SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

ANDEMBRY 200 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 200 mg of garadacimab* in 1.2 mL solution.

*Garadacimab is a fully human IgG4 monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

The solution is a slightly opalescent to clear, brownish-yellow to yellow liquid.

The solution has a pH of approximately 6.1 and an osmolality of approximately 470 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ANDEMBRY is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

4.2 Posology and method of administration

This medicinal product should be initiated under the supervision of a physician experienced in the management of patients with HAE.

Posology

The recommended dose in adults and adolescents aged 12 years and older is an initial loading dose of 400 mg ANDEMBRY administered subcutaneously as two 200 mg injections on the first day of treatment followed by a monthly dose of 200 mg garadacimab.

Consideration should be given to discontinuing treatment in patients who have shown insufficient reduction in attacks after 3 months of treatment, in particular in patients with normal C1-INH activity (nC1-INH) (see sections 4.4 and 5.1)

ANDEMBRY is not intended for treatment of acute HAE attacks (see section 4.4)

Missed doses

If a dose of ANDEMBRY is missed, the patient should be instructed to administer the dose as soon as possible.

Special populations

Elderly

No dose adjustment is required for patients above 65 years of age (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Renal impairment

No dose adjustment is required in patients with renal impairment (see section 5.2).

Paediatric population

The safety and efficacy of garadacimab in children less than 12 years have not been established.

No data are available.

Method of administration

ANDEMBRY is intended for subcutaneous administration only.

Each ANDEMBRY pre-filled syringe is intended for single use only (see section 6.6).

The injection should be restricted to the following injection sites: the abdomen, the thighs and the upper outer arms (see section 5.2). Rotation of the injection site is recommended.

ANDEMBRY may be self-administered or administered by a caregiver only after training on subcutaneous injection technique by a healthcare professional.

4.3 Contraindications

Hypersensitivity to the active substance 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

Hypersensivity reactions have not been observed but may theoretically occur. In case of a severe hypersensitivity reaction, discontinue ANDEMBRY administration and institute appropriate treatment.

General

ANDEMBRY is not intended for treatment of acute HAE attacks. In case of breakthrough HAE attack, individualized treatment should be initiated with an approved rescue medicinal product.

There is very limited clinical data available on the use of ANDEMBRY in HAE patients with normal C1-INH activity (see section 5.1).

Some subcategories of nC1-INH HAE may not respond to the treatment with garadacimab due to the alternative pathways involved that do not include FXII-dependent bradykinin production. It is recommended to perform genetic testing according to the current HAE guidelines, if available, and to discontinue the treatment if clinical response is not observed (see sections 4.2 and 5.1).

Interference with coagulation test

ANDEMBRY can prolong activated partial thromboplastin time (aPTT) due to an interaction of garadacimab with the aPTT assay. The extent of aPTT prolongation could be variable depending on drug exposure as well as additional parameters, such as natural variation in FXII levels, and other coagulation factors. The reagents used in the aPTT laboratory test initiate intrinsic coagulation through the activation of FXII in the contact system, therefore inhibition of plasma FXIIa by ANDEMBRY can prolong aPTT in this assay. None of the increases in aPTT in patients treated with ANDEMBRY were associated with abnormal bleeding adverse events. There were no relevant differences in international normalized ratio (INR) between treatment groups.

Garadacimab has not been studied in patients with clinically significant bleeding due to coagulopathy.

There is very limited clinical data on the use of concomitant antiplatelet/anticoagulant medication with garadacimab. Garadacimab inhibits the activity of activated FXII. FXII activation initiates the intrinsic pathway of the coagulation cascade. The impact on the concomitant use of anticoagulants which inhibit the extrinsic pathway is unknown.

Interference with D-Dimer test

Reductions in mean D-dimer values were observed in patients treated with garadacimab, including some patients with values below the lower limit of normal. This should be taken into consideration when interpreting D-Dimer results in patients receiving garadacimab with suspected thromboembolic events.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium free”.

This medicine contains 19.3 mg of proline in each 200 mg/1.2 mL, which is equivalent to 16.1 mg/mL. Proline may be harmful for patients with hyperprolinaemia, a rare genetic disorder in which proline builds up in the body.

