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]

PHARMACOKINETICS:

Absorption	exposure increases proportionally with dose over the dosing range of 1 mg to 100 mg	
Distribution	not studied[3]; 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[3]	
	urine	no information found
	feces	no information found
	terminal half life	11.2 days (range 4.3 to 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] unless specified otherwise

USES:

Primary uses:

Lung Cancer, small cell[1]

Other uses:

*Health Canada approved indication

Developed: 1 October 2024
Revised

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]
- ***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]
- patients should be ***adequately hydrated*** prior to starting treatment[1]
- 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]
- risk of ***tumour lysis syndrome*** may be increased in patients with a high tumour burden and rapidly growing tumour[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]

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]

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 (84%, severe 57%)
	febrile neutropenia (<1%)
	neutropenia (12%, severe 6%)
	thrombocytopenia (33%, severe 3%)
gastrointestinal	*emetogenic potential:* minimal (rare)[2,6]
	constipation (30%, severe <1%)
	nausea (22%, severe 2%)
	vomiting (6-10%)[7]

Developed: 1 October 2024
Revised

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders and administration site conditions	*extravasation hazard:* none[8]
	fatigue/asthenia (51%, severe 10%)
	hypersensitivity (severe <1%)[3]
	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%)
	infection, including opportunistic infections (41%, severe 13%)
	respiratory tract infection (3%)
	pneumonia (9%)
	urinary tract infection (10%)
investigations	activated partial thromboplastin time prolonged (severe 5%)
	alkaline phosphatase increase (22%)
	ALT increase (42%, severe 2%)
	AST increase (44%, severe 3%)
	bilirubin increase (15%)
	creatinine increase (29%, severe <1%)
	hemoglobin decrease (58%, severe 5%)
	sodium increase (26%)
	uric acid increase (severe 10%)
metabolism and nutrition	decreased appetite (34%, severe 3%)
	hypokalemia (50%, severe 5%)
	hypomagnesemia (33%, severe 2%)
	hyponatremia (68%, severe 16%)
	tumour lysis syndrome (1%)
musculoskeletal and connective tissue	musculoskeletal pain (30%, severe 1%)
nervous system	dizziness (7%)
	dysgeusia (36%)
	headache (14%)
	immune effector cell-associated neurotoxicity syndrome (9%); see paragraph following **Side Effects** table
	peripheral neuropathy (7%)
	syncope (2%)
psychiatric	delirium (2%)
	insomnia (6%)

Developed: 1 October 2024
Revised

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
respiratory, thoracic and mediastinal	cough (17%)
	dyspnea (17%, severe 2%)

Adapted from standard reference[1,7] 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 CRS is 14 hours after the most recent dose (range 1-268 hours).[1] Median duration of CRS is 4 days (range 2-6 days).[7] Recurrent CRS has been reported in 24% 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] 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 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, delirium, and encephalopathy. ICANS primarily occurs during cycle 1 and 2; most patients experience ICANS following the day 1 of Cycle 2. Median time to onset from the first dose is 30 days (range 1-154 days); however, 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] 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 CYP450 enzymes, resulting in increased exposure of CYP substrates. Substrates of CYP450 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]

SUPPLY AND STORAGE:

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

Developed: 1 October 2024
Revised

Additional information: Intact vials of drug and IV solution stabilizer are stable at room temperature for up to 24 hours.[1]

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***: reconstitution of the two available vials yields a ***different final concentration for each vial*** (e.g., final concentration of 1 mg vial = 0.9 mg/mL following reconstitution; final concentration of 10 mg vial = 2.4 mg/mL following 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]
- 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]	over 1 h
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. 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.

Developed: 1 October 2024
Revised

Adults:

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

Intravenous:

Cycle Length: 4 weeks[1,7] :

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]

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]

Concurrent radiation: no information found

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

Dosage in renal failure:
CrCl ≥30 mL/min: no adjustment required[1]
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:
bilirubin ≤1.5 x ULN: no adjustment required[1]
bilirubin >1.5 x ULN: no information found

Dosage in dialysis: no information found

Children: safety and efficacy have not been established

Developed: 1 October 2024
Revised

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 Inc. Tarlatamab (AMG 757) Investigator's Brochure - Edition 12.0. Thousand Oaks, California, USA; April 26 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. 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
8. 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
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