swissmedic

Date: 7 August 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

KIMMTRAK

International non-proprietary name: tebentafusp
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 100 µg / 0.5 ml
Route(s) of administration: intravenous
Marketing authorisation holder: Immunocore GmbH
Marketing authorisation no.: 68846
Decision and decision date: approved on 9 May 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
Nab	Neutralising antibodies
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event

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TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UM	Uveal melanoma

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for tebentafusp in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 3 March 2022.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

2.2.2 Approved indication

KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose of KIMMTRAK is 20 µg on Day 1, 30 µg on Day 8, 68 µg on Day 15, and 68 µg once every week thereafter.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	20 May 2022
Formal control completed	24 May 2022
List of Questions (LoQ)	27 July 2022
Response to LoQ	2 October 2022
2nd List of Questions (LoQ)	17 November 2022
Response to 2nd LoQ	23 January 2023
Preliminary decision	10 March 2023
Response to preliminary decision	13 April 2023
Final decision	9 May 2023
Decision	approval

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available assessment report KIMMTRAK - EMEA/H/C/004929/0000, 24 February 2022 issued by the EMA.

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3 Medical context

Advanced uveal melanoma (UM) is a disease of high unmet need. In patients who have developed metastatic disease, prognosis and outcome are poor, typically with median overall survival (OS) of less than 12 months, and in patients with extensive liver metastases median OS is approximately 6 months. No medicinal product is currently authorised in Switzerland specifically for the indication advanced UM. The currently available and recommended medical treatment for the indication advanced UM is unsatisfactory, as despite these therapies median OS is generally ≤ 12 months, and hence more effective or safer treatments are needed.

The present application for KIMMTRAK (tebentafusp) is primarily based on the clinical data from the pivotal Phase 3 open-label RCT IMCgp100-202 (Study 202), and supported by clinical data from the Phase1/2 study IMCgp100-102 (Study 102). Study 102 is an ongoing, single arm study evaluating tebentafusp in the treatment of a previously treated metastatic UM population, i.e. patients who experienced disease progression while on 1 or 2 prior lines of therapy, including chemotherapy, immunotherapy, or targeted therapy. This means that while the pivotal study has been conducted in the 1L setting according to the proposed new indication, the supportive study has been conducted in a 2L+ setting.

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4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report KIMMTRAK - EMEA/H/C/004929/0000, 24 February 2022 issued by the EMA.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The preclinical aspects in this SwissPAR refer to the publicly available assessment report KIMMTRAK - EMEA/H/C/004929/0000, 24 February 2022 issued by the EMA.

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6 Clinical and clinical pharmacology aspects

Swissmedic Clinical Assessment has not assessed the primary data relating to clinical aspects of this application, and its decision relies primarily on the results of the assessment of the foreign reference authority, the EMA. For details reference is made to the publicly available assessment report KIMMTRAK, EMEA/H/C/004929/0000, 24 February 2022.

As described below, the focus of Swissmedic Clinical Assessment has been on updated overall survival (OS) and safety data as well as on immunogenicity results.

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data in this application has been carried out in reliance on previous regulatory decisions by the FDA and EMA. The available assessment reports and corresponding product information were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, refer to the information for healthcare professionals.

6.2 Dose finding and dose recommendation

Refer to CHMP assessment report KIMMTRAK, EMEA/H/C/004929/0000, 24 February 2022.

6.3 Efficacy

Based on the results of the pivotal Study 202, tebentafusp demonstrated a statistically significant improvement in the primary endpoint OS over investigator's choice therapy consisting of single agents (mainly pembrolizumab) in adult patients with HLA-A*02:01-positive advanced UM previously untreated in the metastatic setting (1L treatment setting). The results of the primary analysis after a median follow-up of 14 months (data cut-off (DCO) date 13 October 2020) showed a stratified hazard ratio (HR) of 0.51 (95% confidence interval (CI) 0.37, 0.71) and a median OS of 21.7 months (95% CI 18.6, 28.6) vs. 16.0 months (95% CI 9.7, 18.4). This OS outcome has been confirmed by updated mature OS data.

Progression-free survival (PFS) results for tebentafusp vs. investigator's choice therapy were stratified HR 0.73 (95% CI 0.58, 0.94) and median PFS 3.3 months (95% CI 3.0, 5.0) vs. 2.9 months (2.8, 3.0).

Objective response rates (ORR) for tebentafusp vs. investigator's choice therapy were 9.1% (95% CI 5.9, 13.4) vs. 4.8% (95% CI 1.8, 10.1).

For further details see the information for healthcare professionals and the CHMP assessment report KIMMTRAK, EMEA/H/C/004929/0000, 24 February 2022.

6.4 Safety

Tebentafusp has substantial toxicity, of which the most relevant is associated with cytokine release syndrome (CRS) and skin toxicity. Nonetheless, fatal adverse events and permanent treatment discontinuation in patients on tebentafusp were rare. Thus, overall, based on the available safety data, the toxicity profile appears manageable and acceptable given the poor prognosis of advanced UM and the limited therapeutic options.

The initially submitted safety datasets of pivotal Study 202 and supportive Study 102, which formed the basis of the benefit-risk assessment for the proposed new indication, were outdated. The updated safety data requested by Swissmedic Clinical Assessment were consistent with earlier data.

For further details see the information for healthcare professionals and the CHMP assessment report KIMMTRAK, EMEA/H/C/004929/0000, 24 February 2022.

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Immunogenicity

Additional data requested by Swissmedic Clinical Assessment showed that a substantial proportion of patients developed neutralising antibodies (NAbs) against tebentafusp, i.e. in up to approximately 20% of all patients treated with tebentafusp and 65% of ADA-positive patients. Although the potential for substantial decreases in tebentafusp exposure is high in those patients who develop NAbs, for instance between 41% and 56% of patients with a high NAb titer had exposure values below the limit of the bioanalytical method, overall, high titer NAb formation was limited to 12% of the tebentafusp-treated population. Updated safety data did not show any safety signal of concern related to NAbs. Despite limitations (additional analyses limited to Study 202, small numbers, unclear DCO), available data do not suggest the presence of detrimental effects on OS in NAb-positive patients.