This medicine contains 0.24 mg of polysorbate 80 in each 200 mg/1.2 mL which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No dedicated drug-drug interaction studies have been conducted in humans. Garadacimab has only been studied as a monotherapy and not in combination with other products indicated for long-term prophylaxis of HAE.

Based on population pharmacokinetic analyses, the use of analgesic, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic medications had no effect on the PK of garadacimab. For breakthrough HAE attacks, use of rescue medications such as plasma-derived and recombinant C1-INH or icatibant had no effect on the PK of garadacimab.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data (less than 300 pregnancy outcomes) from the use of garadacimab in pregnant women. A pre- and postnatal development study conducted in pregnant rabbits revealed no evidence of harm to the developing fetus. The study was conducted at subcutaneous doses resulting in exposures of approximately 53 times the exposure achieved (on an AUC basis) at the recommended human dose revealed no evidence of harm to the developing fetus (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of garadacimab during pregnancy.

Breast-feeding

It is unknown whether garadacimab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, and decrease to low concentrations soon afterwards. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANDEMBRY and any potential adverse effects on the breastfed infant from ANDEMBRY or the underlying condition.

Fertility

Effect on fertility has not been evaluated in humans. Garadacimab had no effect on male or female fertility in rabbits (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

In the VANGUARD pivotal trial which included 39 subjects with HAE who received at least 1 dose of garadacimab, the most commonly (5.1%) observed adverse reactions were injection site reactions (ISR) including injection site erythema, injection site bruising, and injection site pruritus.

Tabulated list of adverse reactions

Adverse reactions reported in the clinical trial are listed below in Table 1. The adverse reactions are listed by MedDRA System Organ Class and categories of frequency. Frequencies are defined 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), not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	**Adverse drug reaction**	**Frequency**
General disorders and administration site conditions	Injection site reaction*	Common
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Abdominal pain	Common

*Injection site reactions include erythema, bruising, pruritus and injection site urticaria

Paediatric population

The safety of ANDEMBRY was evaluated in a subgroup of 11 adolescent patients aged 12 to < 18 years old. The safety profile was similar to that observed in adults.

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. Healthcare professionals are asked to report any suspected adverse reactions via the UK Yellow Card Scheme. Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no available information to identify potential signs and symptoms of overdose.

If symptoms should occur, symptomatic treatment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in hereditary angioedema, ATC code: B06AC07

Mechanism of action

Garadacimab is a fully human IgG4/lambda recombinant monoclonal antibody which binds to the catalytic domain of activated Factor XII (FXIIa and βFXIIa) and inhibits its catalytic activity. The inhibition of FXIIa prevents HAE attacks by blocking the cascade of events in the kallikrein (contact) pathway, including the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks.

Clinical efficacy and safety

VANGUARD pivotal study

The efficacy and safety of garadacimab for the prevention of hereditary angioedema attacks in patients 12 years of age and older with Type I or II HAE were evaluated in a phase 3, multicenter, randomized, double-blind, placebo-controlled parallel group study.

The study included 58 adult and 6 adolescent patients (12 years of age and older) who experienced at least 2 attacks during the up to 2-month run-in period. Patients were randomized into 2 parallel treatment arms in a 3:2 ratio (garadacimab 200 mg monthly after an initial 400 mg loading dose or volume-match placebo) for a 6-month treatment period. Adult patients were required to discontinue other prophylactic HAE treatment prior to entering the study. Adolescent patients using long term prophylactic therapy prior to screening were excluded from the study. All patients were allowed to use on-demand medications for treatment of HAE attacks during the study.

Of the 6 adolescent patients included in the study, 4 received garadacimab and 2 received placebo.

Overall, 87.5% of patients had Type I HAE. A family history of HAE was reported for 89.1%, a history of laryngeal edema attacks for 59.4% of patients and 32.8% were on prior prophylactic HAE treatment. During the study run-in period, attack rates of ≥3 attacks/month were observed in 59.4% of patients overall. Baseline number of attacks per month was 3.07 in the garadacimab group compared to 2.52 in the placebo group.

The primary efficacy endpoint was the time-normalised number of HAE attacks from day 0 through the end of the 6-month treatment period. The key secondary endpoints were: the percent reduction in the mean time normalised number of HAE attacks, the number of subjects who were attack free from day 0 through the end of the first 3-months and the percentage of subjects with good or excellent responses to the SGART from day 0 through the end of the 6-month treatment period.

