DRUG NAME: Tarlatamab

SYNONYM(S): tarlatamab-dlle[1], AMG 757[2]

COMMON TRADE NAME(S): IMDELLTRA®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Tarlatamab is a bispecific T-cell engager that simultaneously binds to delta-like ligand 3 (DLL3) on tumour cells and CD3 receptors on T cells. It is composed of two single-chain variable fragment binding domains, connected by a flexible peptide linker.[2] With its dual binding, tarlatamab brings T cells in close contact with DLL3 expressing tumour cells, leading to T-cell activation, release of inflammatory cytokines, and subsequent cell lysis.[1,3]

PHARMACOKINETICS:

Absorption	exposure increases proportionally with dose over the dosing range of 1 mg to 100 mg	
Distribution	limited tissue distribution expected based on the low volume of distribution	
	cross blood brain barrier?	no information found
	volume of distribution	8.6 L (at steady state)
	plasma protein binding	no information found
Metabolism	expected to be degraded into small peptides and amino acids via catabolic pathways	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	renal elimination is unlikely due to the large molecular weight	
	urine	no information found
	feces	no information found
	terminal half life	11.2 days (range 4.3-26.5 days)
	clearance	0.65 L/day
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

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

USES:

Primary uses:

*Lung Cancer, small cell

Other uses:

*Health Canada approved indication

Developed: 1 October 2024
Revised: 1 November 2024

SPECIAL PRECAUTIONS:

Caution:
- severe ***cytokine release syndrome (CRS)*** can occur with tarlatamab; recommended dosing regimen uses a step-up dosing schedule for initiation of treatment[1,3]
- ***premedication*** with dexamethasone is recommended prior to the first two doses of tarlatamab and for patients who have experienced grade 3 CRS with a previous dose[1,3]
- patients should be ***adequately hydrated*** prior to starting treatment[1,3]
- patients may experience ***reduced consciousness*** due to CRS and immune effector cell-associated neurotoxicity syndrome (ICANS); ***driving or operating heavy machinery*** should be avoided until symptoms resolve[1,3]
- avoid tarlatamab in patients with ***active infection***[3]
- ***immunization with live or live-attenuated virus vaccines*** is not recommended for at least 4 weeks prior to treatment and until 6 weeks after treatment with tarlatamab[3]
- risk of ***tumour lysis syndrome*** may be increased in patients with a high tumour burden, rapidly growing tumour, or reduced renal function[3]

Carcinogenicity: No studies have been conducted.

Mutagenicity: No studies have been conducted.

Fertility: No studies have been conducted.

Pregnancy: Tarlatamab has not been studied in pregnant women. Tarlatamab causes T-cell activation and cytokine release which may compromise pregnancy maintenance. Human IgG also is known to cross the placental barrier and therefore, tarlatamab has the potential to be transmitted from mother to fetus. In females of reproductive potential, pregnancy tests are recommended prior to starting treatment and contraception is recommended during treatment and for 2 months after the last dose.[1,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Human IgG is known to be secreted in breast milk. Because of the potential for serious adverse reactions in breastfed infants, women should not breastfeed during treatment and for 2 months after the last dose.[1,3]

