Swiss Summary of the Risk Management Plan for KIMMTRAK® (tebentafusp)

Version 1.0 (dated 17 May 2023)

Based on the EU-RMP Version 1.0 (dated 24 February 2022)

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 KIMMTRAK® 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 KIMMTRAK® in Switzerland, is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedicinfo.ch), approved and authorized by Swissmedic.

Immunocore GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of KIMMTRAK®.

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Summary of risk management plan for KIMMTRAK (tebentafusp)

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

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

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

I. The medicine and what it is used for

KIMMTRAK is authorised for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma (see SmPC for the full indication). It contains tebentafusp as the active substance and it is given intravenously.

Further information about the evaluation of KIMMTRAK's benefits can be found in KIMMTRAK'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/kimmtrak.

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

Important risks of KIMMTRAK, together with measures to minimise such risks and the proposed studies for learning more about KIMMTRAK'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 the case of KIMMTRAK, 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 periodic safety updated 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 KIMMTRAK is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of KIMMTRAK 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 KIMMTRAK. 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	• Cytokine release syndrome • Acute skin reactions
Important potential risks	• None
Missing information	• Use in pregnancy and lactation • Use in patients with clinically significant cardiac disease

II.B Summary of important risks

Important identified risk 1: Cytokine release syndrome	
Evidence for linking the risk to the medicine	Cytokine release syndrome (CRS) is an expected adverse reaction related to immune cell activation caused by tebentafusp. When immune cells are activated, they produce proteins called cytokines. This can cause low blood pressure, fever, chills, nausea, vomiting, tiredness and headache, and less frequently low oxygen levels in the body (hypoxia). Cytokine release syndrome occurred in 88.6% of patients treated with tebentafusp in Study 202. They were mainly non-serious and mild or moderate in severity with only 0.8% patients experiencing severe (Grade 3) reactions. The duration of CRS was generally short (3 days) and only 1.2% patients discontinued tebentafusp because of CRS. CRS typically occurred in the first 3 weekly doses and then reduced in frequency and severity with the next infusions. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Risk factors and risk groups	No risk factors or patient groups were found to have an increased risk of CRS in the clinical studies. The first three infusions of tebentafusp are associated with a greater frequency and severity of CRS.
Risk minimisation measures	Routine risk minimisation measures: • *Guidance on premedication, monitoring and management for CRS based on severity in SmPC section 4.2*

	• *Warning that tebentafusp can cause CRS, what to expect and how to manage CRS in SmPC section 4.4* • *Warning to monitor patients with cardiac disease, QT prolongation and risk factors for cardiac failure in SmPC sections 4.2 and 4.4* • *Recommendation to perform an ECG in all patients before and after treatment with KIMMTRAK in SmPC section 4.4* • *Warning for the patient to inform their doctor or nurse immediately or seek urgent medical attention if they develop symptoms of CRS in PL section 2* • *Guidance that the patient may be given fluids by infusion and the dose of corticosteroids adjusted to help prevent low blood pressure from CRS in SmPC section 4.2 and PL sections 2 and 3* • *Warning for the patient to talk to their doctor or nurse before they are given tebentafusp about heart problems including QT interval prolongation in PL section 2* • *Adverse reaction in SmPC section 4.8* • *Side effect in PL section 4* • *Restricted prescription* Additional risk minimisation measures: • *Treatment Guide for Healthcare Professionals* • *Patient Guide*

Important identified risk 2: Acute skin reactions	
Evidence for linking the risk to the medicine	Tebentafusp targets the peptide gp100 on uveal melanoma tumour cells but can also bind to gp100 on normal melanocytes (melanin-producing cells) in the skin which may lead to acute skin reactions. The most common acute skin reactions include rash, pruritis (itchy rash), erythema (redness of the skin) and oedema (swelling of body). Acute skin reactions occurred in 91.4% of patients treated with tebentafusp in Study 202. They were mainly non-serious and mild or moderate in severity; 5.7% patients experienced serious and 20.0% severe (Grade 3) acute skin reactions. Only 2.0% patients experienced acute skin reactions that led to a dose interruption or a dose reduction and no acute skin reactions resulted in discontinuation of tebentafusp. Acute skin reactions typically occurred following the first three doses of tebentafusp. They were generally manageable with treatments such as oral antihistamines and topical corticosteroids, and reduced in severity with the next infusions. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Risk factors and risk groups	No risk factors or patient groups were found to have an increased risk of acute skin reactions in the clinical studies. The first three infusions of tebentafusp are associated with a greater frequency and severity of acute skin reactions.

Risk minimisation measures	Routine risk minimisation measures: • *Guidance on management of acute skin reactions based on severity in SmPC section 4.2* • *Warning that tebentafusp can cause acute skin reactions, what to expect and how to manage acute skin reactions in SmPC section 4.4* • *Warning for the patient to inform their doctor or nurse immediately or seek urgent medical attention if they develop symptoms of skin reactions in PL section 2* • *Adverse reaction in SmPC section 4.8* • *Side effect in PL section 4* • *Restricted prescription* Additional risk minimisation measures: • *None*

Missing information 1: Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: • *Warning not to use tebentafusp during pregnancy in SmPC section 4.6 and PL section 2* • *Recommendation to use effective contraception in SmPC sections 4.4 and 4.6 and PL section 2* • *Guidance that animal reproduction studies have not been conducted in SmPC sections 4.6 and 5.3* • *Warning that breast-feeding should be discontinued during treatment with tebentafusp in SmPC section 4.6 and PL section 2* • *Restricted prescription* Additional risk minimisation measures: • *None*

Missing information 2: Use in patients with clinically significant cardiac disease	
Risk minimisation measures	Routine risk minimisation measures: • *Warning to monitor patients with cardiac disease, QT prolongation and risk factors for cardiac failure in SmPC sections 4.2 and 4.4* • *Recommendation to perform an ECG in all patients before and after treatment with KIMMTRAK in SmPC section 4.4* • *Information that patients with clinically significant cardiac disease were excluded from study participation in SmPC sections 4.2 and 5.1* • *Warning for the patient to talk to their doctor or nurse before they are given tebentafusp about heart problems including QT interval prolongation in PL section 2* • *Restricted prescription* Additional risk minimisation measures: • *None*

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 KIMMTRAK.

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

Physician Survey to Assess the Effectiveness of the additional Risk Minimisation Measures (aRMM) for KIMMTRAK (tebentafusp)

Purpose of the study:

The study will assess the following:

a) Physicians' understanding of the important safety information detailed in the Treatment Guide for Healthcare Professionals to minimise the severity of CRS with tebentafusp.

b) Healthcare professionals' distribution of the Patient Guide to patients treated with tebentafusp.