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Andembry ®

Factor XIIa Inhibitor Monoclonal Antibody

INN: Garadacimab

Swiss Summary to the Risk Management Plan

Version number of RMP: 1.0

Marketing Autorisation Holder: CSL Behring AG

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Andembry ® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Andembry in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. CSL Behring AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Andembry.

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The medicine and what it is used for

Garadacimab is investigated for routine prevention of recurrent attacks of Hereditary Angioedema (HAE) in patients aged 12 years and older (see SmPC for the full indication). Garadacimab is a factor XIIa inhibitor monoclonal antibody as the active substance, and it is given subcutaneously.

Further information about the evaluation of garadacimab's benefits can be found in garadacimab's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage link to the EPAR summary landing page.

Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of garadacimab, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size - the amount of medicine in a pack is chosen to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures. In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of garadacimab is not yet available, it is listed under 'missing information' below.

List of important risks and missing information

Important risks of garadacimab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential, with only important potential risks identified for garadacimab to date. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been

established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Severe hypersensitivity including anaphylaxis
Missing information	Safety in pregnancy and breastfeeding Long-term safety in adults Long-term safety in adolescents

Summary of important risks

Important potential risk: Severe hypersensitivity including anaphylaxis	
Evidence for linking the risk to the medicine	Evidence source: Unconfirmed class effect as seen in literature (Cáceres et al, 2019; Sachs and Merk, 2018).
Risk factors and risk groups	Throughout the evolution from murine, chimeric, and humanised to completely human products, there has been a significant reduction in the immunogenic risks associated with monoclonal Antibodies (mAbs) that resemble endogenous human immunoglobulins more closely (Cui et al, 2017). As garadacimab is a fully human IgG4 mAb, the risk of Hypersensitivity Reactions (HSRs) is expected to be minimal. However, an inherent risk of developing a HSR to any product should be considered when giving a product for the first time. In case of the different kinds of HSRs, the non-allergic acute HSRs (also known as anaphylactoid or a non-Immunoglobulin E–mediated reaction) usually already occur with the first application and their symptoms decrease with subsequent use. Real allergic reactions (immunoglobulin (Ig) E-mediated) usually do not manifest themselves when used for the first time, as a sensitisation phase must precede them. However, if preformed or cross-reacting antibodies are present in the patient, the allergic reactions can also occur with the first application (Sachs and Merk, 2018). Pre-medications such as acetaminophen, anti-histaminic or corticosteroids are considered as standard procedure for keeping the risk for HSRs with mAbs to a minimum. However, due to the fact that most injection reactions with mAbs take place following the first or second infusion, the value of premedication on subsequent infusions may decrease (Cáceres et al, 2019).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 (Contraindications), 4.4 (Warnings and precautions for use) PL Section 4 Additional risk minimisation measures: None
Missing Information: Safety in pregnancy and breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 (Fertility, pregnancy, and lactation) Additional risk minimisation measures:

	None
Missing Information: Long-term safety in adults	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, 4.4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-Authorisation Safety Study to further characterise Long-term safety in adults and Long-term safety in adolescent patients. See "Post-authorization development plan "of this summary for an overview of the post-authorisation development plan.
Missing Information: Long-term safety in adolescents	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 (Paediatric population), 5.1 Pharmacodynamic properties Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-Authorisation Safety Study to further characterise Long-term safety in adults and Long-term safety in adolescent patients. See "Post-authorization development plan " of this summary for an overview of the post-authorisation development plan.

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Post-authorization development plan

Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of garadacimab.

Other studies in post-authorization development plan

The following additional pharmacovigilance activities are included in the post-authorisation development plan:

Category 3: Garadacimab Non-Interventional Post-Authorisation Safety Study: Long Term Safety in Adults and Adolescents

Purpose of the planned study:

CSL Behring will conduct a non-interventional Post-Authorisation Safety Study with garadacimab in adults and adolescents with HAE in an observational manner in a real-world setting to further characterize the missing information of Long-term safety in adults and Long-term safety in adolescents.

Primary Objective: To describe the real-world long-term safety profile of garadacimab in adult and adolescent participants with HAE.

Exposure: Exposure to garadacimab for HAE long-term prophylaxis over a targeted follow-up period of 4 years according to routine clinical practice and physician discretion.

Endpoints:

1. Incidence rate and characteristics of AEs while on treatment with garadacimab (eg, AE term, severity, seriousness, duration, relatedness and event outcome) in adults and adolescents.
2. In adolescents, impact of garadacimab on sexual maturation, bone growth and cognitive development. This study will employ assessments to measure these outcomes, such as Tanner staging to assess sexual maturation, standardized growth charts for bone growth, and academic performance for cognitive development.

Study Design:

This will be a non-interventional, observational cohort study conducted with a targeted follow-up period of 4 years.

Study Population:

The study will include approximately 150 individuals with HAE ≥12 years of age and who have been prescribed garadacimab by their treating physician for treatment of HAE.

Milestones:

Submission of feasibility assessment in April 2025 (within 3 months of EC decision).

Protocol submission in April 2025 (within 3 months of EC decision).

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Registration in the EU PAS Register in February 2026.

Study start in April 2026.

Study completion in April 2034.

Final study report in April 2035.

Garadacimab Non-Interventional Post-Authorisation Safety Study: Long Term Safety in Adults and Adolescents Planned	<u>Primary Objective:</u> To describe the real-world long-term safety profile of garadacimab in adult and adolescent participants with HAE. <u>Endpoints:</u> Incidence rate and characteristics of AEs while on treatment with garadacimab (eg, AE term, severity, seriousness, duration, relatedness and event outcome) in adults and adolescents. In adolescents, impact of garadacimab on sexual maturation, bone growth and cognitive development. This study will employ assessments to measure these outcomes, such as Tanner staging to assess sexual maturation, standardized growth charts for bone growth, and academic performance for cognitive development. <u>Study Design and Participants:</u> This will be a non-interventional, observational cohort study conducted with a targeted follow-up period of 4 years. The study will include approximately 150 individuals with HAE ≥12 years of age and who have been prescribed garadacimab by their treating physician for treatment of HAE.	Long-term safety in adults and Long-term safety in adolescents	Submission of feasibility assessment	April 2025 (within 3 months of EC decision)
			Protocol submission	April 2025 (within 3 months of EC decision)
			Registration in the EU PAS Register	February 2026
			Start of study	April 2026
			Study completion	April 2034
			Final report of study results	April 2035

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Summary of changes to the Swiss RMP Summary

Version	Date	Change History	Comment
01	20-Mar-2025	Initial document	Initial document, based on EU RMP Version 1.0, 20-Dec-2024