IMCIVREE

10 mg/ml, solution for injection

Summary of the Risk Management Plan (RMP) for IMCIVREE (setmelanotide)

Document Version: 1.0

Date: 21 August 2025

Based on EU RMP version 2.3

(Data lock point 24 May 2023)

Disclaimer:

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 IMCIVREE 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 IMCIVREE in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Pharma services oehler GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of IMCIVREE.

I. The medicine and what it is used for

IMCIVREE is authorised for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 2 years of age and above (see SmPC for the full indication). It contains setmelanotide as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of IMCIVREE's benefits can be found in IMCIVREE's SwissPAR, including in its plain-language summary, available on the Swissmedic website.

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

Important risks of IMCIVREE, 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 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 minimize its risks.

Together, these measures constitute routine risk minimisation 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 IMCIVREE is not yet available, it is listed under'missing information' below.

II.A List of important risks and missing information

Important risks of IMCIVREE 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 IMCIVREE. 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:

List of important risks and missing information	
Important identified risks	None
Important potential risks	Melanoma Prolonged penile erections Depression (including suicidal ideation) Benzyl alcohol accumulation in young children
Missing information	Use in pregnant/breastfeeding women Use in hepatic impairment Use in severe renal impairment Long-term use

II.B Summary of important risks

Important identified risk: None	
Important potential risk: Melanoma	
Evidence for linking the risk to the medicine	There is no evidence from non-clinical data, clinical data or the drug class for the development of melanoma, however given the limited exposure in the clinical development program, melanoma is considered an important potential risk. Facial hyperpigmentation correlating microscopically with increased epidermal pigment was observed at all setmelanotide doses tested in studies in cynomolgus monkeys. This effect was reversible off drug. This skin darkening was not associated with differentiation or proliferation of melanocytes and is considered to be a pharmacological effect of setmelanotide activity at the MC1R.

Risk factors and risk groups	Risk factors for the development of melanoma include ultraviolet light exposure, moles, fair skin, freckling and light hair, family or personal history of melanoma, having a weakened immune system, being older, being male, and xeroderma pigmentosum.
Risk minimisation measures	Routine risk minimisation measures • SmPC sections « Warnings, Precautions» and « Undesirable effects » • PL section »When is caution required.. » and « Which side effects can… » • SmPC section « Warnings, Precautions» recommends full body skin examinations be conducted before and during treatment with setmelanotide to monitor pre- existing and new skin pigmentary lesions. • PL section »When is caution required.. » recommends a skin examination to be conducted before and during treatment. • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032

Important potential risk: Prolonged penile erections	
Evidence for linking the risk to the medicine	Medicines that activate melanocortin receptors are known to potentially cause erections in male patients. Rare cases of prolonged erections in male patients have been described in the literature with other medicines in the drug class. Spontaneous penile erections, an effect associated with MC4R agonism, have been reported in IMCIVREE-treated patients. Occurrence of these events did not appear to correlate with dose or duration of dosing, as the number of events did not increase with dose or duration of dosing.

Risk factors and risk groups	No risk factors or risk groups have been identified to date in IMCIVREE-treated patients. Patients with sickle cell anaemia or trait, thrombocythemia, polycythaemia or multiple myeloma or who are prone to venous thrombosis or who have a hyperviscosity syndrome may be at increased risk of priapism.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section « Warnings, Precautions » • PL section »When is caution required.. » and « Which side effects can… » • SmPC section « Warnings, Precautions » includes the statement that patients who have an erection lasting greater than 4 hours should seek emergency medical attention. • PL section »When is caution required.. » recommends patients seek urgent medical care if they experience an erection lasting greater than 4 hours. • Legal status: prescription only medication Additional risk minimisation measures: • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032

