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient *[see Patient Counseling Information (17)]*.

Initiate individualized treatment in case of an acute HAE attack.

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur. The signs and symptoms of hypersensitivity reactions may include hives (local and generalized), tightness of the chest, difficulty breathing, wheezing, hypotension, and/or anaphylaxis during or after injection of HAEGARDA. In case of severe hypersensitivity, discontinue HAEGARDA administration and institute appropriate treatment. Epinephrine should be immediately available for treatment of severe hypersensitivity reaction *[see Patient Counseling Information (17)]*.

5.2 Thromboembolic Events

At the recommended subcutaneous dose, a causal relationship between thromboembolic events (TEEs) and the use of HAEGARDA has not been established *[see Patient Counseling Information (17)]*. Thrombosis has occurred in treatment attempts with high doses of C1-INH intravenous (I.V.) for prevention or therapy of capillary leak syndrome before, during or after cardiac surgery (unapproved indication and dose).

5.3 Transmissible Infectious Agents

Because HAEGARDA is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by processes demonstrated to inactivate and/or remove certain viruses during manufacturing *[see Description (11) and Patient Counseling Information (17)]*. Despite these measures, such products may still contain human

pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated.

All infections thought by a physician possibly to have been transmitted by HAEGARDA should be reported by lot number, by the physician or other healthcare provider, to the CSL Behring Pharmacovigilance Department at 1-866-915-6958.

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Of the 90 subjects randomized in the double-blind, placebo-controlled, cross-over study *[see Clinical Studies (14)]*, 86 subjects received at least one dose of HAEGARDA and 86 subjects received at least one 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 (35)	12 (28)	27 (31)	21 (24)
Immune System Disorders	Hypersensitivity‡	3 (7)	2 (5)	5 (6)	1 (1)
Infections and Infestations	Nasopharyngitis	8 (19)	1 (2)	9 (11)	6 (7)
Nervous System Disorders	Dizziness	0 (0)	4 (9)	4 (5)	1 (1)

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: Injection site bruising, coldness, discharge, erythema, hematoma, hemorrhage, induration, edema, pain, pruritus, rash, reaction, scar, swelling, urticaria, warmth.
‡ Includes: hypersensitivity, pruritus, rash, and urticaria.

Of the injection site reactions occurring after treatment with HAEGARDA, 95% were of mild intensity and 83% resolved within 1 day after onset.

7 DRUG INTERACTIONS

No interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no prospective clinical data from HAEGARDA use in pregnant women. C1-INH is a normal component of human plasma. Animal developmental or reproduction toxicity studies have not been conducted with HAEGARDA. In the U.S. general population, the estimated background risk of major birth defects occurs in 2-4% of the general population and miscarriage occurs in 15-20% of clinically recognized pregnancies.

Data
In a retrospective case collection study, 22 pregnant women with type I HAE and ranging in age from 20 to 38 years received C1-INH doses of 500 or 1000 IU per I.V. administration for the treatment of acute attacks before, during, and/or after pregnancy (total of 35 pregnancies). No adverse events were associated with C1-INH treatment before, during, or after pregnancy.[1]

In an observational registry (overall 318 subjects) data were collected on 11 pregnancies in 10 subjects (16 to 40 years old) receiving up to 3000 IU C1-INH (I.V. administration) to treat or prevent HAE attacks. No adverse events were associated with C1-INH treatment.[2]

8.2 Lactation

Risk Summary
There is no information regarding the excretion of HAEGARDA in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HAEGARDA and any potential adverse effects on the breastfed infant from HAEGARDA or from the underlying maternal condition.

Data
In a retrospective case collection study, breastfeeding was documented for neonates from 21 of 35 births with a median duration of 4.8 months (ranging from 1 to 34 months). Mothers were treated postpartum with C1-INH doses up to 1000 IU per I.V. administration for the treatment of acute HAE attacks. No adverse events to the mothers were associated with C1-INH treatment after pregnancy. No information regarding the effect on the breastfed infant was reported.[1]

8.4 Pediatric Use
The safety and effectiveness of HAEGARDA were evaluated in a subgroup of six 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.

8.5 Geriatric Use
The safety and effectiveness of HAEGARDA were evaluated in a subgroup of eight 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.

10 OVERDOSAGE

No case of overdose has been reported. Doses corresponding to up to 117 IU/kg S.C. have been administered twice weekly in a fixed-dose clinical study.

11 DESCRIPTION

HAEGARDA is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1-INH to be reconstituted for S.C. administration. HAEGARDA is prepared from large pools of human plasma from U.S. donors. The potency of C1-INH is expressed in International Units (IU), which is related to the current WHO Standard for C1-INH products.