As a prerequisite for approval, the applicant was asked to adequately reflect the NAb-related information in the information for healthcare professionals, including a statement that an association between the presence of NAbs and reduced efficacy cannot be excluded – see the information for healthcare professionals for further details.

6.5 Final clinical and clinical pharmacology benefit-risk assessment

Based on the available data, and following the adaptations to the information for healthcare professionals as mandated by Swissmedic, the benefit-risk balance of tebentafusp was considered positive for the proposed new indication:

*KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.*

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for KIMMTRAK was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

KIMMTRAK®

Composition

Active substances

Tebentafusp.
Tebentafusp is a fusion protein, produced by recombinant DNA technology in *Escherichia coli* cells.

Excipients

Citric acid monohydrate (E330), di-sodium hydrogen phosphate anhydrous (E339), mannitol (E421), trehalose dihydrate, polysorbate 20 (E432), water for injections q.s. ad solutionem pro 0.5 ml.
One vial (0.5 ml) contains 0.94 mg sodium.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for intravenous infusion (sterile concentrate).
One 0.5 ml vial contains 100 micrograms of tebentafusp, corresponding to a concentration before dilution of 200 mcg/ml.
Clear, colourless to slightly yellowish solution in a single-dose vial.

Indications/Uses

KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Dosage/Administration

KIMMTRAK should be administered under the direction and supervision of a physician experienced in the use of anti-cancer agents and the treatment of cytokine release syndrome (CRS) and only in appropriately equipped, specialised centres that have multidisciplinary teams with sufficient experience to provide intensive medical care for potential severe complications. Patients should be monitored closely and at least the first three infusions of KIMMTRAK should be administered in a hospital setting (see «Warnings and precautions»).

Patients treated with KIMMTRAK must have HLA-A*02:01 genotype determined by any validated HLA genotyping assay.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

The recommended dose of KIMMTRAK is 20 micrograms on Day 1, 30 micrograms on Day 8, 68 micrograms on Day 15, and 68 micrograms once every week thereafter (see section «Instructions for handling»). Treatment with KIMMTRAK should be continued while patient is deriving clinical benefit and in the absence of unacceptable toxicities (see «Properties/Effects»).

Premedication

To minimize the risk of hypotension associated with cytokine release syndrome (CRS), intravenous fluids should be administered prior to starting KIMMTRAK infusion based on clinical evaluation and the volume status of the patient.
For patients with preexisting adrenal insufficiency on maintenance systemic corticosteroids, adjusting the corticosteroid dose should be considered to manage the risk of hypotension.

Dose adjustments

No dose reductions of KIMMTRAK are recommended. KIMMTRAK should be withheld or discontinued to manage adverse reactions as described in Table 1 and Table 2.

If CRS is suspected, the symptoms should be identified and promptly managed according to recommendations in Table 1 and taking into account current consensus-based guidelines. A supportive treatment of CRS (i.e., administration of oxygen, antipyretic agents, intravenous fluids, corticosteroids, and vasopressors) and laboratory testing to monitor disseminated intravascular coagulopathy (DIC), hematologic parameters, and pulmonary, cardiac, renal, and hepatic function should be considered. The majority (84%) of episodes of CRS started the day of infusion (range 1-3 days). Among cases that resolved, the median time to resolution of CRS was 2 days.

See Table 2 for management guidelines for acute skin reactions.

Table 1: CRS grading and management guidance

CRS grade*	Management
Grade 1 Temperature ≥ 38 °C No hypotension or hypoxia	▪ Continue treatment with KIMMTRAK. Monitor for escalation in CRS severity.
Grade 2 Temperature ≥ 38 °C	▪ Continue treatment with KIMMTRAK. ▪ For Grade 2 CRS, if hypotension and hypoxia do not improve within 3 hours or CRS

Hypotension that responds to fluids and does not require vasopressors Oxygen requirement includes low flow nasal cannula (delivery of oxygen ≤ 6 l/min) or blow-by	worsens, proceed as for Grade 3 CRS. Administer premedication with systemic corticosteroid prior to next dose, followed by close monitoring in a hospital setting (see «Warnings and precautions»).
Grade 3 Temperature ≥ 38 °C Require a vasopressor with or without vasopressin Require high flow nasal cannula (delivery of oxygen > 6 l/min), face mask or non-rebreather mask or Venturi mask	▪ Withhold KIMMTRAK until CRS and sequelae have resolved ▪ Resume KIMMTRAK at same dose level (i.e., do not escalate if Grade 3 CRS occurred during initial dose escalation; resume escalation once dosage is tolerated) ▪ For Grade 3 CRS, administer premedication with systemic corticosteroid if not already administered prior to next dose, followed by close monitoring in a hospital setting (see «Warnings and precautions»).
Grade 4 Temperature ≥ 38 °C Require multiple vasopressors (excluding vasopressin) Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation).	▪ Permanently discontinue KIMMTRAK

* Based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading of CRS criteria (Lee et al. 2019).

