Treatment Guide for Healthcare Professionals

Important information about ▼KIMMTRAK® (tebentafusp)

Information to assist healthcare professionals in:

- Description of the symptoms of Cytokine Release Syndrome (CRS), including severity, frequency, time to onset, treatment, and resolution, in patients treated with tebentafusp.
- How to manage CRS based on severity grade, including the recommendation to administer corticosteroid premedication for Grade 2 CRS that is persistent or recurrent or any Grade 3 CRS.
- How to monitor patients for the first three infusions and for subsequent infusions.
- How to minimise the risk of hypotension associated with CRS.
- Description of the ECG schedule and management requirements based on the ECG results.
- Recommendation to carefully monitor patients with cardiac disease, QT prolongation and risk factors for cardiac failure.
- Information on the importance of informing patients of the risk of CRS and the need to immediately contact their doctor or nurse if they develop symptoms of CRS.
- Information on the importance of reporting adverse reactions with details of how to report.

▼ This medicinal product is subject to additional monitoring. The additional risk minimisation material is provided by Immunocore (Ireland) Limited as a condition of the KIMMTRAK marketing authorisation.

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About this brochure

This brochure is intended to summarise important safety information about tebentafusp with patient monitoring, medical management of CRS, management of ECG schedule and handling of patients with cardiac risk factors.

This information is intended to assist healthcare professionals in communicating key safety messages to patients receiving tebentafusp therapy and in caring for patients receiving tebentafusp therapy.

It does not contain all the information about this product. Please always consult the Summary of Product Characteristics (SmPC) before prescribing, preparing or administering tebentafusp.

Tebentafusp is indicated for:

Treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. It 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.

Cytokine Release Syndrome (CRS):

In clinical trials CRS, which may be serious or life threatening, have occurred following tebentafusp infusion. It decreased in frequency and severity following each subsequent tebentafusp infusion. Monitor for at least 16 hours following the first three infusions and then as clinically indicated.

Symptoms of CRS:

- Pyrexia
- Hypotension
- Hypoxia
- Chills
- Nausea
- Vomiting
- Fatigue
- Headache

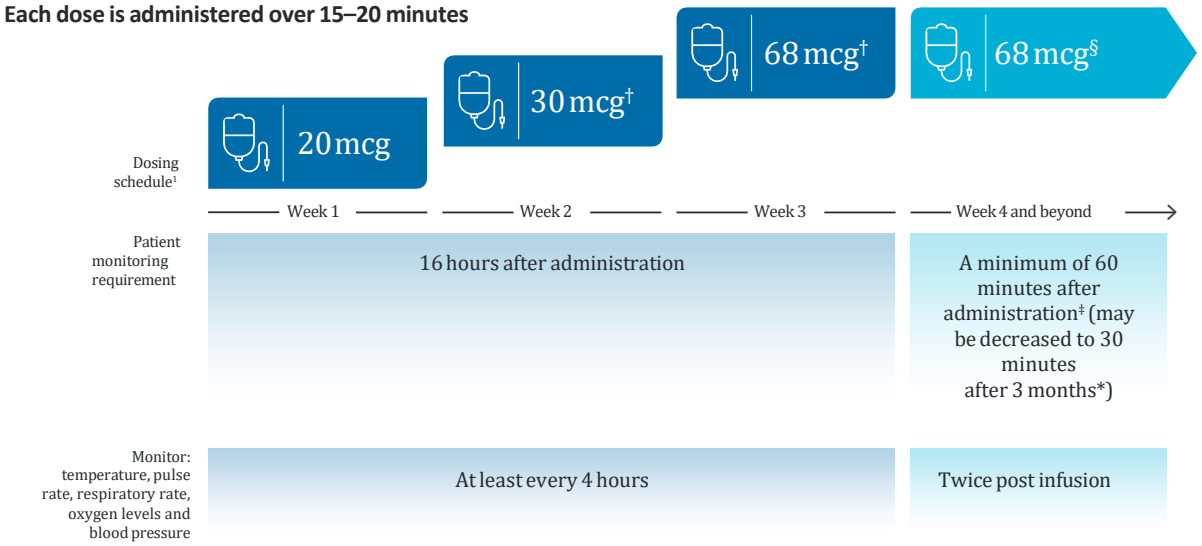
Clinical manifestation of CRS (severity, frequency, onset time, treatment options):

- In clinical trials it was seen that tebentafusp commonly causes mild to moderate CRS, which if not identified and treated appropriately may become life-threatening or fatal.
- Most patients typically experienced CRS following each of the first 3 tebentafusp infusions with decreasing severity and frequency.
    - The majority of episodes of CRS started at the day of infusion.
    - CRS led to permanent discontinuation in 1.2% of patients.
    - All CRS symptoms were reversible and were mostly managed with IV fluids, antipyretics, or a single dose of systemic corticosteroids.
    - 0.8% of trial patients required treatment with tocilizumab.
    - Pyrexia was noted in nearly all cases of CRS.

