1. NAME OF THE MEDICINAL PRODUCT

ANDEMBRY 200 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen 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.

Excipients with known effect

Each pre-filled pen contains 19.3 mg of proline and 0.24 mg of polysorbate 80.

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 healthcare professional experienced in the management of patients with HAE.

Posology

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

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

ANDEMBRY is not intended for the 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).

Renal and hepatic impairment

No dose adjustment is required in patients with renal or hepatic 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 use only.

Each ANDEMBRY unit (pre-filled pen) 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

Hypersensitivity reactions have not been observed but may theoretically occur. In case of severe hypersensitivity reactions, administration of garadacimab should be discontinued, and appropriate treatment instituted.

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 are limited data available on the use of garadacimab in HAE patients with nC1-INH (see section 5.1).

Some subcategories of nC1-INH HAE may not respond to treatment with garadacimab due to alternative pathways that do not include FXII activation. It is recommended to perform genetic

testing, if available, according to the current HAE guidelines 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.

Excipients

This medicinal product contains 19.3 mg of proline in each pre-filled pen 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 medicinal product contains 0.24 mg of polysorbate 80 in each pre-filled pen 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. 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 amount of data from the use of garadacimab in pregnant women. Monoclonal antibodies such as garadacimab are transported across the placenta mainly during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. A pre- and postnatal development study conducted in pregnant rabbits 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. Consequently, transfer of IgG antibodies to the newborns through milk may happen during the first few days. In this short period, a risk to the breast-fed child cannot be excluded. Afterwards, garadacimab could be used during breast-feeding if clinically needed.

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

The most commonly observed adverse reactions associated with ANDEMBRY were injection site reactions (ISR) including injection site erythema, injection site bruising, injection site pruritus and injection site urticaria, headache and abdominal pain.

Tabulated list of adverse reactions

Table 1 summarises adverse reactions observed in the *VANGUARD pivotal trial*, which included 39 subjects with HAE who received at least 1 dose of ANDEMBRY.

The frequency of adverse reactions listed in Table 1 is defined using the following convention: 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).

Table 1: Adverse drug reactions (ADRs) obtained from clinical studies with ANDEMBRY

System organ class	Adverse drug reaction	Frequency
General disorders and administration site conditions	Injection site reactions*	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 subjects aged 12 to < 18 years old. No difference from the overall safety profile was seen between adults and children.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing authorisation is extremely important. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are requested to report any suspected new or serious adverse reaction via:

- Saudi Arabia:

The National Pharmacovigilance Centre (NPC):
SFDA Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

- United Arab Emirates:

Emirates Drug Establishment
United Arab Emirates
Email: pv@ede.gov.ae
Tel: 80033784

- Other GCC states:
Please contact the relevant competent Authority

4.9 Overdose

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

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, the first factor activated in the contact system, prevents HAE attacks by blocking the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks.

Pharmacodynamic effects
Concentration-dependent inhibition of FXIIa-mediated kallikrein activity was demonstrated after subcutaneous administration of ANDEMBRY once monthly in patients with HAE.

Clinical efficacy and safety

VANGUARD pivotal study

The efficacy of ANDEMBRY for the routine prevention of recurrent attacks of hereditary angioedema in adult and adolescent patients 12 years of age and older with Type I or II HAE was studied in a phase 3, multicenter, randomised, double-blind, placebo-controlled parallel group study.

The study contained 64 patients aged 12 years and older including 58 adult and 6 pediatric patients who experienced at least 2 attacks during the up to 2-month run-in period. Patients were randomised 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. Patients were required to discontinue other prophylactic HAE treatment prior to entering the study. All patients were allowed to use on-demand medications for treatment of HAE attacks during the study.

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 treatments. During the study run-in period, attack rates of ≥ 3 attacks/month were observed in 59.4% of patients overall. Mean baseline number of attacks per month was 3.07 in the ANDEMBRY group compared to 2.52 in the placebo group.

The primary efficacy endpoint was the time-normalised number of HAE attacks from day 1 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 1 through the end of the first 3-months the percent of subjects with good or excellent responses to the SGART from day 1 through the end of the 6-month treatment period.

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

	ANDEMBRY 200 mg (N = 39)	**Placebo (N = 25)**
Number of evaluable patients, n	39	24[a]
Primary endpoint		
Total number of HAE attacks from Day 1 to 182	63	264
Time-normalised number of HAE attacks from Day 1 to 182		
Mean (95% CI)	0.27 (0.05, 0.49)	2.01 (1.44, 2.57)
P-value*	< 0.001	
Adjusted LS mean[b] (95% CI)	0.22 (0.11, 0.47)	2.07 (1.49, 2.87)
Secondary endpoints		
Percent reduction in time-normalised number of HAE attacks relative to placebo[c]		
Mean (95% CI)	86.51 (57.84, 95.68)	
P-value*	< 0.001	
Percent (number) of subjects who were attack free from day 1 through the end of month 3	71.79 (28)	8.33 (2)
P-value*	< 0.001	
Percent (number) of subjects with good or excellent response to SGART at day 182	82 (31)	33 (8)
P-value*	< 0.001	

HAE – hereditary angioedema; ITT – intent to treat; N – number of patients in the ITT analysis set; LS – least squares; CI – confidence interval; SGART – Subjects Global Assessment of Response to Therapy

[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] Median percent reduction for this endpoint was 100

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

Additional non-hierarchically tested secondary endpoints from day 1 to 182 were the mean (median) time-normalised number of HAE attacks requiring on-demand treatment, 0.23 (0.0) in subjects treated with ANDEMBRY compared to 1.86 (1.35) in the placebo group, and the mean (median) time-normalised number of moderate to severe HAE attacks, 0.13 (0.0) in subjects treated with ANDEMBRY compared to 1.35 (0.83) in the placebo group.