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.[4,5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (27%, severe 6%)
	leukopenia (44%, severe 4%)
	lymphopenia (16%, severe 15%)
	febrile neutropenia (<1%)
	neutropenia (14%, severe 6%)
	thrombocytopenia (12-34%, severe 2-4%)
cardiac	sinus tachycardia/tachycardia (4%)
	sinus bradycardia (2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential:* low[6]
	abdominal pain (13%)
	constipation (30%, severe <1%)
	diarrhea (12%, severe <1%)
	nausea (22%, severe 2%)
	vomiting (12%, severe <1%)
general disorders and administration site conditions	*extravasation hazard:* none[7]
	chills (7%)
	edema (7%)
	fatigue/asthenia (51%, severe 10%)
	hypersensitivity (severe <1%); includes rash and bronchospasm
	pyrexia (36%)
immune system	***cytokine release syndrome*** (55%, severe 2%); see paragraph following **Side Effects** table
infections and infestations	candida infection (3%)
	COVID-19 infection (9%, severe <1%)
	infection, including opportunistic infections (41%, severe 12-13%)
	respiratory tract infection (3%)
	pneumonia (9%, severe 4%)
	urinary tract infection (10%, severe 1%)
investigations	activated partial thromboplastin time prolonged (severe 5%)[1]
	alkaline phosphatase increase (22%, severe <1%)
	ALT increase (42%, severe 2%)
	AST increase (44%, severe 3%)
	blood bilirubin increase (15%, severe 2%)
	creatine kinase increase (27%, severe 1%)
	creatinine increase (29-31%, severe <1%)
	sodium increase (26%)
	uric acid increase (severe 10%)[1]
	weight loss (13%, severe 1%)
metabolism and nutrition	decreased appetite (34%, severe 3%)
	hyperglycemia (9%, severe 1%)
	hypoalbuminemia (8%)
	hypokalemia (12%, severe 2%)
	hypophosphatemia (6%, severe <1%)
	hypomagnesemia (13%, severe <1%)

Developed: 1 October 2024
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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyponatremia (17%, severe 6%)
	tumour lysis syndrome (1%)
musculoskeletal and connective tissue	musculoskeletal pain (30%, severe 1%)
nervous system	dizziness (5-7%)
	dysgeusia (36%)
	headache (14%)
	immune effector cell-associated neurotoxicity syndrome (4-9%); see paragraph following **Side Effects** table
	peripheral neuropathy (6-7%)
	taste disorder (6%)
psychiatric	confusion (6%, severe 1%)
	delirium (2%)
	insomnia (6%)
respiratory, thoracic and mediastinal	cough (17%)
	dyspnea (17%, severe 2%)
skin	pruritus (11%)
	rash (8%, severe 1%)
vascular	hypertension (8%, severe 4%)
	hypotension (8%, severe 1%)

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

Cytokine release syndrome (CRS) occurs in approximately 50% of patients receiving tarlatamab. Most patients experience grade 1 or 2 reactions, but serious or life-threatening reactions can occur. Signs and symptoms may include fever, chills, hypotension, hypoxia, tachycardia, headache, fatigue, nausea, vomiting, and elevated liver enzymes. Serious complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. Most events occur during the first cycle with 43% of patients experiencing CRS following the first dose (1 mg). The incidence of CRS decreases with each subsequent dose, occurring in 29% of patients after the second dose (10 mg) and in 9% after subsequent doses. Median time to onset of all grade CRS is 15 hours after the most recent dose (range 0-165 hours). Median duration of CRS is 4 days (range 2-6 days).[8] Recurrent CRS has been reported in 23% of patients. To mitigate the risk of CRS, tarlatamab is initiated in a step-up dosing regimen. Premedication with dexamethasone is recommended prior to the first two doses of tarlatamab, and intravenous fluids are administered immediately following each dose in cycle 1. For patients who have experienced grade 3 CRS with a previous dose, premedication with dexamethasone and intravenous hydration is recommended for subsequent cycles. If CRS is suspected, withhold tarlatamab until symptoms resolve and manage symptoms promptly. Depending on severity of the reaction, management may include supportive care, corticosteroids, and tocilizumab. Permanently discontinue tarlatamab for recurrent grade 3 reactions and all grade 4 reactions.[1,3] For management of cytokine release syndrome (CRS), see BC Cancer Protocol SCCRS ***Cytokine Release Syndrome Management***.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is reported in 4-9% of patients. Although most events are mild to moderate in severity, serious or life-threatening events can occur. Signs and symptoms of ICANS may include headache, confusion, disorientation, speech disturbances, seizures, motor weakness, ataxia, tremor,

Developed: 1 October 2024
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delirium, amnesia, and encephalopathy. ICANS primarily occurs during cycle 1 and 2 with most patients experiencing ICANS following Cycle 2 Day 1.[1,3] Median time to onset is 3 days (range 1-15 days) from the most recent dose[3], but onset may be delayed to several weeks after administration. Median duration of ICANS is 33 days (range 1-93 days). Recurrent ICANS is reported in 2% of patients. ICANS can occur concurrently with CRS, following the resolution of CRS, or in the absence of CRS. Management of ICANS may include temporary dose interruption, corticosteroids, anti-seizure medications, and supportive care. Patients experiencing neurologic toxicity should avoid driving or operating heavy machinery until the symptoms resolve.[1,3] For inpatient management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), see BC Cancer Protocol SCICANS ***Immune Effector Cell-Associated Neurotoxicity Syndrome Management.***

