swissmedic

Date: 4 April 2025

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Andembry

International non-proprietary name:	garadacimab
Pharmaceutical form:	Solution for injection in pre-filled pen
Dosage strength(s):	200 mg
Route(s) of administration:	subcutaneous (s.c.) injection
Marketing authorisation holder:	CSL Behring AG
Marketing authorisation no.:	69553
Decision and decision date:	approved on 24 February 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EFD	Embryo-fetal development
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HAE	Hereditary angioedema
HC	Health Canada
HPLC	High-performance liquid chromatography
HSA	Health Sciences Authority (Singapore)
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	intravenously
K_D	Dissociation constant
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
MHRA	Medicines & Healthcare products Regulatory Agency (UK)
Min	Minimum

MRHD	Maximum recommended human dose
N/A	Not applicable
NAS	New active substance
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPND	Pre- and postnatal developmental
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SwissPAR	Swiss Public Assessment Report
$T_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration (Australia)
T_{max}	Time to maximum concentration
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status

The applicant requested new active substance status for garadacimab in the above-mentioned medicinal product.

Orphan drug status

The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.

Orphan drug status was granted on 15 November 2022.

Work-sharing procedure

The applicant requested a work-sharing procedure with Australia, Canada, UK and Switzerland).

The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic - and the pharmaceutical industry.

The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Routine prevention of attacks of hereditary angioedema in adult and adolescent patients (aged 12 years and older).

2.2.2 Approved indication

ANDEMBRY is indicated for the long-term prophylaxis of recurrent acute attacks of hereditary angioedema (HAE) in adult and paediatric patients aged 12 years and older (see "Warnings and precautions" and "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:

Posology and method of administration

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

Posology

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.

No dose adjustment is required for elderly patients or patients with hepatic or renal impairment.

Missed doses

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

Method of administration

Andembry is intended for subcutaneous (SC) use only.

Each Andembry unit (pre-filled syringe with needle safety device or pre-filled pen) is intended for single use only (see section 6.6).

The injection should be restricted to the recommended 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 SC injection technique by a healthcare professional.

Requested dosage and pack size:

Unit pack containing 1 pre-filled autoinjector with 1.2 ml of solution for s.c. injection (200 mg garadacimab)

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	30 November 2023
Formal objection	06 December 2023
Response to formal objection	11 December 2023
Formal control completed	02 January 2024
List of Questions (LoQ)	15 May 2024
Response to LoQ	01 July 2024
2nd List of Questions (LoQ)	08 October 2024
Response to 2nd LoQ	23 October 2024
Preliminary decision	09 January 2025
Response to preliminary decision	26 January 2025
Final decision	24.02.2025
Decision	approval

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

4 Nonclinical aspects

The nonclinical development programme for Andembry containing the new active substance garadacimab followed relevant ICH guidelines. The pivotal safety studies were performed in compliance with GLP regulations.

4.1 Pharmacology

The pharmacodynamic *in vitro* and *in vivo* studies demonstrated that garadacimab binds specifically to the serine protease domain of activated Factor XII (FXIIa and βFXIIa) and identified mouse, rabbit, and cynomolgus monkey as relevant nonclinical species.

The affinities (K_D) of garadacimab to human, mouse, rabbit and cynomolgus monkey βFXIIa were 0.14 nM, 0.7 nM, 0.4 nM and 19 nM, respectively. Garadacimab did not bind to rat FXIIa.

In vitro, garadacimab inhibited FXIIa activities in human, cynomolgus monkey, mouse and rabbit plasma, but had no effect on other relevant human activated serine proteases (e.g. FVIIa, FIXa, FXa, FXIa). The antibody induced a prolongation of the activated partial thromboplastin time (aPTT) in plasma from human and nonclinical species. The inhibitory activity of garadacimab on FXIIa was demonstrated in plasma from healthy human donors, patients with hereditary angioedema (HAE; types I/II/III), and patients with acquired angioedema. Furthermore, garadacimab was an effective Kallikrein-Kinin System inhibitor, preventing bradykinin formation. *In vivo*, garadacimab demonstrated activity in murine models for systemic and cutaneous anaphylaxis. Following intraperitoneal administration, garadacimab effectively inhibited oedema formation in mice.

The ability to trigger effector function is known to be poor for human IgG4, therefore the risk for induction of relevant Fc-related effect functions by garadacimab (IgG4) is considered low.

