DRUG NAME: Daratumumab

SYNONYM(S): HuMax-CD38[1]

COMMON TRADE NAME(S): DARZALEX®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Daratumumab is a human IgG1 kappa monoclonal antibody that targets the transmembrane glycoprotein CD38. It potently inhibits the growth of CD38-expressing tumour cells and may induce tumour cell lysis by utilizing multiple effector functions in malignancies expressing CD38. Daratumumab has direct and indirect antitumour activity including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, induction of apoptosis, and immunomodulatory functions that deplete immune suppressor cells, leading to T-cell expansion and activation.[2,3]

PHARMACOKINETICS:

Absorption	increases in Cmax and AUC are more than dose-proportional after repeat dosing[4]	
Distribution	target-mediated disposition, primarily confined to the vascular system with limited extravascular distribution[4]	
	cross blood brain barrier?	no information found
	volume of distribution[5]	4.4-4.7 L
	plasma protein binding	no information found
Metabolism	likely catabolically metabolized via degradation into small peptides and amino acids	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	nonlinear elimination; clearance decreases with increasing dose and repeat dosing[1,2]	
	urine	no information found
	feces	no information found
	terminal half life	9 days (single dose); 18 days (repeat dosing)
	clearance[4]	0.42 mL/h/kg (single dose); 0.3 mL/h/kg (repeat dosing)

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Multiple myeloma

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- ***infusion reactions*** are sometimes reported; pre-medicate with corticosteroids, antihistamines, and antipyretics and administer post-infusion corticosteroids[2]

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- patients with ***chronic obstructive pulmonary disease*** may require additional short and long acting bronchodilators plus inhaled corticosteroids post-infusion[2]
- ***herpes zoster reactivation*** may occur; initiate antiviral prophylaxis within one week of starting treatment and continue for three months following treatment completion[2,5]
- ***hepatitis B reactivation*** has been reported with daratumumab; HBV screening (HBsAg and anti-HBc) is suggested for all patients prior to initiation of daratumumab; if either test is positive, prophylaxis with lamivudine 100 mg/day orally is indicated during daratumumab treatment and for 6 months after it is discontinued[6,7]
- daratumumab interferes with ***cross-matching*** and ***red blood cell antibody screening***; type and screen patients prior to initiating daratumumab treatment if possible[5]

Special populations: Neonates or infants exposed to daratumumab *in utero* should not receive live vaccines until a hematological evaluation has been completed.[2]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: no information found

