Drug Monograph

A - Drug Name

tebentafusp

COMMON TRADE NAME(S): Kimmtrak®

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B - Mechanism of Action and Pharmacokinetics

Tebentafusp is a bispecific antibody that consists of 2 domains: a soluble T-cell receptor (targeting domain) that targets gp100 peptides presented by HLA-A*02:01 on the uveal melanoma tumour cell surface, and a single-chain fragment of an anti-CD3 antibody (effector domain) that targets polyclonal T-cells. Once bound to the uveal melanoma tumour cell, an immune synapse is formed and T cells are redirected and activated to release inflammatory cytokines and cytolytic proteins. This results in direct lysis of uveal melanoma tumour cells (in vitro).

Distribution		
	Linear, dose-proportional pharmacokinetics.	
	Cross blood brain barrier?	no
	PPB	no information available
	Distribution Sites	Does not distribute extensively. Preclinical biodistribution studies showed accumulation in highly vascular organs (e.g. heart, lung, liver, kidneys) was rapidly cleared between 8 to 24 hours.
Metabolism		
	Expected to be to be degraded into small peptides and amino acids via catabolic pathways.	
	Active metabolites	unknown

	Inactive metabolites	unknown
Elimination	Based on molecular size, small amounts may be excreted in urine. Classical drug metabolic elimination not expected to be an important clearance mechanism for large proteins (monoclonal antibodies (mAbs), fusion proteins, etc.) such as tebentafusp.	
	Half-life	7.5 hours (terminal)

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C - Indications and Status

Health Canada Approvals:

- Uveal melanoma

Refer to the product monograph for a full list and details of approved indications

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D - Adverse Effects

Emetogenic Potential: Low

The following adverse events occurred in ≥ 10% of metastatic uveal melanoma patients receiving tebentafusp in a randomized, open-label trial that compared first line treatment with tebentafusp vs. other systemic monotherapies (pembrolizumab, ipilimumab or dacarbazine). Severe or life-threatening adverse effects may also be included from other sources and post-marketing. Side effects that may be associated with CRS have been denoted with ^.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (16%) (9% severe)	E
	Hypotension (39%) (3% severe) ^	I
	Tachycardia (10%)	E
Dermatological	Other (47%) (Skin and hair colour changes)	E D
	Rash, pruritus (83%) (18% severe)	E D

Gastrointestinal	Abdominal pain (45%)	E
	Anorexia, weight loss (18%)	E
	Constipation (18%)	E
	Diarrhea (25%)	E
	Nausea, vomiting (49%) (2% severe) ^	I E
General	Edema (45%) (including peripheral edema)	E
	Fatigue (64%) (6% severe)	E
	Fever (76%) (4% severe) ^	I E
Hematological	Anemia (10%) (<1% severe)	E
Hepatobiliary	↑ ALT (21%) ^	I E D
	↑ AST (23%) ^	I E D
	↑ Bilirubin (11%) ^	I E D
Immune	Cytokine release syndrome (89%) (<1% severe)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (11%) (↓ PO4)	E
Musculoskeletal	Musculoskeletal pain (22%)	E
Nervous System	Dizziness (11%)	E
	Headache (31%) ^	I E
	Paresthesia (11%)	E
Respiratory	Cough, dyspnea (18%)	E
	Hypoxia (2%) ^	I

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Refer to the T-Cell Engaging Antibodies guideline for a detailed description of CRS and its management.

The most common side effects for tebentafusp include cytokine release syndrome, rash, pruritus, fever, fatigue, nausea, vomiting, skin or hair hypo-/hyper-pigmentation, abdominal pain, edema, hypotension and headache. Some of these adverse effects may be associated with CRS.

Cytokine release syndrome (CRS) has been reported with tebentafusp (77% of patients, ≥ Grade 2) and may be life-threatening. Fever and hypotension were often the first indications of CRS, with fever being present in nearly all cases; other signs and symptoms include chills, nausea, vomiting, fatigue, headache, elevated transaminases (see below), and less commonly, hypoxia. Cardiac events have been reported, rarely, in association with CRS. The majority (84%) of CRS cases

started on the day of infusion with a median time to resolution of 2 days. Sixty percent of patients experienced CRS (≥ Grade 2) with more than one infusion; patients should be monitored for at least 16 hours following the first infusions in an appropriate health care setting (including fluid status, vital signs, and oxygenation level) and appropriate therapy provided. Treatment may need to be withheld or discontinued depending on persistence and severity of CRS (see Dosing section).