In vivo secondary pharmacology studies investigated the biological activity and the potential anti-thrombotic effects of garadacimab in clinically relevant thrombotic and/or bleeding animal models. Garadacimab inhibited experimental arterial thrombosis and FXIIa without increasing bleeding risk or affecting prothrombin time in mice and rabbits. In addition, in rabbits treated intravenously (IV) with 10 mg/kg garadacimab, no changes were noted in haematological parameters, including red blood cells, white blood cells, platelet counts, haemoglobin concentration and haematocrit.

No garadacimab-related effects on the cardiovascular, central nervous and respiratory systems were observed in animals at clinically relevant doses.

4.2 Pharmacokinetics

The pharmacokinetic (PK) profile of garadacimab in male cynomolgus monkeys following subcutaneous (SC) administration revealed a dose-dependent increase in exposure based on C_{max} and AUC and showed typical monoclonal antibody behaviour with biphasic clearance curves. The time to maximum concentration (T_{max}) ranged from 3 to 4 days, while the half-life ($t_{1/2}$) ranged from 8.6 to 17.7 days, and the bioavailability was approximately 66%. Toxicokinetic data showed no sex dependency or a tendency to accumulate following repeated SC administration. The PK parameters are comparable with those in humans (i.e. T_{max} = 6 days, $t_{1/2}$ = 19 days). In addition, the PK properties of two formulations of garadacimab (100 vs 170 mg/mL) after a single SC administration to rabbits showed an adequate and similar profile compared to monkeys without sex-differences.

In accordance with ICH S6(R1), studies on metabolism or excretion were not conducted.

In rabbits, garadacimab concentrations were measured in fetal and maternal serums, demonstrating that garadacimab crosses the placenta.

Garadacimab led to the formation of ADA in mice, monkeys and rabbits. The formation of treatment-related antibodies in the nonclinical studies had no major impact on garadacimab serum concentrations, but were associated with adverse immunogenic type reactions to garadacimab treatment.

4.3 Toxicology

The toxicological profile of garadacimab was well characterised in repeat-dose toxicity studies in mice up to 4 weeks and cynomolgus monkeys up to 6 months. Doses up to 200 mg/kg were administered SC every 4 days or once weekly. Repeat-dose administration of garadacimab triggered immunological reactions in both species, resulting in mortality or necessitating euthanasia due to animal welfare concerns. However, cynomolgus monkeys tolerated the treatment well at doses up to 60 mg/kg once weekly. While there were treatment-related histopathological changes at the injection sites, characterised by a non-adverse inflammatory response (haemorrhage, inflammatory lesions and/or scabs), these tended to resolve after the recovery period. Overall, there were no garadacimab-related ante-mortem or post-mortem findings.

In accordance with ICH S6(R1), no genotoxicity studies were conducted.

No carcinogenicity studies were performed. The applicant provided an adequate risk assessment in accordance with ICH S6(R1). Garadacimab is not anticipated to pose a toxicological risk to paediatric patients 12 years of age and older, and is not expected to have carcinogenic potential when administered to patients.

Reproductive and developmental safety evaluation of garadacimab included separate fertility studies in male and female rabbits, as well as embryo-fetal development (EFD) and pre- and postnatal developmental (PPND) studies conducted exclusively in rabbits following IV and/or SC administration with doses up to, and including, 100 mg/kg/occasion. This aligns with ICH S6(R1), as rats are considered unsuitable, and mice have been observed to develop immunological responses such as anaphylaxis. The expected pharmacologically-related prolonged aPTT was observed in all studies. Garadacimab was well tolerated in both sexes, with no effects on male or female fertility endpoints. Systemic exposures at the NOAEL (100 mg/kg) were 103- and 83-fold above clinical exposure based on $AUC_{0\text{ - }30\text{ days}}$. In the EFD study, garadacimab was not maternotoxic or embryotoxic and did not cause malformations in fetuses (i.e. teratogenicity). In the PPND study, treatment with garadacimab was well tolerated by the maternal rabbits and had no effects on the survival or development of the F1 generation. Although there were no adverse findings in these studies, the use of garadacimab during pregnancy and lactation is not recommended due to the transfer via the placenta and/or possibly in milk. This is adequately addressed in the Information for healthcare professionals.

The systemic exposures (AUC) at the NOAELs in the toxicity studies with garadacimab are large multiples of the predicted human therapeutic exposure in patients with hereditary angioedema (AUC = 10,300 µg·h/mL).

