Summary of the Risk Management Plan for AGAMREE®

Active substance: vamorolone

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Marketing Authorisation Holder: Santhera Pharmaceuticals (Schweiz) AG

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 AGAMREE 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 AGAMREE in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Santhera Pharmaceuticals (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of AGAMREE.

Summary of the risk management plan

This is a summary of the risk management plan (RMP) for AGAMREE. The RMP details important risks of AGAMREE, how these risks can be minimised, and how more information will be obtained about AGAMREE's risks and uncertainties (missing information).

AGAMREE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how AGAMREE should be used.

This summary of the RMP for AGAMREE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of AGAMREE's RMP.

I. The medicine and what it is used for

AGAMREE is indicated for the treatment of Duchenne Muscular Dystrophy (DMD) (see SmPC for the full indication). It contains vamorolone as the active substance and it is given by oral route.

Further information about the evaluation of AGAMREE's benefits can be found in AGAMREE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/agamree*.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of AGAMREE, together with measures to minimise such risks and the proposed studies for learning more about AGAMREE's 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 so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. 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 (PSUR) 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 AGAMREE is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of AGAMREE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of AGAMREE. 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	Infections due to immunosuppression, hepatotoxicity, acute adrenal insufficiency (adrenal crisis)
Missing information	Use in patients above 12 years of age Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension).

II.B Summary of important risks

Potential risk: Infections due to immunosuppression	
Evidence for linking the risk to the medicine	This is a known effect of glucocorticoids but clinically relevant infections due to immunosuppression trend has not been yet detected with vamorolone. Part of the vamorolone pharmacological activity is also based on agonistic effect on Glucocorticoid Receptor (GR).
Risk factors and risk groups	Immunocompromised patients Use in combination with live attenuated vaccines Duration of treatment and dose
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 Patient information leaflet section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** An observational Post Authorisation Safety Study (PASS*) to further characterise and quantify long-term safety profile of AGAMREE

*A PASS is a study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures.

Potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Weak pre-clinical signal, nature of findings similar to those observed with other glucocorticoids. No valid safety signal in human data to date with vamorolone.
Risk groups or risk factors	Patients with existing hepatic impairment
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3 and 4.4 Patient information leaflet section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** An observational PASS to further characterise and quantify long-term safety profile of AGAMREE

Potential risk: Acute adrenal insufficiency (Adrenal crisis)	
Evidence for linking the risk to the medicine	This is a known effect of glucocorticoids, however events of acute adrenal insufficiency or adrenal crisis per se have not been fully characterised for vamorolone.
Risk groups or risk factors	Sudden withdrawal of vamorolone treatment in all age groups Acute stress situation (e.g. infection) in all age groups
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.8 Patient information leaflet sections 2 and 4 **Additional risk minimisation measures to address the risk:** A Patient Alert Card to support early recognition and treatment of adrenal crisis **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** An observational PASS to further characterise and quantify long-term safety profile of AGAMREE

Missing information 1: Use in patients above 12 years of age	
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** VBP15-006, a Phase II Open-Label, Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with Duchenne Muscular Dystrophy (DMD) An observational PASS to further characterise and quantify long-term safety profile of AGAMREE

Missing information 2: Safety on long-term use (in particular regarding bone fractures, weight gain, growth, hyperglycemia, dyslipidemia and hypertension)	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** An observational PASS to further characterise and quantify long-term safety profile of AGAMREE

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

II.C.2 Other studies in post-authorisation development plan

A. Post Authorisation Safety Study

A multi-registry non-interventional, post-authorization study to evaluate the safety in children 2 years and older with DMD treated with vamorolone suspension (AGAMREE) compared to standard of care.

Purpose of the study:

To investigate the long-term safety profile of vamorolone within the target age group. Specifically, the following important potential risks will be evaluated:

- Infections due to immunosuppression
- Hepatotoxicity
- Acute adrenal insufficiency (adrenal crisis).

Additionally, the following missing information will be evaluated:

- Use in patients above 12 years of age
- With respect to safety in long-term use:
    - Bone fractures
    - Weight gain
    - Growth
    - Hyperglycemia,
    - Dyslipidemia.
    - Hypertension

B. Study VBP15-006

VBP15-006, a Phase II Open-Label, Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys Ages 2 to <4 Years and 7 to <18 Years with Duchenne Muscular Dystrophy (DMD).

Purpose of the study:

The VBP15-006 study has been initiated as part of a Paediatric Investigation Plan, in order to ensure that the necessary safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy data are collected to further characterise the benefit –risk in the target population (2 to below 4 years of age as steroid-naive subjects; 7 to below 18 years both steroid-treated and steroid-naive subjects).

The purpose of including the VBP15-006 study as part of this Pharmacovigilance plan is to generate and evaluate assess the missing information "use in patients above 12 years of age".