SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Haegarda 2000 IU

Haegarda 3000 IU

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: human C1-esterase inhibitor (from human plasma)

Haegarda 2000 IU:

Haegarda 2000 IU contains 2000 IU per injection vial.

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

Haegarda 2000 IU contains 500 IU/ml human C1-esterase inhibitor after reconstitution with 4 ml water for injections.

The total protein content of the reconstituted solution is 65 mg/ml.

Haegarda 3000 IU:

Haegarda 3000 IU contains 3000 IU per injection vial.

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

Haegarda 3000 IU contains 500 IU/ml human C1-esterase inhibitor after reconstitution with 5.6 ml water for injections.

The total protein content of the reconstituted solution is 65 mg/ml.

Excipients with known effect:
Sodium up to 486 mg (approximately 21 mmol) per 100 ml solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Haegarda 2000 IU:
Powder and solvent for solution for injection.

White Powder.
Clear, colourless solvent.

Haegarda 3000 IU:
Powder and solvent for solution for injection.
White Powder.
Clear, colourless solvent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Haegarda for subcutaneous injection is indicated for prevention of recurrent Hereditary Angioedema (HAE) attacks in adolescent and adult patients with C1-esterase inhibitor deficiency.

4.2 Posology and method of administration

Haegarda is intended for self-administration by subcutaneous injection. The patient or care giver should be trained on how to administer Haegarda as needed.

Posology
The recommended dose of Haegarda s.c. is 60 IU/kg body weight twice weekly (every 3-4 days).

At the doctor's discretion, an alternative dose of 40 IU/kg body weight twice weekly (every 3-4 days) may be given.

Paediatric population
Posology in adolescents is the same as in adults.
Haegarda is not indicated in children under the age of 12 years.

Method of administration
Subcutaneous injection only

For instructions on reconstitution of the medicinal product before administration see section 6.6.

The suggested site for the subcutaneous injection of Haegarda is the abdominal area. In the clinical trials, Haegarda was injected into a single site.

The reconstituted preparation should be administered by subcutaneous injection at a rate tolerated by the patient.

4.3 Contraindications

Individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

In case of an acute HAE attack, individualised treatment should be initiated.

Thromboembolic events (TEE)
Thrombosis has occurred in treatment attempts with high doses of C1-INH i.v. for prophylaxis or therapy of capillary leak syndrome before, during or after cardiac surgery under extracorporeal circulation (unlicensed indication and dose).
At the recommended s.c. 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. 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.

Haegarda 2000 IU contains less than 1 mmol sodium (23mg) per vial, that is to say essentially ‘sodium-free’.

Haegarda 3000 IU contains up to 29 mg sodium per vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data that suggest no increased risk from the use of human C1-esterase inhibitor products in pregnant women. Human C1-esterase 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.

In three studies, which included 344 patients, data from 36 women (50 pregnancies) were collected and no adverse events were associated with C1-INH treatment before, during, or after pregnancy and women delivered healthy babies.

Breastfeeding
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.

Fertility
Human C1-esterase inhibitor is a physiological component of human plasma. No studies on reproduction and developmental toxicity have been performed with Haegarda in animals.

4.7 Effects on ability to drive and use machines

Haegarda has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions were collected from Study 3001, the pivotal phase 3 study in patients (n= 86) with HAE who received Haegarda subcutaneously. Eligible patients were also able to participate in an open-label extension study (Study 3002) for up to 140 weeks (n= 126).
The frequency of adverse reactions is based on events related to Haegarda. It is estimated on a per-patient basis and categorised as: Very common (≥1/10), Common (≥1/100 to <1/10),
Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000)

MedDRA System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Nasopharyngitis	Very common
Immune system disorders	Hypersensitivity (Hypersensitivity, Pruritus, Rash, and Urticaria)	Common

Nervous system disorders	Dizziness	Common
General disorders and administration site conditions	Injection site reactions[a]	Very common
[a]Injection site bruising, Injection site coldness, Injection site discharge, Injection site erythema, Injection site haematoma, Injection site haemorrhage, Injection site induration, Injection site oedema, Injection site pain, Injection site pruritus, Injection site rash, Injection site reaction, Injection site scar, Injection site swelling, Injection site urticaria, Injection site warmth.		

Paediatric population
The safety profile of Haegarda was evaluated in a subgroup of eleven patients, 8 to <17 years of age, in both studies (Study 3001, Study 3002) and was consistent with overall safety results.

Other special populations

Elderly population
The safety profile of Haegarda was evaluated in a subgroup of ten patients, 65 to 72 years of age, in both studies (Study 3001, Study 3002) and was consistent with overall safety results.