The local tolerance of garadacimab, evaluated through SC administration in a rabbit tolerance study and as part of repeat-dose toxicity studies in mice and cynomolgus monkeys, demonstrated a low potential for irritation, which is not expected to occur in humans.

There are no safety concerns regarding excipients, drug substance-related or drug product-related impurities/ degradation products, or identified extractables/leachables from the container closure system.

Based on the ERA, there is no particular risk for the environment.

The RMP adequately addresses the nonclinical findings and their relevance for clinical use.

No specific studies in juvenile animals have been conducted with garadacimab.

4.4 Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of garadacimab is considered to be sufficiently well characterised. The submitted nonclinical data support the approval of Andembry in the proposed indication. The relevant information has been included in the Information for healthcare professionals.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for ANDEMBRY was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:

The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ANDEMBRY®

Composition

Active substances

Garadacimab (made from genetically modified CHO (Chinese Hamster Ovarian) cells).

Excipients

L-histidine, L-arginine hydrochloride, L-proline, Polysorbate 80, Water for injection

Pharmaceutical form and active substance quantity per unit

Solution for injection in a prefilled pen for subcutaneous administration.
Each single-use prefilled pen contains 200 mg of Garadacimab in 1.2 mL of solution.

Garadacimab is a recombinant, fully human, monoclonal antibody (IgG4/λ-light chain) produced by recombinant DNA technology in Chinese Hamster Overian (CHO) cells

Slightly opalescent to clear, brownish-yellow to yellow solution, with a pH of approximately 6.1. The solution has an osmolality of approximately 470 mOsm/kg.

Indications/Uses

ANDEMBRY is indicated for long-term prophylaxis of recurring acute attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 12 years and older (see “warnings and precautions” and “Clinical efficacy”).

Dosage/Administration

ANDEMBRY is not intended for the treatment of acute HAE attacks (see “Warnings and precautions”).

This medicinal product should be initiated under the supervision of a healthcare professional experienced in the management of patients with HAE.
ANDEMBRY may be self-administered or administered by a caregiver only after training on SC injection technique by a healthcare professional.
Each ANDEMBRY unit (prefilled pen) is intended for single use only.

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

Dosage
Adults and young people aged 12 and over:
The recommended dose of ANDEMBRY 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.

The benefit of an initial loading dose compared to treatment without a loading dose has not been investigated.*Missed doses* If a dose of ANDEMBRY is missed, administer as soon as possible with at least 1 month in between subsequent doses.

Method of Administration
ANDEMBRY is intended for subcutaneous (SC) administration only.
The injection should be restricted to the recommended injection sites: the abdomen, the thighs, and the upper outer arms. Changing location of the injection site is recommended. It is recommended that the upper arm injection site should be used only when the patient is assisted by a caregiver. See also “Instructions for handling”.

Paediatric population
ANDEMBRY is not approved for use in children under 12 years of age.

Elderly population
The available data on 13 patients ≥ 65 years old indicate that no dose adjustments are necessary for this patient population (see section “Pharmacokinetics”).

Hepatic impairment

No studies have been conducted in patients with hepatic impairment. No dose adjustment is required in patients with mild hepatic impairment (see section “Pharmacokinetics”). Only limited data are available for patients with moderate and severe hepatic impairment.

Renal impairment
No studies have been conducted in patients with renal impairment. Only limited data is available in patients with estimated glomerular filtration rate (EGFR)=30-60 mL/min/1.73m2. No dose adjustment is required in patients with mild renal impairment. (see “Pharmacokinetics”). Only limited data are available for patients with moderate and severe renal impairment.

Contraindications

Hypersensitivity to the active ingredient or any of the other ingredients (see “Composition”).

Warnings and precautions

General information
The safety and efficacy of ANDEMBRY for the treatment of acute HAE attacks or for preoperative prophylaxis have not been studied.

There are limited clinical data available on the use of ANDEMBRY in HAE patients with normal C1 esterase inhibitor (C1-INH) activity (see “Clinical efficacy”).

Hypersensitivity
Severe Hypersensitivity reactions have not been observed but may theoretically 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 ANDEMBRY. In case of severe hypersensitivity, discontinue ANDEMBRY administration and institute appropriate treatment. Patients with a history of relevant hypersensitivity reactions were excluded from clinical trials with ANDEMBRY.

Other patient groups with limited evidence
There is limited data on the safety and efficacy of ANDEMBRY in adolescents and in patients aged ≥ 65 years (see “Adverse reactions” and “Clinical efficacy”).
ANDEMBRY has not been studied in patients with coagulation disorders, and clinical experience in patients on concomitant anticoagulation medication is limited.