Reconstituted HAEGARDA has a concentration of 500 IU/mL C1-INH, 65 mg/mL total protein, 10 mg/mL glycine, 8.5 mg/mL sodium chloride and 2.7 mg/mL sodium citrate.

C1 Esterase Inhibitor

C1-INH is a soluble, single-chain highly glycosylated protein containing 478 amino acid residues which belongs to the serine protease inhibitor (serpin) family.

All plasma used in the manufacturing of C1-INH is obtained from U.S. 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.

Viral inactivation and reduction were evaluated in a series of in vitro spiking experiments. The total mean cumulative virus inactivation/reduction is shown in Table 3.

Table 3. Mean Virus Inactivation/Reductions in HAEGARDA

Virus Studied	Pasteurization [log_{10}]	Hydrophobic Interaction Chromatography [log_{10}]	Virus Filtration [log_{10}]	Total Cumulative [log_{10}]
Enveloped Viruses				
HIV-1	≥6.6	≥4.5	≥5.1	≥16.2
BVDV	≥9.2	≥4.7	≥5.3	≥19.2
PRV	6.3	≥6.5	≥7.1	≥19.9
WNV	≥7.0	ND	≥8.0	≥15.0
Non-Enveloped Viruses				
HAV	≥6.4	2.8	≥5.3	≥14.5
CPV	1.4	6.4	≥7.2	≥15.0
B19V	3.9	ND	ND	NA

HIV-1, Human immunodeficiency virus type 1, a model for HIV-1 and HIV-2
BVDV, Bovine viral diarrhea virus, a model for HCV
PRV, Pseudorabies virus, a model for large enveloped DNA viruses
WNV, West Nile virus
HAV, Hepatitis A virus
CPV, Canine parvovirus
B19V, Human Parvovirus B19
ND, Not determined
NA, Not applicable

12 CLINICAL PHARMACOLOGY

12.1 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, alpha$_1$-protease inhibitor, alpha$_2$-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 human cascade systems, 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 absence or low levels of endogenous or functional C1-INH. 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.

12.2 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 S.C. administration of 60 IU/kg HAEGARDA were in the normal range (16 to 38 mg/dL).

12.3 Pharmacokinetics

The pharmacokinetics (PK) of C1-INH were described using population PK analysis.

The PK parameters of C1-INH following twice weekly subcutaneous 60 IU/kg dosing are shown in Table 4.

Table 4. Pharmacokinetic Parameter for HAEGARDA (60 IU/kg) from Population Pharmacokinetic Analysis

Parameter	Mean	95% CI
CL (mL/hr/kg)[*]	1.03	0.90-1.17
Vd (L/kg)[*]	0.05	0.04-0.06
Bioavailability %	42.7	35.2-50.2
C_{max} %	60.7[†]	31.8-128[‡]
C_{trough} %	48.0[†]	25.1-102[‡]
T_{max} (hr)	59[§]	23-134[‡]
Half-life (hr)[‖]	69[§]	24-251[‡]

[*]Calculated based on median weight of 80.7 kg of the population, [†]Geometric mean, [‡]2.5-97.5 percentile of the population, [§]Median, [‖]Apparent half-life.

The steady state PK of S.C. C1-INH is 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 PK of C1-INH was not influenced at the age range of 12-72 years.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

Single subcutaneous administration of HAEGARDA in rabbits at dose levels up to approximately 670 IU/kg did not result in adverse findings.

14 CLINICAL STUDIES

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 ; 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 self-administered HAEGARDA or placebo subcutaneously 2 times per week. Efficacy was evaluated for the last 14 weeks of each treatment period.

Twice per week S.C. doses of 60 IU/kg or 40 IU/kg HAEGARDA resulted in a significant difference in the time-normalized number of HAE attacks (the rate of attacks) relative to placebo (Table 5). The time normalized number of HAE attacks in subjects dosed with 60 IU/kg was 0.52 attacks per month compared to 4.03 attacks per month while receiving placebo ($p < 0.001$). The time normalized number of HAE attacks in subjects dosed with 40 IU/kg was 1.19 attacks per month compared to 3.61 attacks per month while receiving placebo ($p < 0.001$).