Table 2: Recommended management and dose modifications for acute skin reactions

Adverse reactions	Severity[a]	Management
Acute skin reactions (see «Warnings and precautions»)	Grade 2	▪ Withhold KIMMTRAK until Grade ≤ 1 or baseline. ▪ Administer antipruritic regimen (e.g., non-sedating long-acting antihistamine)

		▪ Administer topical corticosteroid treatment for symptomatic rash that does not respond to anti-pruritic regimen. ▪ Consider systemic steroid therapy if symptoms persist. ▪ Resume KIMMTRAK escalation if the current dose is less than 68 mcg, or resume at same dose level if dose escalation has completed
	Grade 3	▪ Withhold KIMMTRAK until Grade ≤ 1 or baseline. ▪ Administer topical corticosteroid and oral corticosteroids ▪ For persistent reactions not responding to oral steroids, consider intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent) ▪ Resume KIMMTRAK at same dose level (i.e., do not escalate if Grade 3 skin reactions occurred during initial dose escalation; resume escalation once dosage is tolerated)
	Grade 4	▪ Permanently discontinue KIMMTRAK ▪ Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI CTCAEv4.03).

Special dosage instructions

Patients with hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. KIMMTRAK has not been studied in patients with moderate or severe hepatic impairment at baseline (see «Pharmacokinetics»), so that for these patients no dose recommendations can be given, and any dosing should only be done after careful individual risk-benefit assessment and with caution and under careful monitoring.

Patients with renal disorders

Based on safety and efficacy analyses, dose adjustment is not necessary in patients with mild to moderate renal dysfunction. No dose recommendations can be made for patients with severe renal impairment because of the lack of pharmacokinetic data; therefore, dosing in patients with severe renal impairment should only be done after careful individual risk-benefit assessment and with caution and careful monitoring (see «Pharmacokinetics»).

Elderly patients

No dose adjustment is required for elderly patients (≥ 65 years of age).

Pediatric population

KIMMTRAK is not approved for use in the pediatric population.

Mode of administration

KIMMTRAK is for intravenous use. The recommended infusion period is 15 to 20 minutes. KIMMTRAK requires dilution with sodium chloride 9 mg/ml (0.9 %) solution for injection containing human albumin for intravenous infusion. Each vial of KIMMTRAK is intended for use as single-dose only. Do not shake the KIMMTRAK vial.

For instructions on dilution and administration of the medicinal product, see section «Instructions for handling».

Monitoring

First three treatment doses (and any subsequent treatment dose with preceding Grade ≥2 CRS)

First three doses of KIMMTRAK should be administered in a hospital setting with overnight monitoring for signs and symptoms of CRS for at least 16 hours. Vital signs should be monitored pre dose and at a minimum of every 4 hours until resolution of symptoms. If clinically indicated, more frequent monitoring or prolongation of hospitalization should be performed. If a CRS Grade 2 where

hypotension or hypoxia do not improve within 3 hours or 3 occurred after a tebentafusp infusion, the next infusion should also be administered in a hospital setting (see «Warnings and precautions»).

Subsequent treatment doses (in cases without preceding Grade ≥ 2 CRS)

After 68 mcg dose level is tolerated (i.e., absence of Grade ≥ 2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate outpatient ambulatory care setting. Patients should be observed for a minimum of 60 minutes following each infusion. For patients who have received outpatient treatment with KIMMTRAK for at least 3 months and have not experienced any interruptions greater than 2 weeks, outpatient monitoring following infusion may be decreased to a minimum of 30 minutes for subsequent doses.

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see «Composition»).

Warnings and precautions

Cytokine release syndrome (CRS)

Most patients experienced CRS following tebentafusp infusions. Diagnosis of CRS was most frequently based on pyrexia followed by hypotension and infrequently hypoxia. Other commonly observed symptoms with CRS included chills, nausea, vomiting, fatigue, and headache.

The majority (84%) of episodes of CRS started the day of infusion (range 1-3 days). Among cases that resolved, the median time to resolution of CRS was 2 days. Pyrexia was noted in nearly all cases of CRS, and in these patients, an increase in body temperature generally occurred within the first 8 hours after tebentafusp infusion. CRS rarely (1.2 %) led to treatment discontinuation.

Patients should be monitored over night for signs or symptoms of CRS for at least 16 hours following first three infusions of tebentafusp. In addition, if grade 2 CRS where hypotension or hypoxia do not improve within 3 hours, or any grade 3 CRS occurs after last tebentafusp infusion additional overnight monitoring for at least 16 hours should be repeated. The monitoring must be in a hospital setting in an area with immediate access to medicinal products and resuscitative equipment to manage CRS (see «Dosage/Administration», «Monitoring»). In addition, patients should be monitored daily at a qualified treatment centre for signs and symptoms of CRS for the first 3 days after the first infusion of tebentafusp, and patients should be instructed to remain in the vicinity of a qualified treatment centre during this period. Any further monitoring will be at the discretion of the physician. If CRS is observed, prompt treatment should be initiated to avoid escalation to severe or life-threatening events and monitoring should be continued until resolution.

Patients should be instructed to seek immediate medical treatment even after discharge from the hospital if signs or symptoms of CRS occur. In these cases, patients should immediately contact their physician regarding any necessary therapeutic measure and potential need for hospitalization.

At subsequent doses, patients should be closely monitored after treatment for early identification of signs and symptoms of CRS (see «Dosage/Administration», «Mode of administration»). Patients with co-morbidities, including cardiovascular disorders, may be at increased risk for sequalae associated with CRS.

Treatment with tebentafusp has not been studied in patients with clinically significant cardiac disease (see «Properties/Effects»). Depending on persistence and severity of CRS Tebentafusp treatment should be withheld or discontinued (see «Dosage/Administration», Table 1).

Acute skin reactions

Acute skin reactions have been reported with tebentafusp infusion, which may be based on its mechanism of action and gp100 expression in normal melanocytes in the skin. Acute skin reactions mainly included rash, pruritus, erythema and cutaneous oedema (see «Undesirable effects»).

Acute skin reactions typically occurred following each of the first three tebentafusp infusions and decreased in severity and frequency over time. Majority of symptoms resolved without any systemic corticosteroid or any long term sequalae.

