DRUG NAME: Tebentafusp

SYNONYM(S): IMCgp100-202[1,2]

COMMON TRADE NAME(S):

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Tebentafusp is a bifunctional fusion protein comprised of two polypeptide chains, a soluble T cell receptor which is fused to a single chain fragment of an anti-CD3 monoclonal antibody. The function of the T cell receptor (TCR) is to target and bind the drug to the melanoma-associated antigen glycoprotein 100 which is overexpressed on the surface of melanoma cells. The function of the antibody single chain fragment (scFv) is to activate the T cells in physical contact with the melanoma cells via cluster of differentiation 3 (CD3), resulting in an immune response targeted towards the malignant tissue. Tebentafusp, therefore, stimulates the immune system to attack the target tissue primarily via cytotoxic T lymphocyte (CTL) killing and stimulation of accessory immune mechanisms.[2]

USES:

Primary uses:	***Other uses:***
Melanoma[2]	

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- severe ***cytokine release syndrome*** has occurred following tebentafusp administration; most events occur after the first dose and decrease in frequency and severity with subsequent doses[2]
- ***overnight hospitalization*** is required for the first cycle (days 1, 8, and 15)[1]
- ***pain*** and/or ***inflammation at the tumour site*** (tumour flare) has been reported with tebentafusp and may be related to immune activation[2]

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. When placebo-controlled trials are available, adverse events will generally be included if the incidence is $\geq$5% higher in the treatment group.

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (12-51%, severe 1-2%)
	lymphopenia (20-91%, severe 13-56%)
	neutropenia (14%, severe 2%)
	thrombocytopenia (16%)
cardiac	atrial flutter, fibrillation (1%)
	sinus tachycardia (1-7%)
	tachycardia (13%)
eye	periorbital edema (31-49%)
gastrointestinal	*emetogenic potential:* low[3,4]
	abdominal pain, upper abdominal pain (7-45%, severe 3%)
	constipation (7-20%)
	diarrhea (11-25%, severe 1%)
	dyspepsia (6%)
	nausea (23-60%, severe 2%)
	vomiting (14-41%, severe 1%)
general disorders and administration site conditions	*extravasation hazard:* none[5]
	chest pain, non-cardiac (8%)
	chills (19-64%, severe 1%)
	edema (45%)
	facial edema (19%)
	fatigue (34-64%, severe 1-6%)
	influenza-like illness (21%)
	peripheral edema (10-31%, severe 1%)
	pyrexia (43-81%, severe 2-5%)
hepatobiliary	hepatotoxicity (severe 1%)
immune system	***cytokine release syndrome*** (1-89%, severe 1%); see paragraph following **Side Effects** table
infections and infestations	conjunctivitis (7%)
	lower respiratory tract infection (7%)
	rhinitis (7%)
	sepsis (5%)
	upper respiratory tract infection (6%)
	urinary tract infection (6%)
injury, poisoning, and procedural complications	infusion-related reaction (1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
investigations	***alkaline phosphatase increase*** (7-34%, severe 3%); see paragraph following **Side Effects** table
	ALT increase (3-52%, severe 9%); see paragraph following **Side Effects** table
	amylase increase (23%, severe 4%)
	AST increase (1-55%, severe 1-13%); see paragraph following **Side Effects** table
	creatinine increase (87%, severe <1%)
	gamma-glutamyltransferase increase (1%)
	hyperbilirubinemia (1-27%, severe 4%); see paragraph following **Side Effects** table
	hypercalcemia (13%)
	hyperglycemia (66%, severe 3%)
	hyperkalemia (29%, severe 2%)
	hypoalbuminemia (47%, severe 2%)
	hypocalcemia (45%, severe 2%)
	hypoglycemia (18%, severe <1%)
	hypokalemia (17%, severe 1%)
	hypomagnesemia (34%)
	hypophosphatemia (51%, severe 11%)
	hyponatremia (30%, severe 3%)
	lipase increase (37%, severe 15%)
metabolism and nutrition	appetite decrease (10-13%)
	hypoalbuminemia (10%)
	hypophosphatemia (10%, severe 7%)
musculoskeletal and connective tissue	arthralgia (12-22%, severe 1%)
	back pain (8-19%, severe 2%)
	extremity pain (12%)
	myalgia (8-14%)
	neck pain (6%)
neoplasms	neoplasms (1%)
	tumour hemorrhage (1%)
	tumour pain/flare (1%); see paragraph following **Side Effects** table
nervous system	dizziness (11%)
	headache (14-31%, severe 1%)
	lethargy (6%)
	paresthesia (13%)
	spinal cord compression (1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
respiratory, thoracic and mediastinal	acute respiratory distress syndrome (1%)
	cough (6%)
	dyspnea (9%, severe 3%)
	pleural effusion (1%)
	pulmonary embolism (1%)
skin and subcutaneous tissue (see paragraph following **Side Effects** table)	dry skin (20-43%, severe 1%)
	erythema (21-24%, severe 2%))
	erythematous rash (17%, severe 6%)
	exfoliation (29%)
	generalized rash (21-26%, severe 1-5%)
	hair colour changes (10-27%)
	hypopigmentation (21-28%)
	maculopapular rash (23-35%, severe 5-11%)
	pruritus, generalized pruritus (23-71%, severe 1-5%)
	rash, generalized rash (21-83%, severe 1-18%)
	vitiligo (12%)
vascular	flushing (14%, severe 1%)
	hypertension (3-10%, severe 2%)
	hypotension (25-45%, severe 3-9%)

Adapted from standard reference[2,6] unless specified otherwise.