INTERACTIONS:

Tarlatamab causes transient elevation of cytokines and may suppress the activity of CYP 450 enzymes, resulting in increased exposure of CYP substrates. Substrates of CYP 450 enzymes with a narrow therapeutic index may require dose adjustment or monitoring for toxicity if given concurrently with tarlatamab. Interactions with CYP substrates are most likely to occur during, and up to 14 days after a CRS event.[1,3]

SUPPLY AND STORAGE:

***Injection*:** Amgen Canada Inc. supplies tarlatamab as 1 mg and 10 mg single-use (preservative free) vials of sterile lyophilized powder. Each vial of tarlatamab is packaged with two 7 mL single-use (preservative free) vials of IV solution stabilizer. Refrigerate. Store in original carton to protect from light.[3]

Additional information: Intact vials of drug and IV solution stabilizer are stable at room temperature for up to 24 hours.[3]

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:

- ***Caution***: ***two vial sizes*** are available; ***final vial concentrations are different*** after reconstitution[1,3]
- ***IV solution stabilizer*** is used to coat the prefilled IV bag before adding reconstituted tarlatamab; do NOT use the IV solution stabilizer to reconstitute tarlatamab[1,3]
- due to a low extraction volume, ***CSTDs should not be used to withdraw*** tarlatamab from the vial; Chemo-Vent® may be used to vent the vial[9]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion[1,3]	over 1 h
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found

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

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***

Intravenous:

Cycle Length: 4 weeks[1,3,8] :

Cycle 1:

Dosing Schedule		Day of treatment	Dose (IV)
Step-up dosing schedule	Step-up dose 1	1	1 mg
	First full treatment dose	8	10 mg
	Second full treatment dose	15	10 mg

(total dose per cycle 21 mg)

Cycle 2 and beyond:
10 mg IV for one dose on day 1 and 15
(total dose per cycle 20 mg)

No dose reductions are recommended[1,3]

Following dose delays: for instruction about restarting tarlatamab, refer to protocol by which patient is being treated as the step-up regimen may need to be repeated[1,3]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated.

Dosage in renal failure: eGFR ≥30 mL/min: no adjustment required[1,3]
eGFR <30 mL/min: no information found

Dosage in hepatic failure: mild impairment (bilirubin ≤1.5 x ULN, any AST): no adjustment required[1,3]
moderate to severe impairment (bilirubin >1.5 x ULN, any AST): no information found

Dosage in dialysis: no information found

Developed: 1 October 2024
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Children: safety and efficacy have not been established

REFERENCES:

1. Amgen Inc. IMDELLTRA® full prescribing information. Thousand Oaks, California, USA; May 2024
2. UpToDate® Lexidrug (database on the Internet). Tarlatamab. UpToDate Inc. Wolters Kluwer., Available at: http://online.lexi.com. Accessed June 11, 2024
3. Amgen Canada Inc. IMDELLTRA® product monograph. Mississauga, Ontario; September 11, 2024
4. Barb Melosky, MD. BC Cancer, Vancouver. Personal Communication. July 29,2024
5. Megan Darbyshire, Tumour Group Pharmacist. Provincial Pharmacy. Personal Communication. July 29,2024
6. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1 2022
7. 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; March 1 2021
8. Ahn M, Cho BC, Felip E, et al. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. N.Engl.J.Med. 2023;389(22):2063-2075
9. de Lemos, M. BC Cancer Provincial Pharmacy Professional Practice Leader and Drug Information Coordinator. SBAR: Preparing Tarlatamab - BC Cancer Recommendation vs. Product Monograph. BC Cancer - Systemic Therapy Program 2024

Developed: 1 October 2024
Revised: 1 November 2024