Pregnancy: Human and animal studies are not available, however IgG1 monoclonal antibodies s are known to cross the placenta. Based on its mechanism of action, daratumumab may cause fetal myeloid or lymphoid cell depletion and decreased bone density. Women of childbearing potential should use effective contraception during treatment and for at least three months after discontinuation.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Human IgG is known to be secreted in human breast milk.[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, and/or determined to be clinically important.[8,9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia (see paragraph following **Side Effects** table)	***anemia*** (27-45%, severe 17-19%)[2,10]
	leukopenia (10-57%, severe 5-19%)
	lymphopenia (6-72%, severe 6-40%)[2,10]
	neutropenia (22-60%, severe 12-20%)[2,10]
	thrombocytopenia (20-48%, severe 14-18%)[2,10]
cardiac	palpitations (3%)
eye	blurred vision (6%)
gastrointestinal	*emetogenic potential:* low[11]
	abdominal pain (6%, severe 1%)
	constipation (15%)
	diarrhea (16%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dyspepsia (3%)
	nausea (27%)
	stomatitis (3%)
	toothache (3%)
	vomiting (14%)
general disorders and administration site conditions	*extravasation hazard:* none[12]
	asthenia (8%, severe <1%)
	chills (10%)
	fatigue (39%, severe 2%)
	flu-like symptoms (5%, severe <1%)
	non-cardiac chest pain, discomfort (3-12%, severe 1%)
	pain (5%, severe <1%)
	peripheral edema (7%, severe <1%)
	physical health deterioration (3%, severe <1%))
	pyrexia (21%, severe <1%)
hepatobiliary	hepatic impairment (4%, severe <1%)
immune system (see paragraph following **Side Effects** table)	***infusion related reactions***: initial infusion (46-48%, severe 7%), subsequent infusions (2-4%, severe <1%)
	cytokine release syndrome (<2%)
infections and infestations (see paragraph following **Side Effects** table)	hepatitis B reactivation[6] (<1%)
	herpes zoster (3%, severe 1%)
	influenza (3%)
	pneumonia (11%, severe 6%)
	upper respiratory tract infection (5-39%, severe 2%)
	urinary tract infection (6%)
investigations	AST increase (20%, severe 1%)
	creatinine increase (21%, severe 2%)
	weight gain (3%)
	weight loss (5%, severe <1%)
metabolism and nutrition	anorexia (14%, severe <1%)
	hypercalcemia (12-32%, severe 3-7%)
	hyperglycemia (8%, severe 3%)
	hyperkalemia (3%, severe <1%)
	hyperuricemia (3%, severe <1%)
	hypoalbuminemia (3-41%, severe 3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypocalcemia (32%)
	hypokalemia (8%, severe <1%)
	hypomagnesemia (6%)
	hyponatremia (5-29%, severe 4%)
musculoskeletal and connective tissue	arthralgia (17%)
	back pain (23%, severe 2%)
	bone pain (10%, severe <1%)
	muscle spasms (6%)
	myalgia (4%)
	pain in extremity (15%, severe <1%)
nervous system	dizziness (8%)
	headache (12%, severe 1%)
	hypoesthesia (5%)
	peripheral sensory neuropathy (4%)
	somnolence (3%, severe <1%)
	tremor (3%)
psychiatric	anxiety (6%)
	confusion (5%, severe 1%)
	insomnia (5%)
renal and urinary	dysuria (3%)
	renal impairment (7%, severe 1%)
respiratory, thoracic and mediastinal	allergic rhinitis (7%)
	bronchospasm (3%, severe 1%)
	cough (21%), productive cough (5%)
	dyspnea (5-15%, severe <1%)
	epistaxis (6%)
	nasal/sinus congestion (5-17%)
	oropharyngeal pain (10%)
	pleural effusion (3%)
	sneezing (3%)
	throat irritation (6%)
	wheezing (5%)
skin and subcutaneous tissue	dry skin (3%)
	hyperhidrosis (3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	rash (3%)
	pruritus (3%)
vascular	hematoma (3%)
	hypertension (10%, severe 5%)
	hypotension (5%, severe <1%)

Adapted from standard reference[2] unless specified otherwise.

Infusion-related reactions are reported in nearly 50% of patients during the first infusion and in 2-4% of patients during subsequent infusions. Reactions generally occur during administration of the infusion or within four hours of its completion. Respiratory symptoms (e.g., cough, wheeze, larynx and throat irritation, nasal congestion), chills, nausea, and vomiting may occur. Severe reactions have also been reported, including bronchospasm, laryngeal and pulmonary edema, hypertension, hypoxia, and dyspnea. To minimize the risk of reaction, premedication with antihistamines, antipyretics, and corticosteroids is recommended. To prevent delayed reactions, oral corticosteroids may also be administered for two days following the infusion, starting one day post-infusion. When dexamethasone is prescribed as part of combination chemotherapy, additional corticosteroid therapy may not be necessary post-infusion. Follow incremental infusion rate increases closely and monitor patients during the entire infusion. Interrupt treatment for reactions of any grade/severity and promptly manage symptoms. Following resolution of a grade 3 (or less) reaction, the infusion may be resumed at a reduced rate of no more than half of the previous rate. Permanently discontinue daratumumab upon the third occurrence of a grade 3 reaction or following a grade 4 (life-threatening) reaction.[2,5,10]

Patients with a history of ***chronic obstructive pulmonary disease*** may have an increased risk of respiratory complications associated with infusion-related reactions. Additional short or long acting bronchodilators and inhaled corticosteroids may be required post-infusion. If no major infusion-related reactions occur during the first four infusions, consider discontinuing the additional inhaled medications.[2]

Daratumumab may increase the ***hematologic toxicity*** (i.e., neutropenia, thrombocytopenia) of other chemotherapeutic agents when given in combination. Daratumumab dose reduction is not required; however, treatment interruption may be required to allow for neutrophil and/or platelet recovery. Supportive care with growth factors and/or platelet transfusions may also be necessary.[2]

