DRUG NAME: Tebentafusp

SYNONYM(S): IMCgp100, Tebentafusp-tebn[1]

COMMON TRADE NAME(S): KIMMTRAK®

CLASSIFICATION: immunotherapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Tebentafusp is a bispecific T-cell engager. It consists of a soluble T cell receptor (TCR) that targets glycoprotein 100 (gp100) and is fused to a single chain antibody fragment targeting CD3. The TCR binds to gp100 peptide presented by HLA-A*02:01 on the surface of melanoma cells. Once bound, it recruits and activates T cells via CD3 receptor. The activated T cells release inflammatory cytokines and cytolytic proteins, resulting in cell lysis of tumour cells.[1-3]

PHARMACOKINETICS:

Absorption	T_{max}=0.5 h, dose proportional increase in AUC and C_{max}	
Distribution	limited extravascular distribution[4]	
	cross blood brain barrier?	no information found
	volume of distribution	7.56 L
	plasma protein binding	no information found
Metabolism	expected to be catabolized into small peptides and amino acids	
	active metabolite(s)	unknown
	inactive metabolite(s)	unknown
Excretion	small amount expected be excreted in the urine[4]	
	urine	no information found
	feces	no information found
	terminal half life	6.8-7.5 hours
	clearance	16.4 L/d
Sex	no clinically meaningful difference	
Elderly	no clinically meaningful difference	
Ethnicity	no clinically meaningful difference	

Adapted from standard reference[1-3] unless specified otherwise.

USES:

Primary uses:
*Melanoma, ocular

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- severe **cytokine *release syndrome (CRS)*** has occurred with tebentafusp[3]
- patients with pre-existing ***cardiovascular disorder*** may be at increased risk for sequelae associated with CRS[4]
- monitor ECG at baseline and as clinically indicated in patients with known risk factors for ***QTc prolongation***[4]
- patients with pre-existing ***adrenal insufficiency*** (e.g., Addison's disease) on maintenance systemic corticosteroids are at increased risk of hypotension; corticosteroid dose may require adjustment[3,4]

Carcinogenicity: No studies have been conducted.

Mutagenicity: No studies have been conducted.

Fertility: No studies have been conducted.

Pregnancy: There is no available data in pregnant women and no reproductive or developmental studies in animals. Based on its mechanism of action, tebentafusp may cause fetal harm.[1] Pregnancy status should be verified prior to treatment in females of reproductive potential. Contraception is recommended during treatment and for at least 1 week after the last dose of tebentafusp for females of reproductive potential.[1]

Breastfeeding is not recommended during treatment due to the potential secretion into breast milk. To reduce the potential of serious adverse reactions in the breastfed child, breastfeeding should be delayed until at least 1 week after the last dose of tebentafusp.[1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[5,6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (10%, severe <1%)
	lymphopenia (20-91%, severe 13-56%)
	neutropenia (14%, severe 2%)
	thrombocytopenia (16%)
cardiac	angina pectoris (<1%)[4]
	arrhythmia (1-10%)[4]
	atrial fibrillation (1-10%)[4]
	heart failure (<1%)[4]
	tachycardia (10-13%); sinus tachycardia (7%)
eye	eyelash hypopigmentation (5%)[7]
	lacrimation increase (3%)
	ocular hyperaemia (2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	periorbital edema
	retinal depigmentation
gastrointestinal	*emetogenic potential:* low[8,9]
	abdominal pain (45%, severe 3%)
	constipation (18%)
	diarrhea (25%, severe 1%)
	dyspepsia (8%)
	nausea (49%, severe 2%)
	vomiting (30%, severe 1%)
general disorders and administration site conditions	*extravasation hazard:* none[10]
	chest pain, non-cardiac (8%)
	chills (48-64%, severe <1%)
	edema (45%); includes peripheral edema and facial edema
	fatigue (64%, severe 6%)
	influenza-like illness (7%)
	pyrexia (76%, severe 4%)
hepatobiliary	hepatotoxicity (<1%)
immune system	anaphylactic reaction (<1%)
	cytokine release syndrome (89%, severe 1%); see paragraph following **Side Effects** table
infections and infestations	nasopharyngitis (8%)
investigations	albumin decrease (47%, severe 2%)
	alkaline phosphatase increase (34%, severe 3%)
	ALT increase (52%, severe 9%); see paragraph following **Side Effects** table
	amylase increase (23%, severe 4%)
	AST increase (55%, severe 13%); see paragraph following **Side Effects** table
	bilirubin increase (27%, severe 4%)
	calcium decrease (45%, severe 2%)
	calcium increase (13%)
	creatinine increase (87%, severe <1%)
	glucose decrease (18%, severe <1%)
	glucose increase (66%, severe 3%)
	lipase increase (37%, severe 15%)
	magnesium decrease (34%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	phosphate decrease (51%, severe 11%)
	potassium decrease (17%, severe 1%)
	potassium increase (29%, severe 2%)
	QTc prolongation (<1%)[4]
	sodium decrease (30%, severe 3%)
metabolism and nutrition	appetite decrease (18%)
musculoskeletal and connective tissue	arthralgia (22%, severe 1%)
	back pain (18%, severe 1%)
	extremity pain (10%)
	myalgia (10%)
	muscle spam (6%)
nervous system	dizziness (11%)
	dysgeusia (7%)
	headache (31%, severe 1%)
	paresthesia (11%)
psychiatric	anxiety (5%)
	insomnia (9%)
respiratory, thoracic and mediastinal	cough (18%, severe <1%)
	dyspnea (13%, severe <1%)
	hypoxia (2%)
skin and subcutaneous tissue (see paragraph following **Side Effects** table)	alopecia (9%)
	cutaneous edema (27%)
	dry skin (31%)
	erythema (25%)
	hair colour changes (20%)
	hyperpigmentation (<20%, severe <1%)[1]; includes ephelides and lentigo[3]
	hypopigmentation (28%, severe <1%)[1]; includes vitiligo (7%)[7]
	night sweats (5%)
	pruritus (69%, severe 5%)
	rash (83%, severe 18%); maculopapular rash (31%)
	skin exfoliation (21%)
vascular	flushing (10%)
	hypertension (16%, severe 9%)
	hypotension (39%, severe 4%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pulmonary embolism (<1%); fatalities reported

Adapted from standard reference[1,3,4] unless specified otherwise.