A statistically significant difference was observed when compared to placebo across the primary and key secondary endpoints included in the hierarchical testing procedure in the Intent-to-Treat (ITT) population as seen in **Table 2.**

Table 2: Results of the primary and secondary efficacy measures (ITT analysis set)

	Garadacimab 200 mg (N = 39)	**Placebo (N = 25)**
Number of evaluable patients, n	39	24[a]
Number of HAE Attacks during Treatment Period	63	264
Primary endpoint – Time-normalized number of HAE attacks per month during treatment period from Day 1 to 182		
Mean (SD)	0.27 (0.683)	2.01 (1.341)
95% CI	0.05, 0.49	1.44, 2.57
Median (IQR)	0.00 (0.0 to 0.31)	1.35 (1.00 to 3.20)
p-value*	< 0.001	
Adjusted LS mean[b] (95% CI)	0.22 (0.11 to 0.47)	2.07 (1.49 to 2.87)
Secondary endpoint - Percent reduction in time-normalized number of HAE attacks per month relative to placebo		
Mean (95% CI)	86.5 (57.9, 95.7)	
Median	100	
p-value*	< 0.001	
Adjusted LS mean[b] (95% CI)	89.2 (75.59, 95.23)	
Secondary endpoint – Number of attack free subjects through Day 91	71.79 (28)	8.33 (2)
P-value*	< 0.001	
Secondary endpoint[c] - Percentage of subjects rating therapy as 'good' or 'excellent' through the SGART at Day 182	82 (31)	33 (8)

P-value*	< 0.001

CI = confidence interval; HAE = hereditary angioedema; ITT = intention-to-treat; N = number of patients in the

ITT Analysis Set; IQR = Interquartile Range; SD = standard deviation; LS = least squares

[a] One patient had a Treatment Period of less than 30 Days and was therefore not included in the analysis

[b] After adjusting for baseline attack rate

[c] The overall response to treatment with the investigational product was self-assessed by the patient using the Subject's Global Assessment of Response to Therapy (SGART). Possible responses are 'none, 'poor', 'fair', 'good' or 'excellent'

* A hierarchical testing procedure controls for the overall alpha level of 5% (2-sided)

Descriptive results of the additional secondary endpoints; the number of HAE attacks requiring on-demand treatment and the number of moderate/severe HAE attacks are provided in **Table 3**.

Table 3: Results of Secondary efficacy measures (ITT analysis set)

	Garadacimab 200 mg (N = 39)	**Placebo (N = 25)**
Number of evaluable patients, n	39	24[a]
Number of HAE Attacks during Treatment Period	63	264
Secondary endpoint – Time-normalized number of HAE attacks requiring on-demand treatment per month from Day 1 to 182		
Mean (SD)	0.23 (0.663)	1.86 (1.412)
Median (Min, Max)	0.00 (0.0, 3.8)	1.35 (0.0, 4.4)
Secondary endpoint – Time-normalized number of moderate[b] or severe[c] HAE attacks from Day 1 to 182		
Mean (SD)	0.13 (0.296)	1.35 (1.166)
Median (Min, Max)	0.00 (0.0, 1.2)	0.83 (0.0, 4.4)

HAE = hereditary angioedema; ITT = intention-to-treat; N = number of patients in the ITT Analysis Set;

SD = standard deviation; Max = maximum; Min = minimum.

[a] One patient had a Treatment Period of less than 30 Days and was therefore not included in the analysis

[b] Causes daily activities to be limited, use of on-demand medication is probable

[c] Causes marked limitation of daily activities, on-demand medication is used

Health related quality of life

Angioedema Quality of Life Questionnaire (AE-QoL) total and domain (functioning, fatigue/mood, fear/shame, and nutrition) scores, compared to the placebo at day 182 was an exploratory endpoint **(Table 4)**. A reduction of six points in the AE-QoL has been defined as the minimal clinically important difference (MCID). Changes from baseline greater than the MCID were observed in 88% of patients treated with garadacimab.