Acute skin reactions can be managed with antihistamine and topical corticosteroids. For persistent or severe symptoms, systemic steroids should be considered. Management of signs and symptoms of skin reactions may require temporary delays of subsequent tebentafusp treatments (see «Dosage/Administration», Table 2).

Cardiac disease

Cardiac events such as sinus tachycardia and arrhythmia have been observed in patients who have received tebentafusp treatment (see «Undesirable effects»). Patients with preexisting cardiovascular disorders may be at increased risk for sequalae associated with CRS and should be monitored carefully. Any patient with signs or symptoms consistent with cardiac events should be evaluated and promptly treated. In addition, appropriate treatment should be administered for any underlying CRS as a precipitating factor.

Cases of QT interval prolongation were reported following tebentafusp treatment (see «Undesirable effects»). Tebentafusp treatment should be administered with caution in patients with history of or predisposition to QT interval prolongation and in patients who are taking medicinal products that are known to prolong QT interval.

An electrocardiogram (ECG) should be performed in all patients before and after tebentafusp treatment during the first 3 weeks of treatment and subsequently as clinically indicated. If QTcF exceeds 500 msec or increases by ≥ 60 msec from baseline value tebentafusp treatment should be withheld and patients should be treated for any underlying precipitating factors including electrolyte abnormalities. Tebentafusp treatment should be resumed once QTcF interval improves to < 500 msec or is < 60 msec from baseline value. Depending on persistence and severity of the cardiac event and any associated CRS tebentafusp treatment should be withheld or discontinued (see «Dosage/Administration», Table 1).
KIMMTRAK has not been studied in patients with history of significant cardiac disease. Patients with cardiac disease, QT prolongation and risk factors for cardiac failure should be monitored carefully.

Anti-drug neutralizing antibodies (ADA)

Neutralizing ADA (NAbs) were detectable in up to 19% (corresponding to up to 65% of all ADA-positive patients) of tebentafusp-treated patients and were associated with reductions in maximum tebentafusp concentrations (C_{max}) of up to 79%. High NAb titers were present in 12% of treated patients, resulting in tebentafusp exposure below the bioanalytical detection limit in up to 56% of these patients. Although no evidence was available regarding the effect of ADA on the safety or efficacy of tebentafusp, the small number of patients does not allow robust conclusions regarding clinical significance. In particular, it cannot be excluded that the presence of Nabs, especially in the presence of high titers, is associated with reduced efficacy (see “Immunogenicity”).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially «sodium-free».

Interactions

No formal drug interaction studies have been performed with tebentafusp.

Initiation of tebentafusp treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 24 hours of the first three doses of tebentafusp in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. These patients should be monitored for toxicity (e.g., warfarin) or drug concentrations (e.g., cyclosporine). The dose of the concomitant medicines should be adjusted as needed.

Pregnancy, lactation

Women of childbearing potential/Contraception

Women of childbearing potential should use effective contraception during treatment with tebentafusp and for at least 1 week after last dose of tebentafusp.

Pregnancy

There are no data from the use of tebentafusp in pregnant women. Animal reproduction studies have not been conducted with tebentafusp (see «Preclinical data»).

Tebentafusp is not recommended during pregnancy and in women of childbearing potential not using contraception. The pregnancy status in females of reproductive potential should be verified prior to initiating tebentafusp treatment.

Lactation

There is insufficient information on the excretion of tebentafusp/metabolites in human milk. A risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with tebentafusp.

Fertility

The effect of tebentafusp on male and female fertility is unknown. No animal studies on fertility have been conducted with tebentafusp (see «Preclinical data»).

Effects on ability to drive and use machines

No corresponding studies have been performed.
During the administration of KIMMTRAK undesirable effets such as fatigue, dizziness and nausea have been reported, which may have an influence on the ability to drive and use machines.

Undesirable effects

Summary of safety profile

The most common adverse drug reactions in patients treated with KIMMTRAK were cytokine release syndrome (88 %), rash (85 %), pyrexia (52 %), pruritus (72 %), fatigue (55 %), nausea (66 %), chills (56 %), abdominal pain (86 %), oedema (56 %), hypo/hyperpigmentation (48 %), hypotension (43 %), dry skin (35 %), headache (32 %) and vomiting (62 %).

Adverse reactions led to permanent discontinuation in 4 % of patients receiving KIMMTRAK. The most common adverse reaction that led to discontinuation of KIMMTRAK was cytokine release syndrome.

Adverse reactions resulting in at least one dose interruption occurred in 32 % of KIMMTRAK-treated patients (dosed weekly) and resulted in a median of one skipped dose. Adverse reactions requiring dosage interruption in ≥ 2 % of patients included fatigue (3 %; Grade 1-3), pyrexia (2.7 %; Grade 1-3), alanine aminotransferase increase (2.4 %; Grade 1-4), aspartate aminotransferase increase (2.4 %; Grade 1-3) abdominal pain (2.1 %; Grade 1-3), and lipase increased (2.1 %; Grade 1-3).

Adverse reactions leading to at least one dose modification occurred in 5.3 % of patients in KIMMTRAK-treated group. Adverse reactions which required dose modification in ≥ 1 % of patients were cytokine release syndrome (1.9 %; Grade 1-3), and hypotension (1.1 %; Grade 2-4).

List of adverse reactions

Table 3 summarizes adverse reactions that occurred in metastatic uveal melanoma patients from two clinical studies (IMCgp100-102 and IMCgp100-202) that received the recommended dosing KIMMTRAK dosing regimen of 20 micrograms on Day 1, 30 micrograms on Day 8 and 68 micrograms on Day 15 and 68 micrograms weekly thereafter (N=378).