Severe ***cytokine release syndrome*** (CRS) has been reported with tebentafusp administration. Increased body temperature has developed within 3 to 4 hours following administration, with additional observed toxicities including severe hypotension, facial and general edema, and chills. Other commonly reported mild to moderate symptoms may include headache, fatigue, nausea, and vomiting. Most CRS events occur after the first dose, with decreasing frequency and severity after subsequent doses. CRS may be managed with corticosteroids, intravenous fluids, and other symptomatic measures.[2]

Skin toxicity is among the most frequent treatment emergent adverse events with tebentafusp, possibly driven by reactivity to gp100 expressing skin melanocytes. Rash may also be associated with edema, skin induration, erythema, flushing, periorbital edema, desquamation, and dry skin. Although serious cases of skin rash have been reported with tebentafusp, rashes are generally mild to moderate in severity and abate with or without treatment. The median time to resolution of grade 3 skin toxicity is 4 days, although low grade rash can persist longer. The majority of rash symptoms reduce in severity and duration with repeat dosing, and by the fourth dose, symptoms are typically mild or absent. Pruritus may be managed with antihistamines and topical corticosteroids. Intravenous corticosteroids are indicated for severe cases of rash, particularly if the rash is associated with other symptoms such as pyrexia, chills, and hypotension.[2]

Acute ***transaminase elevations***, including grade 3 or 4 elevations, have been observed after the first several doses of tebentafusp. Some cases of increased transaminases have involved concurrent mild to moderate elevations of bilirubin. ***Hepatoxicity*** has also been reported in patients with liver metastases and in the setting of cytokine release

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syndrome. Most cases resolve without therapy with a median time to resolution of 1 week; however, corticosteroids may be required. Patients experiencing transient hepatoxicity have been re-dosed with tebentafusp and have experienced decreased severity of their symptoms and/or a subsequent return to their baseline following additional doses. Chronic elevations in liver function tests have been associated with disease progression.[2]

Tumour flare/pain has been reported with tebentafusp and may be due to inflammation secondary to immune activation. Clinical manifestation may vary according to the anatomic location of the tumour, but reported symptoms have included dyspnea, tachypnea, pleuritic effusion, and hypoxia. Patients should be managed symptomatically as indicated. Intravenous corticosteroids may be required for symptoms which persist despite treatment. Pain should be managed as clinically appropriate.[2]

INTERACTIONS: none known[2]

SUPPLY AND STORAGE:

Injection: Immunocore Ltd (Clinigen) supplies tebentafusp as 100 mcg ready-to-use, single use (no preservative) vials in a concentration of 200 mcg/mL. Refrigerate. Store in original packaging.[6,7] Do not shake.[6]

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

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) or filters for dose preparation due to the very low transfer volumes utilized during preparation of tebentafusp[7]; CSTDs may be used for administration[8]
- a calculated volume of commercially licensed ***human albumin*** product (e.g., albumin 5%) must be added to the infusion bag prior to the addition of tebentafusp; final intended concentration of human albumin should be 225-275 mcg/mL[6,7]
- once removed from the ***fridge***, the prepared infusion bag containing tebentafusp should not be refrigerated again; allow time for the refrigerated solution to equilibrate to room temperature before administering[6,7]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[7]	do NOT use
Intermittent infusion[2,6,7]	***over 15 to 20 min;*** administer using ***0.2 micron inline 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

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

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

	Cycle Length:	
Intravenous:	21 days[6]:	**Cycle 1**: 20 mcg IV for one dose on day 1, 30 mcg IV for one dose on day 8, and 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.

REFERENCES:

1. Immunocore Ltd. Clinical Study Protocol IMCgp100-202: A Phase II Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared with Investigator's Choice in HLA-A*0201 Positive Patients with Previously Untreated Advanced Uveal Melanoma. Abington, Oxfordshire, UK; June 11, 2021
2. Immunocore Ltd. Investigator's Brochure Tebentafusp (IMCgp100). Abingdon, Oxfordshire, UK; Feb 15, 2021
3. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 July 2020
4. Alison Weppler. Personal Communication. February 10,2022
5. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; 1 March 2021
6. Immunocore Commercial-LLC. KIMMTRAK® full prescribing information. Conshohocken, PA, USA; Jan 2022
7. Immunocore and Clinigen. MAP Pharmacy Manual – Tebentafusp 0.2 mg/mL formulation. Abingdon, Oxfordshire, UK; May 19, 2021
8. Connie Pfeiffer. Personal Communication. Feb 16,2022

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