Acute skin reactions, including rash, pruritis, erythema and cutaneous edema, have been reported commonly with tebentafusp infusion (91% of patients) and may be related to gp100 expression in normal melanocytes in the skin. Over two thirds of patients experienced either Grade 2 (44%) or Grade 3 (21%) skin reactions which typically occurred 1 day following the first 3 infusions and decreased in severity and frequency with subsequent dosing. The median time to improvement to ≤ Grade 1 was approximately 6 days. Patients should be monitored for skin reactions and treated appropriately (see Dosing section). Most symptoms resolved without the use of systemic corticosteroids.

Elevations in liver enzymes (ALT/AST) were observed in 65% of patients receiving tebentafusp and the majority occurred within the first 3 infusions. Most Grade 3 or 4 ALT/AST elevations improved within 7 days (to ≤ Grade 1). The majority of patients (95%) in the clinical trial had pre-existing liver metastasis, and severe cases were mostly related to CRS (8% of patients had an increase in LFTs ≥ Grade 3 outside of the setting of CRS). The median time to onset for events that occurred outside of the setting of CRS was 129 days.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Patients must have a positive HLA-A*02:01 genotype status prior to treatment with tebentafusp.

IV fluids should be administered as necessary prior to starting tebentafusp infusion to reduce the risk of hypotension associated with CRS

Pre-medications (prophylaxis for CRS):

If previous Grade 3 CRS, or Grade 2 CRS that did not resolve within 2-3 hours :

- Administer corticosteroid (e.g. dexamethasone 4mg or equivalent) at least 30 minutes prior to next dose.

Adults:

Administer tebentafusp according to the following ramp-up schedule:

Intravenous: 20 mcg on Day 1

30 mcg on Day 8

68 mcg on Day 15, and once weekly thereafter

Note: **Inpatient admission may be required for CRS monitoring** (e.g. for the first 3 to 4 infusions). ST-QBP funding for ambulatory administration only.

Coordination with local blood bank is required prior to administration as tebentafusp requires dilution with **human albumin product** (e.g., albumin 5%)

Dosage with Toxicity:

Refer to the T-Cell Engaging Antibodies guideline for a detailed description of CRS and its management.

Toxicity	Grade[a]	Management/ Action
CRS	Grade 1	Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibody Guideline for details.
	Grade 2	Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibody Guideline for details. If symptoms do not resolve to Grade ≤1 within 2–3 hours: • Hold[b,c] until CRS has resolved • Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibody Guideline for details.
	Grade 3	Hold[b,c] until CRS has resolved. Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibody Guideline for details.

	Grade 4	Discontinue. Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibody Guideline for details.
Acute skin reactions	Grade 2 or 3	Hold[b,c] until < Grade 1 or baseline Treat with systemic antihistamine and oral steroids as per local guidelines. If no response to oral steroids, consider IV corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)
	Grade 4	Discontinue. Administer IV corticosteroids (e.g., 2 mg/kg/day methylprednisolone or equivalent)
↑ LFTs	Grade 3 or 4	Hold[d] until ≤ Grade 1 or baseline If no improvement in 24 hours, administer IV corticosteroids
Other adverse effects	Grade 3	Hold[b,c] until ≤ Grade 1 or baseline
	Grade 4	Discontinue

[a]CRS Grade based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (Lee et.al 2019).

[b]Resume at same dose level, once toxicity has resolved.

[c]Do not resume at an escalated dose if adverse reaction occurs during ramp-up. May resume ramp-up once dose is tolerated.

[d]If concurrent Gr. 3 CRS: Resume at same dose level (may resume ramp-up if next dose is tolerated).
If no concurrent Gr. 3 CRS: Resume ramp-up (or same dose level if ramp-up complete).

Dosage with Hepatic Impairment:

No dose adjustment is required. Elevations in ALT and AST at baseline or during treatment did not impact tebentafusp pharmacokinetics.

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Tebentafusp Dose
≥ 30	No dose adjustment required
< 30	No data available

Dosage in the elderly:

No dose adjustment is required. No overall differences in safety and efficacy were observed between patients ≥ 65 years of age compared to younger patients in the pivotal trial (in which 47% of patients were ≥ 65 years of age).

Dosage based on gender:

There was no significant effect of gender on tebentafusp clearance.

Dosage based on ethnicity:

There was no significant effect of race on tebentafusp clearance.

Children:

The safety and efficacy of tebentafusp in children has not been established.