Severe, life-threatening, and fatal ***infections*** are reported with a higher incidence when daratumumab is given in combination with other chemotherapeutic agents. Patients with neutropenia should be closely monitored for signs of infection and promptly treated.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
Coombs test (indirect antiglobulin test)[2]	false positive Coombs test may persist for up to six months post treatment; detection of antibodies to minor serum antigens may be masked	daratumumab binds to CD38 on red blood cells	• type and screen patients prior to starting daratumumab if possible[5] • if emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given[13]

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AGENT	EFFECT	MECHANISM	MANAGEMENT
Serum protein electrophoresis (SPE) and immunofixation (IFE) assays[2]	false positive SPE and IFE assay results in patients with IgG kappa M-protein	daratumumab is detected on SPE and IFE assays used for monitoring endogenous M-protein	• additional tests may be required to evaluate response

SUPPLY AND STORAGE:

***Injection*:** Janssen Inc. supplies daratumumab as 100 mg and 400 mg single-use, preservative-free vials in a concentration of 20 mg/mL. Refrigerate. Do not shake. Protect from light.[2]

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:
- diluted solution may develop small, translucent to white proteinaceous particles; do not use if visible opaque particles are observed[2]
- administer with a 0.22 or 0.2 micron low protein binding in-line filter[2]
- infusion should be completed within 15 hours[2]
- compatibility data supports compounding to a final concentration of 0.4 to 4.5 mg/mL[14]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found				
Intramuscular	no information found				
Direct intravenous	do NOT use[10]				
Intermittent infusion	Refer to protocol by which patient is being treated over 3.25-15 h[15-18]; rapid infusion (over 90 min) has been used[16,17,19-22]				
	In the absence of other guidelines, the following incremental infusion rate may be used[15-18]				
		Dilution volume	Initial rate (first hour)	Rate increment[a]	Maximum rate
	Cycle 1, day 1*	1000 mL	50 mL/h	50 mL/h every hour	200 mL/h
	alternate regimen*: Cycle 1, days 1,2	500 mL	50 mL/h	50 mL/h every hour	200 mL/h
	Cycle 1, day 8[b]	500 mL	50 mL/h	50 mL/h every hour	200 mL/h
	subsequent infusions[c]	500 mL	100 mL/h	50 mL/h every hour	200 mL/h
Continuous infusion	no information found				

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

Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

[a]escalate only in the absence of infusion reactions
[b]escalate only if there were no infusion-related reactions during the first 3 hours of the **first** infusion
[c]escalate only if there were no infusion-related reactions during a final infusion rate of ≥100 mL/h during the **first two** infusions
*Alternate regimen: the first dose of daratumumab (cycle 1, day 1) is split into two equal doses and administered over two consecutive days (becoming cycle 1, days 1 and 2).

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:	***4 weeks***[15,18,23,24]:	**Cycles 1, 2:** ***16 mg/kg IV for one dose* on days 1, 8, 15, and 22*** (total dose per cycle 64 mg/kg) *Alternate regimen for Cycle 1 day 1 (split dosing): ***8 mg/kg IV for one dose on days 1 and 2*** (total dose per cycle 64 mg/kg) **Cycles 3-6:** ***16 mg/kg IV for one dose on days 1 and 15*** (total dose per cycle 32 mg/kg) **Cycle 7 onward:** ***16 mg/kg IV for one dose on day 1*** (total dose per cycle 16 mg/kg)
	3-4 weeks[5]:	Cycles 1-3 (q3weekly): 16 mg/kg IV for one dose on days 1, 8, and 15 (total dose per cycle 48 mg/kg) Cycle 4-8 (q3weekly): 16 mg/kg IV for one dose on day 1 (total dose per cycle 16 mg/kg) Cycle 9 onward (q4weekly): 16 mg/kg IV for one dose on day 1 (total dose per cycle 16 mg/kg)

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

	Cycle Length:
Concurrent radiation:	no information found
Dosage in myelosuppression[2]:	dose adjustment is not recommended, however to allow for recovery, dose may be delayed; refer to protocol by which patient is being treated
Dosage in renal failure[2]:	no starting dose adjustment required
Dosage in hepatic failure[2]:	mild impairment: no adjustment required moderate/severe impairment: no information found
Dosage in dialysis:	no information found
Children:	no information found

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