The adverse drug reaction frequency is listed by MedDRA System Organ Class (SOC) at the preferred term level. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions in patients treated across studies with KIMMTRAK monotherapy

	Adverse reactions	**All grade (%) N=378**	**Grade ≥ 3 (%)**
Infections and infestations			
Very common	Nasopharyngitis	11	0.3
Immune system disorders			
Very common	Cytokine release syndrome[1]	88	0.8
Metabolism and nutrition disorders			
Very common	Hypomagnesaemia	34	0
Very common	Hyponatraemia	36	4
Very common	Hypocalcaemia	46	1.6
Very common	Decreased appetite	23	0.5
Very common	Hypokalaemia	19	1.9
Uncommon	Tumour lysis syndrome	0.3	0.3

Psychiatric disorders			
Very Common	Insomnia	13	0
Common	Anxiety	7	0.3
Nervous system disorders			
Very common	Headache[2]	33	0.5
Very common	Dizziness	15	0
Very common	Paraesthesia	11	0
Common	Taste disorder	8	0
Cardiac disorders			
Very common	Tachycardia[2]	16	0.3
Common	Arrhythmia[2]	2	0.5
Common	Angina pectoris[2]	1.3	1.1
Common	Atrial fibrillation[2]	1.1	0.5
Uncommon	Cardiac failure[2]	0.3	0.3
Vascular disorders			
Very common	Hypotension[2]	43	7
Very common	Flushing	11	0
Very common	Hypertension	17	8
Respiratory, thoracic and mediastinal disorders			
Very common	Cough	22	0.3
Very common	Dyspnoea	16	1.3
Common	Oropharyngeal pain	9	0
Common	Hypoxia[2]	3	1.3
Gastrointestinal disorders			
Very common	Nausea[2]	58	2.4
Very common	Abdominal pain	52	4
Very common	Vomiting[2]	35	1.6
Very common	Diarrhoea	28	1.6
Very common	Constipation	22	0.2
Very common	Dyspepsia	18	0.2
Skin and subcutaneous tissue disorders			
Very common	Rash	85	18.3
Very common	Pruritus	73	4.8
Very common	Dry skin	35	0.3

Very common	Hypo/ hyperpigmentation[4]	49	0.3
Very common	Erythema	28	0.5
Very common	Alopecia	10	0
Very common	Night sweats	11	0.5
Musculoskeletal and connective tissue disorders			
Very common	Arthralgia	29	1.3
Very common	Back pain	26	1.1
Very common	Myalgia	15	0.3
Very common	Pain in extremity	12	0.8
Common	Muscle spasm	7	0.5
General disorders and administration site conditions			
Very common	Pyrexia[2]	80	4.5
Very common	Fatigue[3]	67	5.6
Very common	Chills[2]	57	0.8
Very common	Oedema[5]	52	1.3
Very common	Influenza like illness	11	0
Investigations			
Very common	Lymphocyte count decreased	89	57
Very common	Blood creatinine increased	87	1.3
Very common	Anaemia	59	2
Very common	Aspartate aminotransferase increased	58	12
Very common	Blood phosphate decreased	54	15
Very common	Alanine aminotransferase increased	51	8
Very common	Lipase increased	44	16

Very common	Blood alkaline phosphatase increased	41	5
Very common	Blood bilirubin increased	29	5
Common	Amylase increased	7	1.6
Common	Gamma glutamyltransferase increased	3.7	2.6
Common	White blood cell count increased	1.1	0
Uncommon	Electrocardiogram QT prolonged	0.3	0
Uncommon	Blood glucose increased	0.8	0.8

[1] CRS was adjudicated using the ASTCT consensus grading of CRS criteria (Lee et al. 2019). Adjudicated CRS is provided in lieu of investigator reported CRS.

[2] Some of the events may be associated with CRS or may be isolated reported events.

[3] Includes fatigue and asthenia.

[4] Includes achromotrichia acquired, ephelides, eyelash discolouration, eyelash hypopigmentation, hair colour changes, lentigo, pigmentation disorder, retinal depigmentation, skin depigmentation, skin discolouration, skin hyperpigmentation, skin hypopigmentation, solar lentigo, vitiligo.

[5] Includes eye oedema, eye swelling, eyelid oedema, periorbital swelling, periorbital oedema, swelling of eyelid, pharyngeal oedema, lip oedema, lip swelling, face oedema, generalized oedema, localized oedema, oedema, oedema peripheral, peripheral swelling, swelling, swelling face.

Description of specific adverse reactions and additional information

Cytokine release syndrome (CRS)

In clinical study IMCgp100-202, cytokine release syndrome (confirmed based on ASTCT consensus grading 2019) occurred in 89 % of KIMMTRAK treated patients. The overall incidence of CRS included 12 % Grade 1, 76 % Grade 2 and 0.8 % Grade 3 events. Most commonly observed symptoms with CRS included chills, nausea, vomiting, fatigue, hypotension, and headache. Grade 3 events that may be observed in association with CRS include tachycardia, hypoxia, angina pectoris, atrial flutter, and left ventricular dysfunction.

The majority (84 %) of episodes of CRS started the day of infusion. The median time to resolution of CRS was 2 days. CRS rarely (1.2 %) led to treatment discontinuation. All CRS symptoms were reversible.

For clinical management of CRS, see «Dosage/Administration», Table 1.

Acute skin reactions

In Study IMCgp100-202, acute skin reactions occurred in 91 % of patients treated with KIMMTRAK. including any grade rash (83 %), pruritis (69 %), erythema (25 %) and cutaneous oedema (27 %). Most skin reactions were Grade 1 (28 %) or 2 (44 %) and some KIMMTRAK treated patients experienced Grade 3 (21 %) events. Among patients with observed rash, patients commonly experienced rash (55 %), rash maculo-papular (31 %) and skin exfoliation (21 %). Grade 3 adverse reactions of rash were reported in 5 % of patients and included rash (2.4 %) and rash maculopapular (1.6 %).