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F - Administration Guidelines

- Tebentafusp requires dilution with sodium chloride containing **human albumin** (e.g. 5%, 20% or 25%; concentration will vary depending on availability from local blood bank) to prevent adsorption to the infusion bag.
- Dilute human albumin in 100 mL 0.9% Sodium Chloride Injection to make a final albumin concentration between 225 to 275 mcg/mL. See product monograph for more information.
- Compatible with polyolefins [e.g. polyethylene (PE) and polypropylene (PP)] or polyvinyl chloride (PVC) infusion bags.
- DO NOT use a closed system transfer device for preparation of tebentafusp infusion.
- Do not flush needle/syringe on transfer when adding the required volume of tebentafusp to the human albumin and 0.9% Sodium Chloride preparation.
- Mix gently. Do not shake.
- Administer by IV infusion over 15 to 20 minutes, through a low protein binding 0.2 micron in-line filter infusion set.
- Do not mix or administer with other drugs.
- Flush the IV line with 0.9% Sodium Chloride after each dose.
- Monitor patients for at least 16 hours following the first infusions in an appropriate health care setting. If no Grade ≥ 2 hypotension, monitor for at least 30 minutes following subsequent infusions (in an ambulatory care setting). Refer to the T-Cell Engaging Antibodies guideline for more information.

- Store unopened vials refrigerated (2°C to 8°C) and protect from light

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any of its components.

Other Warnings/Precautions:

- Severe CRS has occurred with tebentafusp; ensure infusions are administered where there is immediate access to medications and equipment required to manage CRS, and that patients are euvolemic prior to initiating infusion.
- Patients with significant cardiac disease were excluded from clinical trials. Patients with pre-existing cardiovascular disorders may be at increased risk for complications associated with CRS and should be monitored.
- Caution and monitor ECG in patients with history or predisposing factors to QT interval prolongation; cases of QT interval prolongation were reported following tebentafusp treatment.
- Patients with pre-existing adrenal insufficiency on maintenance systemic corticosteroids are at an increased risk of hypotension; consider adjusting corticosteroid dose.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unknown
- Fetotoxicity: Unknown
  Based on the mechanism of action, tebentafusp may cause fetal harm. No human or animal studies have been conducted to assess fetotoxicity but molecules of similar molecular weight can cross the placenta.
- Teratogenicity: Unknown
  Tebentafusp is **not recommended** for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 week** after the last dose.
- Lactation:
  Breastfeeding is **not recommended** during treatment and for at least **1 week** after the last dose. It is unknown if tebentafusp is excreted into human milk.
- Fertility effects: Unknown

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H - Interactions

Tebentafusp causes transient release of proinflammatory cytokines that may suppress CYP450 enzymes, especially during the first 24 hours following each of the first 3 doses. Monitor patients receiving concomitant CYP450 substrates, especially those that have a narrow therapeutic index, for increased substrate concentrations or toxicity.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	↑ substrate concentration and/or toxicity	cytokines may suppress CYP450	Monitor and adjust dose of substrates with narrow therapeutic index (e.g. warfarin) if necessary
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain	↑ substrate concentration and/or toxicity	cytokines may suppress CYP450	Monitor and adjust dose of substrates with narrow therapeutic index (e.g. cyclosporine) if necessary

HMG-CoA reductase inhibitors)			
Anti-hypertensives	↑ hypotension	Additive	Consider holding anti-hypertensives for 24 hours before/after tebentafusp infusion for the first 6 doses.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Refer to the T-Cell Engaging Antibodies guideline for monitoring of CRS during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests (AST, ALT and total bilirubin)	Baseline and as clinically indicated
Creatinine	Baseline and as clinically indicated
CBC	Baseline and as clinically indicated
Clinical toxicity assessment for CRS	Monitor frequently during and after ramp-up doses.* At each visit and as clinically indicated after ramp-up phase.
CRP, ferritin, coagulation tests (e.g. aPTT, INR, PT, fibrinogen)	Baseline and as clinically indicated
Clinical toxicity assessment for skin reactions, GI or cardiac effects.	At each visit

*Ramp-up doses are step-up dose 1, 2 and first treatment dose.

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
ECG	Baseline and as clinically indicated (especially during the first 3 weeks of treatment) for patients at risk of QT prolongation.

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J - Supplementary Public Funding

High Cost Therapy Funding Program (HCTFP website)

- Tebentafusp (Inpatient) - Unresectable or Metastatic Uveal Melanoma

New Drug Funding Program (NDFP Website)

- Tebentafusp (Outpatient) - Unresectable or Metastatic Uveal Melanoma

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K - References

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August 2025 Updated Dosing, Administration and Clinical Monitoring sections, added links to T-Cell Engaging Antibody Guideline.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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