Table 4: AE-QoL total score and domains change from baseline to day 182 (ITT Analysis Set)[a]

AE-QoL total score and domains change from baseline to day 182[b], mean (SD)	**ANDEMBRY 200mg (N=39)**	**Placebo (N=25)**
Patients Included in the Analysis, n	33	20
Total Score	-26.5 (17.9)	-2.2 (19.1)
Functioning	-35.8 (23.2)	1.9 (29.6)
Fatigue/Mood	-21.1 (22.9)	-5.8 (27.1)
Fears/Shame	-28.0 (24.1)	-2.5 (18.6)
Nutrition:	-16.7 (23.3)	-0.6 (16.5)

CI = confidence interval; HAE = hereditary angioedema; ITT = intention-to-treat; Max = maximum;

Min = minimum; N = number of patients in the ITT Analysis Set; SD = standard deviation.

[a] Angioedema Quality of Life is only answered by patients of age ≥ 18 years.

[b] A lower AE-QoL score represents greater improvement

The safety and efficacy profile in paediatric patients 12 years of age and older was consistent with that

of the overall population.

VANGUARD Open Label Extension Study

Patients who completed VANGUARD (n=57) in addition to patients from a phase 2 study (n=35) rolled over into the VANGUARD open-label extension study which also enrolled 69 new patients. From the start of treatment through 21.1 months (median duration of exposure 13.8 months) 96/161 (59.6%) patients remained attack-free. The safety and efficacy profile in adolescent patients ages 12 years and older (n=10) was consistent with that of the overall population.

Normal C1-INH HAE population

Normal C1-INH HAE includes patients with known or unknown mutations. The safety and efficacy of garadacimab was evaluated in 6 patients with known mutations: HAE-FXII (n=3) or HAE-PLG (n=3) in the phase 2 study 2001.

Among the three genetically confirmed HAE-FXII patients enrolled, one withdrew during the second month of the treatment period due to lack of efficacy after showing a reduction in overall attack rate from 4.35 to 3.51 attacks per month and a reduction in severe attacks from 1.09 to 0.58 attacks per month. The remaining two patients completed the initial 12-week treatment period, with one demonstrating a reduction in attack rate from 3.24 to 0.36 attacks per month and the other becoming attack-free from an initial attack rate of 3.20 attacks per month. The response to garadacimab was maintained in both patients during the second treatment period and after rolling over from the phase 2 to the phase 3 Study for an additional 18 months.

The 3 patients with HAE-PLG completed the initial 12-week treatment period and did not continue into the treatment extension period. One patient reported a decrease in their monthly overall attack rate to 1.75 and a severe attack rate to 0.35 during the treatment period, compared to 3.20 and 1.60, respectively, during the run-in period. The remaining two patients reported an increase in their monthly attack rates to 6.8 and 3.17 during the treatment period compared to 2.28 and 1.45 during the run-in period respectively. None of the reported attacks was classified as severe attack.

Overall, the safety profile of garadacimab in patients with nC1-INH was similar to that observed in patients with HAE-C1-INH.

Immunogenicity

Treatment with ANDEMBRY has been associated with development of low-titer treatment emergent anti-drug antibodies (ADA) in 2.9% of treated subjects. The development of ADA against ANDEMBRY did not affect pharmacokinetics (PK), pharmacodynamics (PD), safety or clinical response.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with ANDEMBRY in one or more subsets of the paediatric population in the prevention of hereditary angioedema attacks (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Multiple dose pharmacokinetics of garadacimab have been studied in patients with HAE. In the *VANGUARD pivotal trial*, patients treated with 200 mg garadacimab SC once monthly presented mean (SD) area under the curve over the dosing interval at

steady-state ($AUC_{tau,ss}$), maximum concentration at steady-state ($C_{max,ss}$), and minimum concentration at steady-state ($C_{min,ss}$) of 10300 (3380) μg·h/mL, 21.2 (6.58) μg/mL, and 9.30 (3.73) μg/mL, respectively. Steady-state exposure of garadacimab was achieved after the initial subcutaneous administration of loading dose of 400 mg (2 doses of 200 mg).

Absorption

Following SC administration, the time to maximum concentration is approximately 6 days. The site of SC injection (thigh, arm, or abdomen) did not affect the absorption of garadacimab.

The mean absolute bioavailability of garadacimab in HAE patients was 39.5% on the basis of the population pharmacokinetic analysis.

Distribution

The mean (SD) apparent volume of distribution of garadacimab in patients with HAE is 7.42 litres (4.20). Garadacimab is a monoclonal antibody and is not expected to bind to plasma proteins.