Acute skin reactions typically occurred following each of the first three KIMMTRAK infusions, with decreasing frequency of ≥ Grade 3 reactions (dose 1; 17 %, dose 2; 10 %, dose 3; 8 %, dose 4; 3 %). The median time to onset of acute skin reactions was 1 day in the KIMMTRAK treated patients and median time to improvement to ≤ Grade 1 was 6 days.

For clinical management of acute skin reactions, see «Dosage/Administration», Table 2.

Elevated liver enzymes

In Study IMCgp100-202 where 95 % of patients had preexisting liver metastasis, ALT/AST increase to ≥ Grade 1 were observed in 65 % of patients treated with KIMMTRAK. Elevations in bilirubin have been reported in 27 % of patients and these were primarily associated with increase in size of liver metastasis. The majority Grade 3 or 4 ALT/AST elevations generally occurred within the first 3 KIMMTRAK infusions. Most patients experiencing Grade 3 or 4 ALT/AST elevations had improvement to ≤ Grade 1 within 7 days.

Immunogenicity

Treatment -emergent anti-drug antibodies (ADA) against tebentafusp were detected in 33 % and 29 % of patients receiving tebentafusp across all doses in study IMCgp100-102 and study IMCgp100-202, respectively. The median onset time to ADA formation was 6 to 9 weeks after start of tebentafusp treatment.

Neutralizing ADA (NAbs) were detectable in 15-19% (corresponding to 60-65% of all ADA-positive patients) of patients treated with tebentafusp in the IMCgp100 102 and IMCgp100 202 studies. The median time to NAbs formation was 13 to 16 weeks after treatment initiation, and NAbs were

persistent in the majority of these patients. The occurrence of NAbs was associated with a reduction in maximum tebentafusp concentrations (C_{max}) of 67% to 79%. High NAb titers (i.e. above the median ADA titer) was detectable in approximately 12% (corresponding to 40-52% of all ADA-positive patients). Almost all patients with high Nab titers had a reduced tebentafusp exposure, in 41-56 % of these patients, tebentafusp exposure was below the bioanalytical detection limit.
There was no evidence of effect of ADA on the safety or efficacy of tebentafusp, although the small number of patients, who presented a high ADA titer, does not allow robust conclusions regarding clinical significance. In particular, it cannot be excluded that the presence of Nabs, especially in the presence of high Nabs titers which were observed in 12% of those treated, is associated with reduced efficacy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no information on overdose with tebentafusp. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately.

Properties/Effects

ATC code

L01XX75

Mechanism of action

Tebentafusp is a bispecific fusion protein, comprised of a T cell receptor (TCR; targeting domain) fused to an antibody fragment targeting CD3 (cluster of differentiation 3; effector domain). The TCR end binds with high affinity to a gp100 peptide presented by human leukocyte antigen – A*02:01 (HLA-A*02:01) on the cell surface of uveal melanoma tumour cells, and the effector domain binds to the CD3 receptor on the polyclonal T cell.

An immune synapse is formed when the TCR targeting domain of tebentafusp binds to uveal melanoma cells and the CD3 effector domain binds to polyclonal T cells. This immune synapse results in redirection and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of uveal melanoma tumour cells.

Pharmacodynamics

Transient and clinically nonsignificant reduction in lymphocyte counts in blood was observed after treatment with tebentafusp. Lymphocytes decreased the day after the first 3 doses and returned to baseline prior to subsequent doses.

After treatment with tebentafusp, transient increases in serum levels of proinflammatory cytokines and chemokines were observed in samples collected after the first three doses. Peak levels were observed between 8 to 24 hours after treatment with tebentafusp and levels returned to baseline prior to subsequent doses.

Clinical efficacy

Study IMCgp100-202: Previously untreated metastatic uveal melanoma

Study IMCgp100-202 was a randomised, open label, multicentre study that enrolled HLA-A*02:01 positive metastatic uveal melanoma patients who were naïve to systemic therapy. Patient could not have received previous systemic treatment or localized (liver--directed) therapy for metastatic uveal melanoma except for a prior surgical resection of oligometastatic disease. Patient were excluded for presence of symptomatic or untreated brain metastasis, symptomatic congestive heart failure, QT interval corrected by Fridericia's formula (QTcF) > 470 msec or congenital long QT syndrome, acute myocardial infarction, or unstable angina pectoris less than 6 months prior to treatment initiation.

Patients were randomised (2:1) to receive tebentafusp weekly by intravenous infusion according to the recommended intra-patient dosing regimen «Dosage/Administration» or investigator's choice treatment (pembrolizumab, ipilimumab, or dacarbazine) at the approved doses of these agents until disease progression or unacceptable toxicity.

Treatment breaks for up to 2 consecutive weeks were allowed. Randomisation was stratified by lactate dehydrogenase (LDH) status, a known prognostic factor for unresectable or metastatic UM.

The primary efficacy outcome was overall survival (OS) in all patients randomised in the study. Tumour assessments were conducted every 12 weeks. Additional efficacy outcomes were investigator assessed progression free survival (PFS) A total of 378 patients were randomised; 252 to tebentafusp-treated group and 126 to the investigator's choice treated group (pembrolizumab: 82 %; ipilimumab: 12 %; or dacarbazine: 6 %). The median age was 64 years (range 23 to 92 years); with 49.5 % of patients ≥ 65 years, 87 % were white, 50 % were female. Baseline ECOG performance status was 0 (72 %) or 1 (20.4 %) or 2 (0.3 %), 36 % had elevated LDH level, and 95 % had liver metastasis.

After completion of the primary efficacy analysis, patients from the investigator's choice arm were permitted to crossover to the tebentafusp treatment. With a median duration of follow up of 22.4 months, the updated OS continued to favour the tebentafusp arm (HR= 0.58; 95 % CI: 0.44, 0.77). At the time of analysis, 16 patients had crossed over to tebentafusp treatment.