For safety with respect to transmissible agents, see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

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 and were well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, Drugs used in hereditary angioedema: C1-inhibitor, plasma derived
ATC code: B06AC01

C1-esterase inhibitor is a plasma glycoprotein with a molecular weight of 105 kD and a carbohydrate moiety of 40 %. Its concentration in human plasma ranges around 240 mg/l. Besides its occurrence in human plasma, also the placenta, the liver cells, monocytes and platelets contain C1-esterase inhibitor.

C1-esterase inhibitor belongs to the serine-protease-inhibitor-(serpin)-system of human plasma as do also other proteins like antithrombin III, alpha-2-antiplasmin, alpha-1-antitrypsin and others.

Mechanism of action

Under physiological conditions C1-esterase inhibitor blocks the classical pathway of the complement system by inactivating the enzymatic active components C1s and C1r. The active enzyme forms a complex with the inhibitor in a stoichiometry of 1:1.

Furthermore, C1-esterase inhibitor represents the most important inhibitor of the contact activation of coagulation by inhibiting factor XIIa and its fragments. In addition, it serves, besides alpha-2-macroglobulin, as the main inhibitor of plasma kallikrein.

The therapeutic effect of Haegarda in hereditary angioedema is induced by the substitution of the deficient C1-esterase inhibitor activity.

Clinical efficacy and safety

The efficacy and safety of Haegarda for routine prophylaxis to prevent HAE attacks were demonstrated in a multicentre, randomised, double-blind, placebo-controlled, crossover study (Study 3001). 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 randomised 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. Eligible patients were also able to participate in an open-label extension study for up to 140 weeks (Study 3002). Approximately half of the subjects enrolled in the extension study participated in Study 3001 (64/126, 50.8%), which contributed to the similarities between study populations.

Study 3001:

Twice per week S.C. doses of 60 IU/kg or 40 IU/kg Haegarda resulted in a significant difference in the time-normalised number of HAE attacks (the rate of attacks) relative to placebo (Table 1). The time-normalised 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-normalised 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 1. Time-normalised Number of HAE Attacks (Number/Month)

	60 IU/kg Treatment Sequences (N = 45)		40 IU/kg Treatment Sequences (N = 45)	
	PRODUCT	**Placebo**	**PRODUCT**	**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 – Placebo**		**40 IU/kg – 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 randomised subjects; n = number of subjects with data; LS = Least squares.
* From a mixed model.

The median (25th, 75th percentile) percentage reduction in the time-normalised number of HAE attacks relative to placebo was 95% (79, 100) on 60 IU/kg 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-normalised 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.

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-normalised 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.

Study 3002:
The long-term safety and efficacy of Haegarda for routine prophylaxis to prevent HAE attacks were demonstrated in an open-label, randomized, parallel-arm study. The study assessed 126 adult and paediatric subjects with symptomatic HAE type I or II, consisting

of 64 roll-over patients from study 3001 and 62 non-rollover patients. The median (range) age of subjects was 41.0 (8-72) years.

Patients with a monthly attack rate of 4.3 in 3 months before entry in the study were enrolled and treated for a mean of 1.5 years; 44 patients (34.9%) had more than 2 years of exposure.

Mean steady-state C1-INH functional activity increased to 52.0% with 40 IU/kg and 66.6% with 60 IU/kg.

Incidence of adverse events was low and similar in both dose groups (11.3 and 8.5 events per patient-year for 40 IU/kg and 60 IU/kg, respectively).

The mean (SD) time-normalised number of HAE attacks was 0.45 (0.737) attacks per month for 40 IU and 0.45 (0.858) attacks per month for 60 IU.

The percentage of responders (95% CI) with a ≥50 % reduction in the time-normalised number of HAE attacks on Haegarda relative to the time-normalised number of HAE attacks used to qualify for participation in Study 3002 was 93.5 % (84.6 %, 97.5 %) in the 40 IU/kg treatment arm and 91.7 % (81.9 %, 96.4 %) in the 60 IU/kg treatment arm.

The percentage of subjects with a time-normalised HAE attack frequency of <1 HAE attack per 4-week period was 79.4 % for 40 IU/kg and 85.7 % for 60 IU/kg.

The percentage of HAE attack-free subjects was 34.9 % for 40 IU/kg and 44.4 % for 60 IU/kg (throughout the study duration with the maximum duration of exposure of >2.5 years).
Of 23 patients receiving 60 IU/kg for more than 2 years, 19 (83 %) were attack-free during months 25 to 30 of treatment.

The mean time-normalised number of uses of rescue medication was 0.26 (0.572) use per month for 40 IU/kg and 0.31 (0.804) uses per month for 60 IU/kg.