The exploratory endpoint of 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 **(Table 3)** showed improvement in the ANDEMBRY treated patients. 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 ANDEMBRY.

Table 3: 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 200 mg (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)

ITT = intention-to-treat; 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 efficacy profile in pediatric patients 12 years of age and older (n=6) 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 16.7 months (median duration of exposure 9.49 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 (plasminogen) (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. Both patients continued garadacimab for the duration of the second treatment period of 20 and 17 months, after which both patients rolled over into the phase 3 extension study and received garadacimab for an additional 18 months and remained attack free.

Additionally, 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% (5/172) of treated subjects. Due to the low titer of ADA registered in these subjects, neutralizing antibodies could not be detected. However, although the clinical relevance of ADA could not be fully established, available data indicate that there was no apparent impact of the presence of ADA on safety or efficacy.

Paediatric population

The European Medicines Agency 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

In the *VANGUARD pivotal trial*, patients treated with 200 mg garadacimab subcutaneous 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) mcg·h/mL, 21.2 (6.58) mcg/mL, and 9.30 (3.73) mcg/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 subcutaneous administration, the time to maximum concentration is approximately 6 days. The site of subcutaneous injection (thigh, arm, or abdomen) did not affect the absorption of garadacimab. The absorption rate of garadacimab was 0.00824/h. 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 was 7.42 litres (4.20). Garadacimab is a monoclonal antibody and is not expected to bind to plasma proteins.

Biotransformation

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.

Elimination

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

Special populations

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

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.

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

Renal and hepatic impairment

Dedicated studies on subjects with renal or hepatic impairment were not conducted.

As IgG monoclonal antibodies are mainly eliminated via intracellular catabolism, renal impairment or hepatic impairment is not expected to influence clearance of garadacimab.
Based on population pharmacokinetic analysis, hepatic impairment had no effect on the pharmacokinetics of garadacimab.

In a population pharmacokinetic analysis, renal impairment (estimated glomerular filtration rate: ≥90 mL/min [normal, N=149], 60 to <90 mL/min [mild, N=22], and 30 to <60 mL/min [moderate, N=1]) had no effect on the pharmacokinetics of garadacimab.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated-dose toxicity.

Reproductive toxicity

Male and female fertility were unaffected based upon no observed adverse findings on mating, fecundity, fertility indices, on maternal reproductive parameters, embryo survival or sperm assessment in sexually mature rabbits that received garadacimab intravenously once every three days resulting in approximately 83- and 103-fold the exposure (based on AUC) in females and males, respectively, at the recommended human dose of 200 mg subcutaneously once monthly.

In a pre- and post-natal development study, pregnant rabbits were administered garadacimab subcutaneously once every five days from implantation through weaning. There was no maternal and off-spring, through six months of age, garadacimab-related toxicity in rabbits receiving subcutaneous garadacimab resulting in approximately 53-fold the clinical exposure (based on AUC) at the recommended human dose of 200 mg subcutaneously once monthly.

Garadacimab crossed the placenta in rabbits. With subcutaneous administration of garadacimab corresponding to approximately 53-fold the clinical exposure (based on AUC) at the recommended human dose of 200 mg subcutaneously once monthly, at gestation day 29, fetal plasma concentrations were 40.8% of maternal concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Arginine monohydrochloride
Proline
Polysorbate 80 (E 433)
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 ºC – 8 ºC).

Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

Do not return ANDEMBRY to refrigerated storage after storage at room temperature.

6.5 Nature and contents of container

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. Each pre-filled syringe is assembled with a pen.

ANDEMBRY is available as unit packs containing 1 pre-filled pen and in multipacks containing 3 (3 packs of 1) assembled pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 discoloured or contain particles should not be used.

Do not shake.

<u>Administration steps</u>

After removing the pre-filled pen 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. Rotation of the injection site is recommended (see section 4.2).

Injection with the pre-filled pen may take up to 15 seconds.

Listen for the first ‘click’ (this signals the start of injection, and the yellow plunger will start to move across the window). Keep pressing and watch the yellow plunger move down to fill the window. A second ‘click’ will be heard and the viewing window will be completely yellow. Wait an extra 5 seconds to make sure the full dose was received.

Each pre-filled pen is for single use only. Discard the pre-filled pen 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.

7. MARKETING AUTHORISATION HOLDER

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

8. DATE OF REVISION OF THE TEXT

February 2025