Table 5. Time-normalized Number of HAE Attacks (Number/Month)

	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)	0.5 (0.8)	4.0 (2.3)	1.2 (2.3)	3.6 (2.1)
Min, Max	0.0, 3.1	0.6, 11.3	0.0, 12.5	0.0, 8.9
Median	0.3	3.8	0.3	3.8
LS Mean (SE)*	0.5 (0.3)	4.0 (0.3)	1.2 (0.3)	3.6 (0.3)
95% CI for LS Mean*	(0.0, 1.0)	(3.5, 4.6)	(0.5, 1.9)	(3, 4.3)
Treatment difference (within-subjects)	**60 IU/kg HAEGARDA – Placebo**		**40 IU/kg HAEGARDA – Placebo**	
LS Mean* (95% CI)	-3.5 (-4.2, -2.8)		-2.4 (-3.4, -1.5)	
p-value*	< 0.001		< 0.001	

CI = confidence interval; HAE = hereditary angioedema; N = number of randomized 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% (79, 100) on 60 IU/kg HAEGARDA and 89% (70, 100) 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 83% (73%, 90%). Ninety percent (90%) of subjects on 60 IU/kg responded to treatment and 76% 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% (64%, 83%) and 50% (39%, 61%), respectively. The percentages of subjects with ≥70% and ≥90% reductions in comparison to placebo in the time-normalized number of HAE attacks were 83% and 58% on 60 IU/kg and 67% and 43% on 40 IU/kg. Seventy-one percent (71%) of subjects on 60 IU/kg and 53% 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.

A total of 40% of subjects on 60 IU/kg and 38% of subjects on 40 IU/kg were attack-free, and the median rate of HAE attacks per month was 0.3 on both doses.

HAEGARDA resulted in a significant difference in the time−normalized number of uses of rescue medication (the rate of rescue medication use) relative to placebo. A dose of 60 IU/kg resulted in a mean rate of rescue medication of 0.3 uses per month, compared to 3.9 uses per

month with placebo. A dose of 40 IU/kg resulted in a mean rate of rescue medication use of 1.1 uses per month, compared to 5.6 uses per month with placebo.

15 REFERENCES

1. Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, et al. Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate. *Am J Obstet Gynecol.* 2010;203:131.e1-7.
2. Fox J, Vegh AB, Martinez-Saguer I, et al. Safety of a C1-inhibitor concentrate in pregnant women with hereditary angioedema. *Allergy Asthma Proc*. 2017;38(3):216-221.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HAEGARDA is supplied in a kit containing a lyophilized powder in a single-use vial.

HAEGARDA is packaged with Sterile Water for Injection, USP (4 mL for reconstitution of 2000 IU or 6 mL for reconstitution of 3000 IU) and one Mix2Vial filter transfer set. Not made with natural rubber latex.

Nominal Strength	Fill Size Color Indicator	Kit NDC
2000 IU	Fuschia	63833-828-02
3000 IU	Yellow	63833-829-02

Storage and Handling

- When stored at temperatures up to 30°C (86°F), 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.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Product Information).

All risks and benefits of HAEGARDA should be discussed with the patient/caregiver before prescribing or administering it to the patient.

Inform patients/caregivers to immediately report the following to their physician:

- Signs and symptoms of allergic hypersensitivity reactions, such as hives, tightness of the chest, difficulty breathing, wheezing, hypotension and/or anaphylaxis experienced during or after injection of HAEGARDA *[see Warnings and Precautions (5.1)]*.

- Signs and symptoms of a thromboembolic event, including 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 *[see Warnings and Precautions (5.2)]*.

Inform all patients/caregivers:

- HAEGARDA is indicated for HAE prophylaxis and should not be used for the treatment of acute HAE attacks. Patients/caregivers should be counselled regarding the appropriate course of action if breakthrough HAE attacks occur while on HAEGARDA, including:
  - Individualized rescue treatment for acute HAE attacks.
  - Situations in which to seek immediate medical attention, such as acute laryngeal HAE attacks.
- Patients/caregivers must ensure an adequate supply of HAEGARDA when traveling.
- Because HAEGARDA is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent *[see Warnings and Precautions (5.3) and Description (11)]*. Inform patients of the risks and benefits of HAEGARDA before prescribing or administering it to the patient.
- Patients with known risk factors for thromboembolic events are at an increased risk for these events *[see Warnings and Precautions (5.2)]*.
- Ensure that the patient/caregiver has access to and has received training in the administration of subcutaneous epinephrine and/or other appropriate supportive therapy for the treatment of any acute anaphylactic or severe hypersensitivity reaction *[see Warnings and Precautions (5.1)]*.

Advise female patients:

- Patients should notify their physician if they become pregnant or intend to become pregnant while taking HAEGARDA *[see Use in Specific Populations (8.1)]*.
- Patients should notify their physician if they are breastfeeding or plan to breastfeed while taking HAEGARDA *[see Use in Specific Populations (8.2)]*.