An increase in body temperature generally occurred within the first 8 hours after Tebentafusp infusion.

If CRS is observed, prompt treatment with supportive care including antipyretics, intravenous fluids, tocilizumab, or corticosteroids should be initiated to avoid escalation to severe or life-threatening events and monitoring should be continued until resolution.

Tebentafusp Patient Monitoring & Dosing:



The starting dose is 20 mcg for week 1. The dose increases to 30 mcg for week 2 and 68 mcg for weeks 3 and beyond.
One 0.5 mL KIMMTRAK vial contains 100 micrograms of tebentafusp, corresponding to a concentration before dilution of 200 mcg/mL.

† Do not escalate dose level if Grade 3 CRS or skin reactions occurred; resume escalation once dosage is tolerated. Kimmtrak treatment should be permanently discontinued if Grade 4 CRS or skin reactions are experienced at any time during treatment.

§ After 68 mcg dose level is tolerated (i.e., absence of Grade ≥2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate out-patient ambulatory care setting.

‡ If patients experience Grade 3 or 4 hypotension during any of the first three KIMMTRAK infusions, patients should be monitored every hour for at least 4 hours in an outpatient setting for the next three infusions. If the third infusion was not well tolerated (Grade ≥ 2 hypotension requiring medical intervention), follow monitoring guide as for the first 3 infusions.

* 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.

More frequent monitoring, or additional testing, should be made using clinical judgement or by institutional standards. For at least the first 3 infusions, patients should be monitored during infusion and at least for 16 hours after infusion is complete in a hospital setting with overnight monitoring.

- Based on clinical trials, 16 hours is the likely time frame for presentation of CRS symptoms.
- Ensure that healthcare providers administering tebentafusp have immediate access to medications including tocilizumab and resuscitative equipment to manage CRS.
- After infusion 3, and once the patient tolerates the most recent infusion without hypotension requiring medical intervention (e.g., giving IV fluids), subsequent doses can be administered in appropriate out-patient ambulatory care setting.

First 3 infusions of tebentafusp: during infusions and 16-hour monitoring post-infusion

Before dosing and every 4 hours (at a minimum) thereafter, check vital signs:

- temperature
- pulse rate
- respiratory rate
- blood pressure
- oxygenation level

If clinically indicated, more frequent monitoring or prolongation of hospitalization should occur.

In cases of hypotension (Grade 3 or 4), consider vital sign monitoring at least every hour for at least 4 hours for the next three infusions.

Starting with the 4th Infusion: Minimum 60-minute monitoring following each infusion

If the third infusion was well tolerated (i.e., absence of Grade ≥ 2 hypotension requiring medical intervention):

- Observe patient for a minimum of 60 minutes following each infusion for 3 months.

If the third infusion was not well tolerated (Grade ≥ 2 hypotension requiring medical intervention):

- Follow monitoring guide as for the first 3 infusions.
- Check vital signs before dosing and every 4 hours, or as clinically indicated.
- 16-hour monitoring post-infusion in a hospital setting with overnight monitoring.

If infusions were given in an outpatient setting for at least 3 months and patient has not experienced any interruptions greater than 2 weeks:

- Outpatient monitoring following infusion may be decreased to a minimum of 30 minutes for subsequent doses.

CRS Management Guidance:

No dose reductions of tebentafusp are recommended. Tebentafusp may be withheld or discontinued for CRS, as summarized below.