Paediatric population
The safety and effectiveness of Haegarda were evaluated in a subgroup of 11 patients 8 to <17 years of age, in the randomised, double-blind, placebo-controlled, crossover, routine prophylaxis trial (Study 3001) and the randomised, open-label, active treatment-controlled study (Study 3002). Results of subgroup analysis by age were consistent with overall study results.

5.2 Pharmacokinetic properties

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

Absorption

Following twice weekly subcutaneous dosing, Haegarda 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 (24, 250 hours), 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 s.c. administration of 60 IU/kg Haegarda. The mean (95% CI) relative bioavailability (F) of Haegarda after s.c. administration was estimated to be approximately 43% (35.2, 50.2%).

Distribution and Elimination
The population mean (95% CI) clearance and apparent volume of distribution of Haegarda 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 s.c. Haegarda 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 (8 to 72 years), was found not to influence the PK of C1-INH.

5.3 Preclinical safety data

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

No investigations on carcinogenicity and reproductive toxicology have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Glycine
Sodium chloride
Sodium citrate

Solvent:
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products and diluents.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After reconstitution the physico-chemical stability has been demonstrated for 48 hours at max. of 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 (25^0C). The reconstituted product should only be stored in the **vial**.

6.4 Special precautions for storage

Do not store above 30 °C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Immediate containers

Haegarda 2000 IU:
Powder (2000 IU) in a vial (Type II glass) with a stopper (bromobutyl rubber), blue seal (aluminium) and grey flip-off cap (plastic).

4 ml of solvent in a vial (Type I glass) with a stopper (chlorobutylrubber), blue seal (aluminium) and grey flip-off cap (plastic).

Haegarda 3000 IU:
Powder (3000 IU) in a vial (Type II glass) with a stopper (bromobutyl rubber), blue seal (aluminium) and lemon flip-off cap (plastic).
5.6 ml of solvent in a vial (Type I glass) with a stopper (chlorobutyl rubber), blue seal (aluminium) and lime flip-off cap (plastic).

Haegarda 2000 IU presentation:
Box containing:
1 vial with powder
1 solvent vial (4 ml)
1 filter transfer device 20/20 (Mix2Vial)

Administration set (inner box):
1 disposable syringe (5 ml)
1 hypodermic needle
1 subcutaneous injection set
2 alcohol swabs
1 plaster

Haegarda 3000 IU Presentation:

Box containing:
1 vial with powder
1 solvent vial (5.6 ml)
1 filter transfer device 20/20 (Mix2Vial)

Administration set (inner box):
1 disposable syringe (10 ml)
1 hypodermic needle
1 subcutaneous injection set
2 alcohol swabs
1 plaster

Not all pack sizes may be marketed.

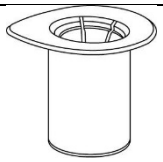
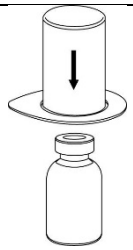
6.6 Special precautions for disposal and other handling

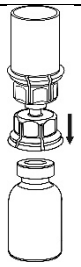
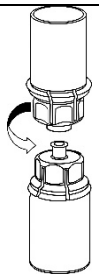
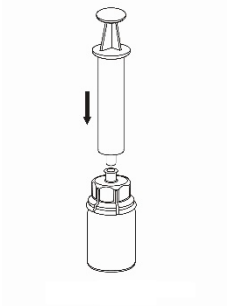
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Method of administration

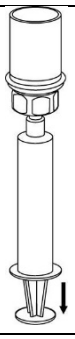
General instructions
- The reconstituted solution for Haegarda should be colourless and clear to slightly opalescent.
- After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use solutions that are cloudy or have deposits.
- Reconstitution and withdrawal must be carried out under aseptic conditions. Use the syringe provided with the product.

Reconstitution
Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	2. Place the solvent 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 solvent vial stopper.

 3	3. 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.
 4	4. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
 5	5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counterclockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
 7	7. Draw air into an empty, sterile syringe. Use the syringe provided with the product. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application

 8	8. While keeping the syringe plunger pressed, invert the system upside down and draw the solution into the syringe by pulling the plunger back slowly.

 9	9. 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 counterclockwise.

Application
The product can be administered using a hypodermic needle or a subcutaneous infusion kit.

7. MANUFACTURER

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

8. REGISTRATION HOLDER

CSL Behring Ltd.
4 Dolev st.,
Ra'anana 4366204
Israel

9. REGISTRATION NUMBERS:

Haegarda 2000 IU: 171-69-36497
Haegarda 3000 IU: 171-70-36498

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