ANDEMBRY has not been studied in patients with thromboembolism.

Effects on diagnostic methods

In clinical studies, a reduction in D-dimer concentrations was observed, in some cases below the lower normal range. The clinical relevance of this observation is unclear. Garadacimab can prolong activated partial thromboplastin time (aPTT) due to an interaction of Garadacimab with the aPTT assay. The increases in aPTT in patients treated with Garadacimab were not associated with bleeding adverse events. There were no clinically relevant differences in international normalized ratio (INR) between treatment groups.

Interactions

Garadacimab has only been studied as a monotherapy and not in combination with other products indicated for long-term prophylaxis of HAE (see “Clinical efficacy”). No dedicated drug interaction studies have been conducted in humans. Antibodies are not metabolized in the liver and therefore CYP enzyme-mediated interactions are unlikely. Based on pharmacokinetic population analysis, 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.

Pregnancy, lactation

Pregnancy

Until now, there is no or only very limited experience (less than 300 pregnancy outcomes) with the use of Garadacimab in pregnant women. Animal studies did not provide any evidence of direct or indirect adverse health effects related to reproductive toxicity (see “Preclinical data”).Monoclonal antibodies 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. For Garadacimab, the available toxicological data from animals show that the placental barrier was crossed. As a precautionary measure, use of ANDEMBRY should be avoided 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. A risk for the newborn/breastfed child cannot be ruled out. A decision must be made whether to discontinue breast-feeding or treatment with ANDEMBRY. The benefits of breastfeeding for the child and the benefits of the therapy for the mother must be weighed up.

Fertility

Effect of Garadacimab on fertility has not been evaluated in humans. Animal experimental studies have shown no impairment on male or female fertility(see section “Preclinical data”).

Effects on ability to drive and use machines

No relevant studies have been conducted with ANDEMBRY.

Undesirable effects

Summary of the safety profile

The most commonly observed adverse reactions (13.37%) associated with ANDEMBRY were injection site reactions (ISRs) including injection site erythema, injection site bruising, injection site pruritus and injection site urticaria. Almost all of these ISRs were of mild intensity and resolved within 1-3 days with no change in dosage.

Tabulated list of adverse reactions

All clinical studies, including 172 subjects treated with ANDEMBRY, were assessed for the adverse drug reactions (ADRs) determination. The table below summarizes ADRs observed in the Pooled Summary conducted with ≥ 200 mg ANDEMBRY on 172 HAE patients.

The following list of adverse reactions is based on experience from clinical trials and is displayed by system organ class and frequency in Table 1 below: 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) and not known (cannot be estimated from the available data).

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

MedDRA Standard System Organ Class	Adverse Reaction (Preferred Term)	Frequency (To be captured in SmPC)
General disorders and administration site conditions	Injection site reaction*	Very Common (13.37%)

Nervous system disorders	Headache	Common
Gastrointestinal disorders	Abdominal pain	Common
* Injection site reactions include erythema, bruising, pruritus, and injection site urticaria		

Description of selected adverse reactions

Injection site reactions

In the Pooled Summary, 53 incidents of injection site reactions were observed in 23 patients who received ANDEMBRY, of which 51 were mild and 2 were moderate. Temporal relationship (began within 1-3 days after investigational product administration and the majority resolved with no change in dosage) was identified for all 53 injection site reactions and were assessed as related to ANDEMBRY.

In an open-label clinical study, which included 57 patients who rolled over from VANGUARD, 161 patients with HAE administered ANDEMBRY® 200 mg subcutaneously every month. Injection site reactions (e.g., injection site bruising, injection site erythema, injection site haematoma, injection site pruritus, injection site urticaria) were reported in 16 (10%) patients.

In an open label study in healthy adults, comparing the pre-filled pen (N = 66) with the pre-filled syringe (N = 66) after single application, injection site reactions were ovserved in 24.2% (hardening 15.2%, pain 9.1%, redness 4.5%) after using the pre-filled pen versus 9.1% (hardening 4.5%, pain 4.5%, redness 3.0%) after using the pre-filled syringe.

Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ANDEMBRY or other Garadacimab products.