Self-administration - Ensure that the patient/caregiver receives clear instructions and training on S.C. administration in the home or other appropriate setting and has demonstrated the ability to perform S.C. injection.

- The patient (or caregiver) has the necessary dexterity and comprehension to be trained to self-administer.
- Instruct patients/caregivers to record the lot number from the HAEGARDA vial label every time they use HAEGARDA.

The attached HAEGARDA “Patient Product Information (PPI)” contains more detailed instructions for patients/caregivers who will be self-administering HAEGARDA.

FDA-Approved Patient Labeling – Patient Product Information (PPI)

HAEGARDA (*hay-GAR-duh*)
C1 Esterase Inhibitor Subcutaneous (Human)
Freeze-Dried Powder for Reconstitution

This leaflet summarizes important information about HAEGARDA. Please read it carefully before using HAEGARDA and each time you get a refill. There may be new information provided. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about HAEGARDA. If you have any questions after reading this, ask your healthcare provider.

Do not attempt to self-administer unless you have been taught how by your healthcare provider.

What is HAEGARDA?

HAEGARDA is an injectable medicine used to prevent swelling and/or painful attacks in adults and adolescents with Hereditary Angioedema (HAE). 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.

HAEGARDA should not be used to treat an acute HAE attack. In case of an acute HAE attack, initiate individualized treatment as discussed with your prescribing health care professional.

Who should not use HAEGARDA?

You should not use HAEGARDA if you have experienced life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product.

What should I tell my healthcare provider before using HAEGARDA?

Tell your healthcare provider about all of your medical conditions, including if you:

- Are pregnant or planning to become pregnant. It is not known if HAEGARDA can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if HAEGARDA passes into your milk and if it can harm your baby.
- 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 provider 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 things may increase your risk of having a blood clot after using HAEGARDA. Also, tell your healthcare provider 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 provider and pharmacist about all of the medicines you take, including all prescription and non-prescription medicines such as over-the-counter medicines, supplements, or herbal remedies.

What are the possible side effects of HAEGARDA?

Allergic reactions may occur with HAEGARDA. Call your healthcare provider or seek emergency support services 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

Because HAEGARDA is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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.

These are not all the possible side effects of HAEGARDA.

Tell your healthcare provider about any side effect that bothers you or that does not go away. You can also report side effects to the FDA at 1-800-FDA-1088.

How should I store HAEGARDA?

- Keep the non-reconstituted HAEGARDA in its original carton to protect from light until ready to use.

- When stored at temperatures of 2-30°C (36-86°F), HAEGARDA is stable for the period indicated by the expiration date on the carton and vial label.
- Do not freeze.

What else should I know about HAEGARDA?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use HAEGARDA for a condition for which it is not prescribed. Do not share HAEGARDA with other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about HAEGARDA. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about HAEGARDA that was written for healthcare professionals. For more information, go to www.HAEGARDA.com or call 1-877-236-4423.

What should I know about self-administration?

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

Instructions for Use

- **Do not attempt to self-administer unless you have been taught how by your healthcare provider.**
- **See the step-by-step instructions for injecting HAEGARDA at the end of this leaflet.** You should always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using HAEGARDA. If you are unsure of the steps, please contact your healthcare provider or pharmacist before using.
- Your healthcare provider will prescribe the dose that you should administer, which is based on your body weight.
- Call your healthcare provider if you miss a dose of HAEGARDA.
- Talk to your healthcare provider before traveling to make sure you have an adequate supply of HAEGARDA**.**
- Use a new needle for each HAEGARDA injection. **Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.**

Reconstitution and Administration

- The 2000 IU HAEGARDA vial contains C1-INH as a lyophilized concentrate for reconstitution with 4 mL of Sterile Water for Injection, USP provided; or, the 3000 IU HAEGARDA vial contains C1-INH as a lyophilized concentrate for reconstitution with 6 mL of Sterile Water for Injection, USP provided.
- Check the expiration date on the product vial label. Do not use beyond the expiration date.
- Work on a clean surface and wash hands before performing the following procedures.

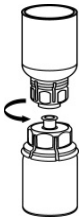
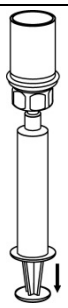
- Use either the Mix2Vial transfer set provided with HAEGARDA or a commercially available double-ended needle and vented filter spike.
- Prepare and administer using aseptic techniques.
- Each vial of HAEGARDA is for single-use only. Promptly use the reconstituted solution. The solution must be used within 8 hours. Discard partially used vials. HAEGARDA contains no preservative.
- After reconstitution and prior to administration inspect HAEGARDA. The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.