The efficacy results are summarized in Table 4.

Table 4: Efficacy results in study IMCgp100-202

Primary and secondary endpoints	**KIMMTRAK (N = 252)**	**Investigator`s choice therapy (N = 126)**
Overall survival (OS) [1]		
Number of deaths	87 (34.5 %)	63 (50 %)
Median months (95 % CI)	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)
HR (95 % CI)[2, 4]	0.51 (0.37, 0.71)	
Stratified log-rank p-value[2]	p = <0.0001	
Progression free survival (PFS)[3, 4]		
Number (%) of patients with event	198 (78.6 %)	97 (77 %)
Median in months (95 % CI)	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)
HR (95 % CI)[4]	0.73 (0.58, 0.94)	
Stratified log-rank p-value[2]	p = 0.0139	
Objective response rate (ORR)[6]		
n (%)	26 (10.3)	6 (4.8)
95 % CI	6.9, 14.8	1.8, 10.1
Complete Response (CR)	1 (0.4)	0
Partial Response (PR)	25 (9.9)	6 (4.8)
Stable Disease (SD)[5]	52 (20.6)	16 (12.7)
Median duration of response		
Months (95 % CI)	9.9 (5.6, 22.1)	9.7 (2.7, --)

CI = Confidence interval, HR = Hazard ratio

[1] Based on a prespecified interim analysis

[2] Two-sided p-value based on log rank test stratified by LDH.

[3] As assessed by investigator using RECIST v1.1 criteria.

[4] Hazard ratio is from a proportional hazards model stratified by LDH status

[5] Based on ≥24 weeks.

[6] Updated based on all patients having opportunity for at least 3 radiological assessments

Study IMCgp100-102: Previously treated metastatic uveal melanoma

Study IMCgp100-102 was a supportive open-label, Phase 2 multicentre study conducted in 127 patients, who were treated with the dosing scheme recommended in «Dosage/Administration». Patients were required to be HLA-A*02:01 positive. Patients were eligible if they had experienced disease progression following at least 1 or more prior lines of liver directed therapy or systemic therapy including immune check point inhibitors in the metastatic setting. Patients were excluded for clinically significant cardiac disease and presence of symptomatic or untreated brain metastasis.

Major efficacy outcome measures included confirmed ORR as assessed by Independent Central Review (ICR) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Secondary efficacy outcomes included PFS, DCR, DOR and OS.

The median age was 61 years, 50 % were female, 99 % were white, the ECOG performance score was 0 (70 %) or 1 (30 %) and 96 % of patients had liver metastasis. Prior treatments included immunotherapy (73 % of patients) including immune checkpoint inhibitors (PD-1/PD-L1; 65 %; CTLA-4; 31 %) and liver directed therapy 45 %. Efficacy results from study IMCgp100-102 are summarised in Table 5.

Table 5: Efficacy results in study IMCgp100-102

Primary and secondary endpoints	**KIMMTRAK (N = 127)**
Confirmed objective response rate[1]	6 (4.7 %)
(95 % CI)	(1.8 %, 10 %)
Complete response (CR)	0
Partial Response (PR)	6 (4.7 %)
Stable Disease (SD)[2]	23 (18.1 %)
Median duration of response	
Months (95 % CI)	8.7 (5.6, 24.5)

[1] As assessed by independent central review using RECIST v1.1 criteria.

[2] Based on ≥ 24 weeks

Pharmacokinetics

Absorption

The pharmacokinetics of tebentafusp appear linear and dose proportional over a dose range of 20 mcg to 68 mcg. Following weekly intravenous infusion in metastatic uveal melanoma patients, the maximum plasma concentrations (C_{max}) reached 4.2 ng/ml - 13.7 ng/ml immediately at the end of

infusion (T = 0.5 hours). No accumulation was observed with a weekly dosing regimen at the target therapeutic doses.

Distribution

Tebentafusp did not distribute extensively and displayed a volume of distribution comparable to blood volume (5.25 l).

Metabolism

The metabolic pathway of tebentafusp has not been characterised. Like other protein therapeutics, tebentafusp is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

The excretion of tebentafusp is not fully characterised. Based on its molecular size that is close to the glomerular filtration size exclusion threshold, small amounts of tebentafusp may be excreted in the urine.

Following administration of tebentafusp in metastatic uveal melanoma patients the estimated systemic clearance was 4. 29 l/d, with a terminal half-life of 6 to 8 hours.

Kinetics in specific patient groups

Population pharmacokinetic analysis indicated that there was no significant effect of weight (43 to 163 kg), gender, race, and age (23 to 91 years) on tebentafusp clearance.

Hepatic impairment

No formal pharmacokinetic studies of tebentafusp have been conducted in patients with hepatic impairment. Population PK analyses demonstrated that baseline and on treatment ALT/AST elevations did not impact tebentafusp pharmacokinetics. No dose adjustments based on ALT/AST levels are recommended.

Renal impairment

No formal pharmacokinetic studies of tebentafusp have been conducted in patients with renal impairment.

No impact on safety or efficacy parameters was identified in patients with mild (creatinine clearance [CrCL] ranging 60 to 89 ml/min) to moderate (CrCL ranging 30 to 59 ml/min) renal impairment and no dose adjustments are recommended. There are limited data from patients (< 5 %) with moderate renal impairment and there is no information available from patients with severe renal impairment (CrCL < 30 ml/min).

Preclinical data

Tebentafusp is a human-specific protein and there are no relevant animal species in which nonclinical toxicology of tebentafusp could be tested.

No carcinogenicity, genotoxicity, or developmental and reproductive toxicity studies have been conducted with tebentafusp.

Other information

Incompatibilities

This medicinal product may be mixed only with those medicinal products listed under «Instructions for handling».