In VANGUARD study, 1 (2.6%) ANDEMBRY in 39 -treated patients showed a very low anti-drug-antibody (ADA)-positive sample (titer: 10) during the 6-month treatment period. Across all studies with ANDEMBRY, the incidence of ADA's was 2.9% (5/172 subjects). Reactions at the injection site were reported in 2 out of 5 (40%) ADA-positive patients compared to 18.6% in ADA-negative patients.Due to the low incidence of ADA formation against ANDEMBRY a comprehensive assessment of the impact on pharmacokinetics (PK), pharmacodynamics (PD), safety or clinical response is not possible. No data are available on the incidence of neutralizing ADA.

Pediatric population

There are limited data for adolescents 12-17 years. The safety of ANDEMBRY has been established in 11 pediatric patients aged 12-17 years in the phase III trials. Due to the small number of patients and the limited treatment and follow-up duration, a comprehensive assessment of the safety of ANDEMBRY in pediatric patients, including effects on growth and development, is not possible.

Geriatric population

The safety of ANDEMBRY were evaluated in patients (N=13) aged 65 years of age or older with HAE in VANGUARD study and VANGUARD Open Label Extension Study. Due to the small number of patients, a comprehensive assessment of the safety of ANDEMBRY in elderly patients aged 65 or older is not possible.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose were reported in clinical studies. There is no available information to identify potential signs and symptoms of overdose.

Properties/Effects

ATC code

B06AC07

Mechanism of action

Garadacimab is a specific inhibitor of activated FXII. Garadacimab is a novel fully human IgG4/lambda recombinant monoclonal antibody which binds to the catalytic domain of activated Factor XII (FXIIa and βFXIIa) and potently inhibits its catalytic activity. FXII is the first factor activated in the contact activation pathway and initiates the inflammatory bradykinin-producing kallikrein-kinin system. The inhibition of FXIIa prevents the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks, thus blocking the cascade of events leading to an HAE attack.

Pharmacodynamics

Concentration-dependent inhibition of FXIIa-mediated kallikrein activity was demonstrated after subcutaneous administration of ANDEMBRY 200 mg once monthly in patients with HAE.

Clinical efficacy

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

The study included 64 adult and pediatric patients (12 years of age and older) who experienced at least 1 HAE attacks/month during the 3 months before the screening examination and the subsequent 2 month run-in period. Patients were randomized into 2 parallel treatment arms (39 ANDEMBRY arm, 25 placebo arm) 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 medications prior to entering the study. Adolescent patients receiving long-term HAE prophylaxis were excluded from participation. All patients were allowed to use on-demand medications for treatment of acute 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 (53.8% ANDEMBRY and 68% placebo) and 32.8% were on prior prophylaxis. During the 3 months prior to screening or initiation of HAE prophylaxis, the median (min., max.) time-normalized number of HAE attacks per month was 2 (1, 10). The most frequent localizations of HAE attacks were cutaneous on the extremities (78%) and abdominal (75%); the localization neck/throat/tongue was reported in 8%. Of the 244 HAE attacks in the run-in period, 30.3% were mild, 59.8% were moderate and 9.8% were severe. During the study run-in period, attack rates of ≥3 attacks/month were observed in 59.4% of patients overall.

ANDEMBRY demonstrated a statistically significant efficacy vs placebo in the Intent-to-treat (ITT) population (see Table 3).

The mean time-normalized number of HAE attacks per month during the 6 months treatment period, the primary endpoint of the study, was 0.27 for the ANDEMBRY arm and 2.01 for placebo arm. The mean reduction in time-normalized attack rate vs placebo was 86.5% (median 100%).

71.8% of the patients treated with ANDEMBRY were attack free throughout the first 3 months of treatment vs. 8.3% of patients treated with placebo. Over the entire 6 months of treatment the

percentage of attack-free patients was 61.5% in the ANDEMBRY arm compared with no patients in the placebo arm.

Table 3: Results of Primary and Secondary Efficacy Measures (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Number of Evaluable Patients, n	39	24[a]
Number of HAE Attacks during the 6 months Treatment Period	63	264
Time-normalized Number of HAE Attacks Per Month		
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	
Percent reduction in time-normalized number of HAE attacks relative to placebo during the 6 months Treatment Period		
Mean (95% CI)	86.5 (95.7, 57.9)	
Median	100	
p-value*	< 0.001	
Patients who were attack free during the first 3 months of treatment (months 1–3)		
Number (%) of patients	28 (71.8)	2 (8.3)
95% CI	56.22, 83.46	2.32, 25.85
p-value*	< 0.001	

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

* A hierarchical testing procedure controls for the two-sided alpha level of 5%

Four pediatric patients 12 years of age and older were treated with ANDEMBRY in the study. Due to the small number of patients, a comprehensive assessment of the efficacy of ANDEMBRY in pediatric patients is not possible...

