Summary of risk management plan for IMCIVREE (setmelanotide)

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

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

This summary of the RMP for IMCIVREE 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 IMCIVREE's RMP.

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 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 6 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 EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/imcivree*

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)
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 clinical data in IMCIVREE-treated patients, melanoma is considered an important potential risk. Skin darkening was seen in clinical trials and in several of the non-clinical studies, and in both settings was reversible upon withdrawal of the drug. In the non-clinical setting, this skin darkening was not associated with differentiation or proliferation of melanocytes and is a pharmacological effect of setmelanotide activity at the MC1R. Four TEAEs within the SOC 'Neoplasm benign, malignant and unspecified (incl cysts and polyps)' that led to study drug discontinuation were reported in the setmelanotide clinical development programme.
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 4.4 and 4.8 • PL section 2 and 4 • SmPC section 4.4 recommends full body skin examinations be conducted before and during treatment with setmelanotide to monitor pre-existing and new skin pigmentary lesions. • PL section 2 recommends a skin examination 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 POMC or LEPR Deficiency Obesity Treated with Setmelanotide, final study report 30 Sep 2031
Important potential risk: Prolonged penile erections	
Evidence for linking the risk to the medicine	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 4.4 • PL section 2 and 4 • SmPC section 4.4 includes the statement that patients who have an erection lasting greater than 4 hours should seek emergency medical attention. • PL section 2 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 POMC or LEPR Deficiency Obesity Treated with Setmelanotide, final study report 30 Sep 2031
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 sections 4.4 • SmPC section 4.4 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 POMC or LEPR Deficiency Obesity Treated with Setmelanotide, final study report 30 Sep 2031

Missing Information: Use in pregnant/breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.6 • PL section 2 • SmPC section 4.6 notes IMCIVREE should not be started during pregnancy or while attempting to get pregnant. • SmPC section 4.6 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 POMC or LEPR Deficiency Obesity Treated with Setmelanotide, final study report 30 Sep 2031
Missing Information: Use in hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC sections 4.2 and 5.2 • PL section 2 • SmPC sections 4.2 and 5.2 note that setmelanotide 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 POMC or LEPR Deficiency Obesity Treated with Setmelanotide, final study report 30 Sep 2031
Missing information: Use in severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures • SmPC sections 4.2 and 5.2 • PL section 2 • SmPC sections 4.2 and 5.2 recommend IMCIVREE not be administered to patients with moderate or 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 POMC or LEPR Deficiency Obesity Treated with Setmelanotide, final study report 30 Sep 2031

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 POMC or LEPR Deficiency Obesity Treated with Setmelanotide, final study report 30 Sep 2031

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 POMC or LEPR Deficiency Obesity Treated with Setmelanotide

Purpose of the study:
This observational registry will provide data to further assess the long-term safety of IMCIVREE as prescribed in routine practice for patients with bi-allelic homozygous POMC or LEPR deficiency obesity, with a focus on characterising and quantifying the important potential risks of special interest, as well as describing the safety in populations underrepresented in the clinical trial development programme.