Table 1: CRS Grading and CRS Treatment guide

CRS grade*	Management
Grade 1 Temperature ≥ 38 °C No hypotension or hypoxia	• Continue treatment and provide symptomatic support. Monitor for escalation in CRS severity.
Grade 2 Temperature ≥ 38 °C 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.	• Continue treatment and administer bolus intravenous fluids and oxygen by low flow nasal canula or blow-by oxygen as needed. • If hypotension and hypoxia do not improve within 3 hours or CRS worsens administer high-dose intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent). • For Grade 2 CRS that is persistent (lasting 2-3 hours) or recurrent (occurrence of ≥ Grade 2 CRS with more than one dose), administer corticosteroid premedication (e.g., dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose

CRS grade*	Management
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 tebentafusp until CRS and sequelae have resolved • Administer high-dose intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent). • Administer tocilizumab as needed - Patient weight ≤ 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight ≥ 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) • Resume tebentafusp 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 corticosteroid premedication (e.g., dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 4 Temperature ≥ 38 °C Require multiple vasopressors (excluding vasopressin) Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation).	• Permanently discontinue tebentafusp • Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)

*Based on ASTCT consensus grading of CRS criteria (Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019 Apr;25(4):625-638.)

How to minimise the risk of hypotension associated with CRS

- Administer intravenous fluids prior to starting tebentafusp infusion based on clinical evaluation and the volume status of the patient.

For patients with pre-existing adrenal insufficiency on maintenance systemic corticosteroids:

- Adjust the corticosteroid dose to manage the risk of hypotension as needed.

ECG schedule and management requirements based on ECG results

- Perform an electrocardiogram (ECG) before and after tebentafusp treatment during the first 3 weeks of treatment and subsequently as clinically indicated.
- Stop tebentafusp infusion if QTcF interval exceeds 500 msec or increases by ≥ 60 msec from baseline value and treat any underlying precipitating factors including electrolyte abnormalities.
- Re-start treatment once QTcF interval improves to < 500 msec or is < 60 msec from baseline value.
- Stop or discontinue tebentafusp treatment depending on persistence and severity of cardiac event and any associated CRS.

Monitoring requirements of patients with cardiac diseases, QT prolongation and risk factors for cardiac failure

Tebentafusp has not been studied in patients with clinically significant cardiac disease or impaired cardiac function. Some cardiac events (e.g., sinus tachycardia and arrhythmia) and cases of QT interval prolongation have been observed in patients receiving tebentafusp treatment. Patients with pre-existing cardiovascular disorders may be at increased risk for sequelae associated with CRS. As CRS occurs frequently in treatment with tebentafusp with associated hypotension, the hypotension may not be tolerated in some patients with cardiovascular disease.

- Carefully monitor patients with cardiac disease, QT prolongation and risk factors for cardiac failure.
- Administer carefully tebentafusp in:
    - patients with history of or predisposition to QT interval prolongation.
    - patients who are taking medicinal products that are known to prolong QT interval.
- Any patient with signs or symptoms consistent with cardiac events should be evaluated and promptly treated.

Important Information for Patients

- Most patients treated with tebentafusp have developed CRS, which can become life-threatening if not promptly treated.
- Discuss with patients the frequency and way of monitoring and the possible side effects that can occur.
- **Remind the patient to alert their doctor or nurse immediately if they experience any of the following signs or symptoms suggestive of CRS:**
    - Fever

    - Tiredness or weakness
    - Vomiting
    - Chills
    - Nausea
    - Low blood pressure
    - Dizziness and light headedness
    - Headache

- To report any side effects to doctor or nurse.
- To hand-over the Patient Guide and PIL

Reporting of suspected adverse events or reactions

Reporting suspected adverse events or reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

Where possible, healthcare professionals should report adverse events or reactions by brand name and batch number.

In the event of a suspected adverse event, please report it to:

Immunocore (Ireland) Limited
Unit 1, Sky Business Centre
Dublin 17, D17 FY82
Ireland

Phone: +44 (0) 2076645100
Toll Free Number: +00 800-74451111
e-mail: medinfo.eu@immunocore.com
http://www.immunocore.com

Alternatively, suspected adverse reactions should be reported to the Health Products Regulatory Authority via:

- Telephoning (01) 676 4971
- https://www.hpra.ie/homepage/about-us/report-an-issue/human-adverse-reaction-form
  By downloading the form at http://www.hpra.ie/homepage/medicines/safety-information/reporting-suspected-side-effects and emailing it to medsafe@hpra.ie or post it to Freepost, Pharmacovigilance Sections, Health Products Regulatory Authority, Earlsfort Centre, Earlsfort Terrace, Dublin 2, DO2 XP77

Further Information

For electronic copies of the Treatment Guide for HCPs and Patient Guide, visit:

http://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine

Or

www.kimmtraksupport.eu

For Questions and medical enquiries

For more information, contact the Immunocore Medical Information Center at +44 (0)1235 438600 or via email info@immunocore.com.

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