VANGUARD Open Label Extension Study is a phase 3, multicenter, open-label study designed to investigate long-term safety (primary objective) and efficacy of ANDEMBRY that enrolled a total of 161 patients. The 161 patients are from: VANGUARD study (n=57), a phase 3, multicenter, randomized, double-blind, placebo-controlled parallel group study; a phase 2 (n=35), multicenter, randomized, placebo-controlled, parallel-arm study; and the remaining patients (n=69) are newly enrolled and naïve to treatment with ANDEMBRY. Overall, 145 (90.1%) patients had Type 1 HAE. Of the 57 subjects from the VANGUARD study, 21 were treated with placebo and when they transitioned

to the VANGUARD OLE and switched to ANDEMBRY (active treatment), they did not receive a loading dose. Treatment with an initial loading dose compared to treatment without a loading dose was not investigated.

At the time of the interim analysis with data cut from 15-JUN-2024, the median duration of exposure was 27.5 months. The observed time-normalized number of HAE attacks, reduction in attack rate and freedom from attacks were consistent with the results from VANGUARD study.
Ten pediatric patients 12 years of age and older were treated with ANDEMBRY in the study. Due to the small number of patients, a comprehensive assessment of the effectiveness of ANDEMBRY in pediatric patients in not possible.

Pharmacokinetics

In the VANGUARD trial, based on pharmacokinetic population analysis, patients treated with 200 mg Garadacimab SC once monthly presented mean (SD) model-predicted 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.

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.

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.

Kinetic specific population

In a population pharmacokinetic analysis, after correcting for body weight (43.3-153 kg), no influence of gender or age (12 to 73 years), 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 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]), and hepatic impairment (indirectly assessed based on Alanine Aminotransferase and Total Bilirubin; normal, N = 246, mild, N = 15; severe, N = 1) had no effect on the PK of Garadacimab.

Preclinical data

Based on conventional studies, preclinical data reveal no special hazard for humans.Garadacimab was well tolerated at dose levels up to 100 mg/kg/occasion IV and 200 mg/kg/occasion SC in both mice and cynomolgus monkeys for up to 5 weeks administered 3 to 9 times and at doses of 30 mg/kg/occasion IV and 60 mg/kg/occasion SC when administered once weekly to monkeys for 26 weeks.
Studies have not been conducted to evaluate the genotoxic and carcinogenic potential of Garadacimab. Garadacimab is not expected to interact directly with DNA or other chromosomal

material, as it is made up entirely of naturally occurring amino acids and contains no inorganic or synthetic linkers or other nonprotein portions.

Male and female fertility were unaffected based upon a lack of adverse findings on mating, fecundity, fertility indices, maternal reproductive parameters, embryo survival or sperm assessment in sexually mature rabbits that received Garadacimab up to doses of 100 mg/kg intravenously once every three days (resulting in approximately 83- and 103-fold the exposure in females and males, respectively, at the recommended human dose of 200 mg SC once monthly based on AUC).

In a pre- and post-natal development repeat-dose toxicity study, pregnant rabbits were administered Garadacimab once every 5 days, from implantation through weaning, with subcutaneous or intravenous doses up to 100 mg/kg/dose. In rabbits receiving subcutaneous Garadacimab, this resulted in approximately 53-fold the exposure (based on AUC) at the recommended human dose of 200 mg SC once monthly. There was no Garadacimab-related toxicity to the parental and infant generation up to 6 months of age.

Other information

Incompatibilities

Not applicable

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack. The preparation does not contain any preservatives.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.
The solution (prefilled pen) may be stored at room temperature, not above 25°C, for up to 2 months, but not beyond the expiry date. Do not return ANDEMBRY to refrigerated storage after storage at room temperature up to 25 °C.

Instruction for handling

Garadacimab is supplied in pre-filled pens.
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 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.
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.
The instruction for use is included in the Patient Information Leaflet.

Authorisation number

69553 (Swissmedic)

Packs

Pack with 1 x 1.2mL solution for injection with a prefilled glas syringe within a fixed dose prefilled pen with 200mg Garadacimab [B]

Marketing authorisation holder

CSL Behring AG, Bern

Date of revision of the text

JANUARY 2025