Elimination

Garadacimab has a mean (SD) apparent clearance of 0.0217 L/h (0.00793) and a terminal elimination half-life of approximately 19 days.

Metabolism

Similar to other monoclonal antibodies, garadacimab is expected to be degraded by enzymatic proteolysis into small peptides and amino acids. Therefore, specific metabolism studies were not conducted with garadacimab.

Special populations

No dedicated studies have been conducted to evaluate the pharmacokinetics of garadacimab in special patient populations including gender, age, pregnant women or the presence of renal or hepatic impairment.

In a population pharmacokinetic analysis, after correcting for body weight (43.3 to 153 kg), no influence of gender, age (12 to 73 years), race or ethnicity was apparent on clearance or volume of distribution of garadacimab.

Based on population pharmacokinetic analyses that included adolescent patients (age range: 12 to 17 years, N=11) who received the same dose (200 mg of garadacimab once monthly) as adults, the mean garadacimab C_{max} and AUC_{tau} at steady state are predicted to be 1.3- and 1.4-fold greater, respectively, in adolescents relative to adults, likely due to lower body weight in adolescent patients.

Although body weight was identified as an important covariate describing the variability of clearance and volume of distribution, the difference is not clinically relevant and no dose adjustments are recommended.

Renal and Hepatic Impairment

As IgG monoclonal antibodies are mainly eliminated via intracellular catabolism, renal impairment or hepatic impairment is not expected to influence clearance of garadacimab.

Accordingly, in a population pharmacokinetic analysis, renal impairment (estimated glomerular filtration rate: ≥90 mL/min/1.73m^2 [normal, N=145], 60 to <90 mL/min/1.73m^2 [mild, N=26], and 30 to <60 mL/min/1.73m^2 [moderate, N=2]) had no effect on the PK of garadacimab.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of general toxicity and toxicity to reproduction. No genotoxicity or carcinogenicity studies were conducted as garadacimab is unlikely to interact directly with DNA or other chromosomal material. In rabbits, male and female fertility was unaffected and in pregnant rabbits, maternal dosing with garadacimab had no effects on embryofetal development or on postnatal development, survival, growth, neurobehavioural or reproductive performances of offspring. In rabbits receiving subcutaneous garadacimab, exposure was ~53-fold the exposure (based on AUC) in humans at the recommended human dose of 200 mg subcutaneously once monthly.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine

L-arginine monohydrochloride

L-proline

Polysorbate 80

Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

ANDEMBRY may be stored at room temperature (up to 25 °C) for a single period of up to 2 months, but not beyond the expiry date.

6.4 Special precautions for storage

Store in a refrigerator (2□C - 8□C).

Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

Do not return ANDEMBRY to refrigerated storage after storage at room temperature (up to 25□C).

Do not use beyond the expiry date.

6.5 Nature and contents of container

Each ANDEMBRY 200mg pre filled syringe contains 1.2 mL of solution in a pre-filled glass syringe (type I glass) with a bromobutyl stopper, 27G x 1/2 5B special thin-walled (STW) staked needle, and is assembled with an extended finger flange and needle safety device. ANDEMBRY is available as unit packs containing 1 assembled pre-filled syringe and in multipacks containing 3 (3 packs of 1) assembled pre-filled syringes.

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal

Before use, ANDEMBRY should be visually inspected for appearance by gentle inversion. The solution should be slightly opalescent to clear, brownish-yellow to yellow. Solutions that are discolured or contain particles should not be used.

Do not shake.

Administration steps

After removing the pre-filled syringe with needle safety device from the refrigerator, wait 30 minutes before injecting to allow the solution to reach room temperature. Inject ANDEMBRY subcutaneously into the abdomen, thigh or upper arm (see section 4.2).

Each pre-filled syringe with needle safety device is for single use only. Discard the pre-filled syringe with needle safety device after injection is completed in a sharps container or closed puncture resistant container.

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

The instructions for use are provided within the Patient Information Leaflet.

7 MARKETING AUTHORISATION HOLDER

CSL Behring GmbH

Emil-von-Behring-Strasse 76

D-35041 Marburg

Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15036/0161

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/01/2025

10 DATE OF REVISION OF THE TEXT

24/01/2025