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Shelf life after opening

The preparation does not contain a preservative. For microbiological reasons, the medicinal product should be diluted and infused immediately after opening.

Shelf life after preparation of solution for infusion

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C.

The diluted preparation for infusion is not preserved. For microbiological reasons, the ready-to-use preparation should be used immediately after dilution. If this is not possible, in-use storage times and conditions are the responsibility of the user.

Special precautions for storage

Store in the refrigerator (2-8°C).
Keep the vial in the outer carton in order to protect the contents from light.
For storage conditions after dilution of the medicinal product, see section «Shelf life after preparation of solution for infusion».
Keep out of the reach of children.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for handling

General precautions

The solution for infusion should be prepared by a healthcare professional using proper aseptic technique throughout the handling of this medicinal product.

Use aseptic technique for dilution and preparation of dosing solutions.

Closed system transfer devices (CSTDs) must not be used for dose preparation of KIMMTRAK solution for infusion.

Parenteral medicinal products and infusion bags should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Preparation

KIMMTRAK must be diluted prior to intravenous administration.

Ensure the following supplies are available prior to preparing KIMMTRAK for administration:

- 1 ml sterile syringes with graduations of 2 decimal places.
- Sterile needles.
- Human albumin; use concentration as per local availability. Local concentrations include but not restricted to 4 % (40 g/l), 5 % (50 g/l), 20 % (200 g/l), 25 % (250 g/l).
- A 100 ml infusion bag containing sodium chloride 9 mg/ml (0.9 %) solution for injection:
  - The infusion bag should be constructed of polyolefins (PO) [such as polyethylene (PE) and polypropylene (PP)] or polyvinyl chloride (PVC).
- A sterile, nonpyrogenic, low protein binding 0.2 micron in-line filter infusion set for administration of the final infusion bag.

Dilution and Administration

A 2-step process is required for preparation of the final KIMMTRAK dose:

Step 1: Prepare the infusion bag

Using aseptic technique, prepare the infusion bag as follows:

a) Using a 1 ml syringe and a sterile needle, withdraw the calculated volume of human albumin into the syringe (see Table 6 below) and add to the 100 ml infusion bag containing sodium chloride 9 mg/ml (0.9 %) solution for injection to make a final human albumin concentration between 225 mcg/ml and 275 mcg/ml.

Table 6: Examples of human albumin concentration and acceptable withdrawal volumes

Human albumin concentration	**Acceptable volume range for addition to 100 ml infusion bag for human albumin concentration between 225 mcg/ml to 275 mcg/ ml**
4 % (40 g/l)	0.63 ml (0.57 ml to 0.69 ml)

5 % (50 g/l)	0.50 ml (0.45 ml to 0.55 ml)
20 % (200 g/l)	0.13 ml (0.12 ml to 0.14 ml)
25 % (250 g/l)	0.10 ml (0.09 ml to 0.11 ml)

b) Gently homogenize the diluted solution by completing the following steps:

i. Invert the infusion bag so that the entry port is positioned at the top of the bag and tap the side of port tubing to ensure that any residual solution is released into the bulk solution.

ii. Mix by gently rotating the bag lengthwise 360 degrees from the inverted position at least 5 times. Do NOT shake the infusion bag.

iii. Repeat (i) and (ii) an additional three times.

Step 2: Preparation of KIMMTRAK solution for infusion

c) Using a 1 ml syringe and a sterile needle, withdraw the required volume of KIMMTRAK 100 micrograms/ 0.5 ml as per the dose required (shown in Table 6 below) and add to the prepared 100 ml infusion bag containing sodium chloride 9 mg/ml (0.9 %) solution for injection, plus human albumin.

d) Do NOT flush the needle and syringe on transfer. Discard the vial containing the unused portion of KIMMTRAK in accordance with local requirements. Do not prepare more than one dose from the vial.

Table 7: KIMMTRAK volumes required for addition to infusion bag

Day of treatment	Dose (mcg) of KIMMTRAK	Volume (ml) of KIMMTRAK
Day 1	20	0.10
Day 8	30	0.15
Day 15 and weekly thereafter	68	0.34

e) Mix the infusion bag by following the same procedure outlined in Step 1b.

Administration

- Administer KIMMTRAK as intravenous infusion only.
- Immediately administer the infusion over 15 to 20 minutes through a dedicated intravenous line. A sterile, nonpyrogenic, low protein binding 0.2 micron in line filter infusion set should be used. Administer the entire contents of the KIMMTRAK infusion bag to the patient.
- Upon completion of KIMMTRAK infusion, flush the infusion line with adequate volume of sterile sodium chloride 9 mg/ml (0.9 %) solution for injection, to ensure that the entire contents of the infusion bag are administered. Do not administer KIMMTRAK as an intravenous push or bolus. Do not mix KIMMTRAK with other drugs or administer other drugs through the same intravenous line.

Storage of prepared infusion bag

- KIMMTRAK does not contain a preservative. The prepared infusion bag should be administered within 4 hours from the time of preparation including the duration of infusion. During the 4 hour window, the KIMMTRAK infusion bag should remain below 30 °C.
- If not used immediately, store the KIMMTRAK infusion bag in a refrigerator at 2 °C to 8 °C for up to 24 hours from the time of preparation which includes the time allowed for equilibration of the infusion bag to room temperature and the duration of the infusion.
- Once removed from the refrigerator, KIMMTRAK infusion bag must not be refrigerated again. Discard unused KIMMTRAK solution beyond the recommended storage time.

Authorisation number

68846 (Swissmedic)

Packs

Type I glass vial with a bromobutyl rubber stopper and an aluminium/plastic flip-off seal, containing 0.5 ml concentrate.

Pack size of 1 vial. (A)

Marketing authorisation holder

Immunocore GmbH, 6343 Risch

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