Part VI: Summary of the risk management plan

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

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

This summary of the RMP for SCENESSE® 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 SCENESSE®'s RMP.

I. The medicine and what it is used for

SCENESSE® is authorised for EPP (see SmPC for the full indication). It contains afamelanotide as the active substance and it is given as a controlled release injectable implant.

Further information about the evaluation of the benefits of SCENESSE® can be found in the medicine'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/scenesse

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

Important risks of SCENESSE®, together with measures to minimise such risks and the proposed studies for learning more about the risks of SCENESSE®, 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 the case of SCENESSE®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 SCENESSE® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of SCENESSE® 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. Identified risks are concerns for which there is sufficient proof of a link with the use of SCENESSE®. 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	• Change of pigmentary expressions • Allergy and hypersensitivity
Important potential risks	• Administration error
Missing information	• Off-label use in paediatric patients • Off-label use in adults • Use in pregnancy and lactation • Use in the elderly • Use in patients with co-morbidities such as clinically significant renal, hepatic or cardiac impairment • Long-term safety data • Pharmacokinetic data

II.B Summary of important risks

Important identified risk: Change of pigmentary expressions	
Evidence for linking the risk to the medicine	SCENESSE® increases the level of melanin pigment in the skin and makes the skin darker. When taking SCENESSE® the contrast in the colour of already darker skin areas (e.g. ephelides, sun spots etc, collectively 'pigmentary expressions') and the surrounding skin can become more intense. It is important to monitor these areas to make sure that any change observed is only a result of the drug's normal activity and that is does not mask a skin condition. Any darkening of pigmentary expressions induced by SCENESSE® is reversible.
Risk factors and risk groups	The risk factors for the development of changes in pigmentary expressions are many and varied and largely depend on the individual's phenotype, personal medical history, family medical history and environmental factors such as previous chronic sunlight exposure.

	Special caution is warranted in patients with: • individual or family history of melanoma (cancer that develops from the pigment-containing cells known as melanocytes) • suspected or confirmed susceptibility to melanoma (see above) of the skin, and/or • individual history of basal cell carcinoma (cancer that grows on parts of your skin that get a lot of sun), squamous cell carcinoma (second most common form of skin cancer), or other malignant or premalignant skin lesions.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8.* *SmPC section 4.4. and PL section 2 where advice is given on skin monitoring and sun protection* *PIL section 2* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Patient guide*
Additional pharmacovigilance activities	*CUV-PASS-001/002* *CUV-RCR-001* See section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Allergy and hypersensitivity	
Evidence for linking the risk to the medicine	The body's immune system helps to fight infections by recognising unknown substances. However, sometimes the immune system can also respond to medicines and this reaction is known as an allergy or hypersensitivity. SCENESSE® is a new drug which has only been tested in a limited number of patients. As with any drug, there is a possibility that some patients may experience an allergic reaction to the drug or any of its components.
Risk factors and risk groups	Patients with a predisposition to allergic reactions and/or a history of hyper-reactivity to proteins and/or polymers are considered at greater risk.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3. and 4.8.* *SmPC section 4.2. states that the patient needs to be observed for 30 minutes to ensure that he/she does not experience*

	allergic or hypersensitivity reactions (immediate type) *PIL sections 2 and 4* Special medical prescription Additional risk minimisation measures: *Healthcare Professional Guide*
Additional pharmacovigilance activities	*CUV-PASS-001/002* *CUV-RCR-001*See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Administration error	
Evidence for linking the risk to the medicine	The implant is administered using a catheter needle; the risk of damage to the implant during the administration can on theoretical grounds not be excluded. The route of administration poses a risk for patients with respect to non-maintenance of sterile conditions in clinical practice and also with respect to application site reactions.
Risk factors and risk groups	There are no known risk groups or risk factors.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2.* *PIL section 3* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide and associated training material*
Additional pharmacovigilance activities	*CUV-PASS-001/002* *CUV-RCR-001*See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Off-label use in paediatric patients	
Evidence for linking the risk to the medicine	SCENESSE® has never been fully evaluated in children. Children up to 17 years of age suffering from EPP must not be administered SCENESSE® as safety and efficacy in children have not been demonstrated.
Risk factors and risk groups	It is conceivable that there may be a temptation to treat adolescents close to 18 years of age may because of their closeness to the adult age threshold. Similar considerations may also apply to younger children of a larger body size.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1., 4.2. and 4.4.*