Reconstitution

The procedures below are provided as general guidelines for the reconstitution of HAEGARDA.

Table 1. HAEGARDA Reconstitution Instructions

1. Ensure that the HAEGARDA vial and Sterile Water for Injection (diluent) vial are at room temperature.	
2. Place the HAEGARDA vial, diluent vial and Mix2Vial transfer set on a flat surface.	
3. Remove flip caps from the HAEGARDA and diluent vials.	
4. Wipe the stoppers with an alcohol swab and allow to dry prior to opening the Mix2Vial transfer set package.	
5. Open the Mix2Vial transfer set package by peeling away the lid (Figure 1). Do not remove the device from the package.	 Figure 1
6. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial (Figure 2).	 Figure 2
7. Carefully remove the clear package from the Mix2Vial transfer set. Do not remove the Mix2Vial transfer set or touch the exposed end of the device (Figure 3).	 Figure 3
8. With the HAEGARDA vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the HAEGARDA vial (Figure 4). The diluent will automatically transfer into the HAEGARDA vial.	 Figure 4

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 (Figure 5). Do not shake the vial.	 Figure 5
10. With one hand, grasp the HAEGARDA side of the Mix2Vial transfer set and with the other hand grasp the blue diluent side of the Mix2Vial transfer set, and unscrew the set into two pieces (Figure 6).	 Figure 6
11. Draw air into an empty, sterile syringe. Use a silicone-free syringe. While the HAEGARDA vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the HAEGARDA vial.	
12. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Figure 7).	 Figure 7
13. Disconnect the filled syringe by unscrewing it from the Mix2Vial transfer set (Figure 8). The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if particles or discoloration is observed.	 Figure 8
14. Use immediately or within 8 hours of reconstitution. Store reconstituted solution at room temperature. Do not refrigerate.	
15. If the dose requires more than one vial, use a separate, unused Mix2Vial transfer set and diluent vial for each product vial. Repeat steps 10-12 to pool the contents of the vials into one syringe.	

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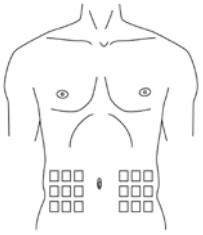
Self-Administration (subcutaneous administration)

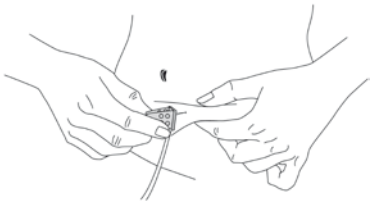
Your healthcare provider will teach you how to safely administer HAEGARDA. Once you learn how to self-administer, follow the instructions provided below.

Table 2. HAEGARDA Self-Administration Instructions

Step 1: Assemble supplies Gather the HAEGARDA syringe, the following disposable supplies (not provided with HAEGARDA), and other items (sharps or other container, treatment diary or log book): • Hypodermic needle or S.C. infusion set • Sterile syringe (Use a silicone-free syringe) • Alcohol wipes • Gloves (if recommended by your healthcare provider)	
Step 2: Clean surface • Thoroughly clean a table or other flat surface using alcohol 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.	
Step 4: Prepare injection site • Select an area on your abdomen (stomach) or another site for the injection as discussed with your doctor (Figure 9). • Use a different place from your last injection; you should rotate the places where you are injecting. • New injection sites should be at least 2 inches (5 centimeters) away from the place where you gave yourself an injection before. • 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 10).	 Figure 9  Figure 10

<table>
<tr><td>Step 5: Injection in the abdominal area
As instructed by your healthcare provider:
• Attach a hypodermic needle or S.C. infusion set (butterfly) as instructed by your healthcare provider. Prime the needle or tubing as required and instructed.

Injection with Hypodermic Needle:
• Insert the needle into the fold of skin (Figure 11).

Injection by S.C Infusion Set:
• Insert the needle into the fold of skin (Figure 12).</td><td> 
Figure 11
 
Figure 12</td></tr>
<tr><td>Step 6: Clean up
• After injecting the entire amount of HAEGARDA, remove the needle.
• Discard any unused solution and all administration equipment in an appropriate manner as per local requirements.</td><td></td></tr>
<tr><td>Step 7: 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.</td><td></td></tr>
</table>

Resources at CSL Behring available to the patient:
For Adverse Reaction Reporting contact:
CSL Behring Pharmacovigilance Department at 1-866-915-6958

Contact CSL Behring to receive more product information:
Customer Support 1-800-683-1288

For more information, visit www.HAEGARDA.com.

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