Depression (including suicidal ideation)	
Evidence for linking the risk to the medicine	Some drugs that target the CNS have been associated with depression or suicidal ideation; however, the exact mechanism is not known.
Risk factors and risk groups	Patients with severe obesity are known to have both depression and suicidal ideation and behaviours. In the general population, other risk factors for depression include the following: • Personal or family history of depression • Major life changes, trauma, or stress • Serious illness or mental illness • Substance abuse • Female gender • Other medications known to cause depression
Risk minimisation measures	Routine risk minimisation measures: • SmPC section «Warnings, Precautions » • SmPC section «Warnings, Precautions » recommends subjects with depression be monitored if treated with IMCIVREE and notes consideration should be given to discontinuing IMCIVREE if patients experience suicidal thoughts or behaviours. • Legal status: prescription only medication Additional risk minimisation measures: • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Important Potential Risk: Benzyl alcohol accumulation in young children	

Evidence for linking the risk to the medicine	Studies have found that benzyl alcohol poisoning can be harmful for premature babies. This is because they may receive higher doses of benzyl alcohol per kilogram of body weight compared to adults. It is believed that the immature liver or kidney of premature babies may struggle to process the byproduct of benzyl alcohol called benzoic acid. This can lead to a buildup of benzoic acid in the body.
Risk factors and risk groups	Patients from 2 to <3 years of age. No risk factors have been identified to date in setmelanotide-treated patients.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section «Warnings, Precautions » • SmPC section «Warnings, Precautions » recommends patients from 2 to <3 years of age to be monitored for any sign of metabolic acidosis while under treatment. • PL section »When is caution required.. » PL section »When is caution required.. » notes that in young children (less than 3 years old), there is an increased possibility that benzyl alcohol could build-up in their body. Children aged 2-<3 years old should be monitored by their doctor for side effects of this build-up (called “metabolic acidosis”). • Legal status: prescription only medication Additional risk minimisation measures: • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032

Missing Information: Use in pregnant/breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures • SmPC section « Pregnancy, Lactation » • PL section »When is caution required.. » • SmPC section « Pregnancy, Lactation » notes IMCIVREE should not be started during pregnancy or while attempting to

	get pregnant. • SmPC section « Pregnancy, Lactation »notes that that if breastfeeding, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from IMCIVREE therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Missing Information: Use in hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC sections « Dosage/Administration » and « Pharmacokinetic properties » • PL section »When is caution required.. » • SmPC sections « Dosage/Administration » and « Pharmacokinetic properties » note IMCIVREE should not be administered to patients with hepatic impairment • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032

Missing information: Use in severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC sections « Dosage/Administration » and « Pharmacokinetic properties » • PL section »When is caution required.. » • SmPC sections « Dosage/Administration » and « Pharmacokinetic properties » recommend specific dose titration in patients with severe renal impairment • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032
Missing information: Long-term use	
Risk minimisation measures	Routine risk minimisation measures • Legal status: prescription only medication Additional risk minimisation measures • None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: • A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet-Biedl Syndrome (BBS), Treated with Setmelanotide, final study report Q3 2032

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 IMCIVREE.

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

A Registry of Patients with Biallelic Pro Opiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency Obesity, or Bardet- Biedl Syndrome (BBS), Treated with Setmelanotide.

Purpose of the study:

This observational registry will provide data to further characterise the long-term safety profile of setmelanotide under real-world conditions but also its long-term effectiveness in patients aged 2 years and older. This Post-Authorisation Safety Study (PASS) will collect data from patients with biallelic homozygous POMC/PCSK1 or LEPR deficiency obesity, or BBS who are prescribed setmelanotide in routine clinical practice.

Primary objective:

- To assess the long-term safety of setmelanotide as prescribed in routine practice for patients with bi-allelic POMC, PCSK1, LEPR deficiency obesity, or BBS according to the current local prescribing information.

Secondary objectives:

- To document the incidence and characteristics of AESIs including the following:
    - Prolonged penile erection
    - Depression (including suicidal ideation)
- To document AESI and new adverse event occurrence in special populations, including:
    - Patients with hepatic impairment
    - Patients with severe renal impairment
    - Use in pregnancy and breastfeeding
- To evaluate the long-term effectiveness of setmelanotide when it is prescribed as part of routine practice
- To describe baseline characteristics and history of obesity in patients treated with setmelanotide
- To assess the risk of potential for benzyl alcohol accumulation in young children

Exploratory objectives:

- To document any cases of melanoma and their characteristics
- To document obesity-related hospitalisations and surgeries