Severe ***cytokine release syndrome*** (CRS) has been reported with tebentafusp. Fever may develop within a few hours following administration with chills, hypotension, and/or hypoxia also reported.[3,4] Other signs and symptoms may include nausea, vomiting, rash, elevated transaminases, fatigue, dizziness, shortness of breath, myalgia, arthralgia, tachycardia, and headache.[3] Although grade 3 events are uncommon (<1%), cardiac events such as angina pectoris, atrial flutter, and left ventricular dysfunction have been reported in association with CRS.[3,4] Grade 2 or higher events occur in 77% of patients. Most patients experience CRS associated with the first 3 infusions and the majority of episodes start the day of infusion. Patients may experience CRS with more than one infusion and the median time to resolution is 2 days.[3] Management of CRS may include administration of fluids, oxygen, corticosteroids, tocilizumab, and other supportive measures. If a grade 3 reaction occurs during initial dose escalation, do not proceed with escalation. Escalation may be resumed once dosage is tolerated. Dexamethasone can be considered as a premedication for subsequent doses in patients who experience grade 2 or higher CRS. Temporary interruption or discontinuation of tebentafusp may be required depending on severity of CRS.[3] For management of CRS, see BC Cancer Protocol SCCRS ***Cytokine Release Syndrome Management***.

Acute skin reactions are common (91%), presumably due to the recognition of gp100-expressing skin melanocytes by tebentafusp. Skin reactions typically occur during the first 3 infusions, with decreasing severity and frequency with repeated dosing. The most common reactions include rash, pruritus, erythema, cutaneous edema, and skin exfoliation.[3,4] The median time for improvement to grade 1 is approximately 6 days. Mild skin reactions may be managed with antihistamines and topical corticosteroids. For a grade 2 or higher reaction, withhold tebentafusp and consider oral or intravenous corticosteroids as indicated. If a grade 3 reaction occurs during initial dose escalation, do not proceed with escalation. Escalation may be resumed once dosage is tolerated. Permanently discontinue tebentafusp for a grade 4 reaction.[3]

Transaminase elevations have been reported in 65% of patients and the majority of events occurred during the first 3 infusions.[3] Most grade 3 or 4 events improve to grade 1 or less within 1 week. Outside the setting of CRS, grade 3 or 4 transaminase elevations have occurred in only 8% of patients, with a median time to onset of 129 days. For management of a grade 3 or 4 event, withhold tebentafusp until improvement to grade 1 or baseline. Consider intravenous corticosteroids if there is no improvement after 24 hours.[3]

INTERACTIONS:

Transient elevation of cytokines by tebentafusp may suppress CYP450 enzyme activities, resulting in increased plasma concentrations of the substrates of those CYP450 enzymes. If tebentafusp is used concurrently with a CYP450 substrate, particularly one with narrow therapeutic index, monitor for toxicity of the substrate and adjust the dose of the substrate as indicated. The risk of interaction is highest during the first 24 hours following each of the first 3 doses.[3]

SUPPLY AND STORAGE:

Injection: Immunocore Ltd (distributed by Medison Pharma Canada Inc) supplies tebentafusp as 100 mcg ready-to-use single-dose (preservative free) vials in a concentration of 200 mcg/mL. Refrigerate. Store in original carton to protect from light. Do not shake.[3]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

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SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

- do NOT use ***closed system transfer devices*** (CSTDs) for dose preparation[3] due to the very low transfer volumes utilized during preparation of tebentafusp; CSTDs may be used for administration[11]
- to prevent adsorption of tebentafusp to the infusion bag, a commercially licensed ***human albumin*** product (e.g., albumin 5%) must be added to the infusion bag prior to the addition of tebentafusp[1]
- calculate the required volume of ***human albumin*** to achieve a final concentration of 250 mcg/mL[1] (acceptable range[3]: 225-275 mcg/mL)
- if the prepared infusion bag is stored in the ***fridge*** prior to administration, allow the bag to equilibrate to room temperature before using; once removed from fridge, do not refrigerate again[3]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[3]	do NOT use
Intermittent infusion[3,12]	***over 15 to 20 min***; administer using 0.2 micron in-line filter
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3 weeks***[3,12,13]	***Cycle 1***: Dose escalation: ***20 mcg IV for one dose on day 1*** ***30 mcg IV for one dose on day 8*** ***68 mcg IV for one dose on day 15*** (total dose per cycle 118 mcg) ***Cycle 2 onwards***: ***68 mcg IV for one dose on days 1, 8, and 15*** (total dose per cycle 204 mcg) No dosage reductions are recommended.

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BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:
Concurrent radiation:	no information found
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required[3] CrCl <30 mL/min: no information found
	calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	mild impairment (total bilirubin ≤1.5xULN): no adjustment required[1] moderate to severe impairment (total bilirubin >1.5xULN): no information found
Dosage in dialysis:	no information found

Children: safety and efficacy not established

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