	PIL sections 1 and 2 *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Restricted distribution*
Additional pharmacovigilance activities	*CUV-PASS-001/002* *CUV-RCR-001*See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Off-label use in adults	
Evidence for linking the risk to the medicine	SCENESSE® has never been fully evaluated in conditions other than EPP. SCENESSE® should not be used in other patient populations as safety and efficacy in these patients have not been demonstrated.
Risk factors and risk groups	It is theoretically possible that there may be a temptation to treat some adult patients off-label because of the perceived benefits of afamelanotide. However, the approval procedures that have to be followed before SCENESSE® is provided, as well as the medical specialisations involved in treating EPP patients at EEECs and their patient populations make the probability of off-label use other than via an approved controlled distribution program negligible.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1.* *PIL section 1* *Special medical prescription* Additional risk minimisation measures: *Healthcare Professional Guide* *Restricted distribution*
Additional pharmacovigilance activities	*CUV-PASS-001/002* *CUV-RCR-001*See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use in pregnancy and lactation	
Evidence for linking the risk to the medicine	SCENESSE® has never been fully evaluated in conditions other than EPP. SCENESSE® should not be used in other patient populations as safety and efficacy in these patients have not been demonstrated.
Risk factors and risk groups	The at-risk groups are women of child bearing potential not using adequate contraception and women who are breastfeeding.

Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6. and 5.3.* *PIL section 2* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*
Additional pharmacovigilance activities	*CUV-PASS-001/002* *CUV-RCR-001* See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use in the elderly greater than 70 years of age	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2.* *PIL section 2* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*
Missing information: Use in patients with co- morbidities such as clinically significant renal, hepatic or cardiac impairment	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1. and 5.2.* *PIL section 2* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*
Missing information: Long-term safety data	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4.* *PIL introduction (black triangle)* *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*
Missing information: Pharmacokinetic data	
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 5.1. *Special medical prescription* Additional risk minimisation measures: *No risk minimisation measures*

II.C Post-authorisation development plan

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

The following studies are conditions of the marketing authorisation:

Study short name: CUV-PASS-001 and -002 EPP Disease Registry

Purpose of the study: Analyses comparing long term safety data and outcome endpoints in EPP patients receiving treatment with SCENESSE® (Treated Group) and those not receiving SCENESSE® (Untreated Group) or having discontinued treatment with SCENESSE® (Discontinued Group) are to be undertaken.

Primary objectives

- Gather long-term safety data of SCENESSE®
- Evaluate compliance with the risk minimisation measures

Secondary objectives

- Evaluate adherence with the controlled distribution program
- Generate data to contribute to knowledge about clinical benefits and to add data on potential clinical effectiveness of SCENESSE®

Study short name CUV-RCR-001 Retrospective Chart Review

Purpose of the study: To address the missing safety data, the establishment of a Disease Registry was imposed as a specific obligation with data to be collected from both EPP patients and physicians. In addition, there was an obligation that the MAH should also undertake a retrospective chart review study.

Primary objectives

- Gather long-term safety data of SCENESSE®
- Evaluate compliance with the risk minimisation measures
- Evaluate compliance with the controlled distribution program

Secondary objectives

- Generate data to contribute to knowledge about clinical effects and to add data on potential clinical effectiveness of SCENESSE®

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

Study short name CUV052 Pharmacokinetic Study

Rationale and study objectives:

Purpose of the study: To collect data on distribution, metabolism and excretion of SCENESSE®

Primary objective

- To determine the pharmacokinetics of afamelanotide in subjects with EPP following administration of one SCENESSE® implant

Secondary objectives

- To determine the pharmacokinetics of afamelanotide in subjects with EPP following administration of a second SCENESSE® implant approximately 60 days after the first implant
- To confirm the safety and tolerability of SCENESSE® 16 mg Implant in subjects with EPP