DRUG NAME: Avelumab

SYNONYM(S): MSB0010718C[1]

COMMON TRADE NAME(S): BAVENCIO®

CLASSIFICATION: monoclonal antibody

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

MECHANISM OF ACTION:

Avelumab is a fully human IgG1 monoclonal antibody immune checkpoint inhibitor that binds to programmed death-ligand 1 (PD-L1) on tumour cells, blocking its interaction with PD-1 and B7-1 receptors on T-lymphocytes. PD-L1 is an immune checkpoint protein expressed on tumour cells and tumour-infiltrating immune cells that down regulates T-cell function; blocking these receptors restores anti-tumour T-cell activity. In vitro, avelumab has been shown to stimulate natural killer cell-mediated direct tumour cell lysis by inducing antibody-dependent cell-mediated cytotoxicity.[2]

PHARMACOKINETICS:

Distribution	expected to be distributed in systemic circulation and to a lesser extent in extracellular space; steady state achieved after 4 to 6 weeks of repeated dosing	
	cross blood brain barrier?	no information found
	volume of distribution	4.72 L
	plasma protein binding	no information found
Metabolism	expected to be degraded into small peptides and amino acids via catabolic pathways (similar to endogenous IgG antibodies)	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	clearance may increase with increasing body weight, however, only a marginal change in exposure is predicted[2,3]	
	urine	no information found
	feces	no information found
	terminal half life	6.1 days
	clearance	0.59 L/day

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Merkel cell carcinoma

*Urothelial carcinoma

*Health Canada approved indication

Other uses:

Lung cancer, non-small cell[4]

Renal cell cancer[5,6]

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SPECIAL PRECAUTIONS:

Caution:
- avoid systemic ***corticosteroids*** or ***immunosuppressants*** *prior* to starting avelumab due to potential interference with the efficacy of avelumab; corticosteroids or immunosuppressants may be used *during* treatment with avelumab for the management of immune-mediated adverse reactions.[1,2]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: No formal fertility studies were conducted; however, no notable effects on reproductive organs in male and female monkeys were reported during repeat dose toxicology studies.[2]

Pregnancy: Avelumab has not been studied in pregnant women. Endogenous IgG1 is known to cross the placental barrier, particularly during the third trimester; therefore, as a humanized IgG1 antibody, avelumab is expected to be transmitted from mother to fetus. In murine models, blocking PD-L1 signalling has disrupted tolerance to the fetus and resulted in increased rates of abortion and stillbirth. Women of reproductive potential should use effective contraception while on avelumab and for one month after treatment has been discontinued.[2,7,8]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should wait at least one month after treatment is completed before breastfeeding.[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.[9,10]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (35-48%, severe 6-9%)[2,8]
	lymphocytopenia (2-49%, severe 2-19%)[1,2,8]
	neutropenia (6-9%, severe ≤1%)
	thrombocytopenia (27%, severe 1%)
cardiac	***immune-mediated myocarditis*** (<1%, severe <1%); has been fatal; see paragraph following **Side Effects** table
endocrine (see paragraph following **Side Effects** table)	***immune-mediated adrenal insufficiency*** (<1%, severe <1%)[2,8,11]
	immune-mediated hyperthyroidism (≤2%)[1,2,11]
	immune-mediated hypopituitarism (<1%)
	immune-mediated hypothyroidism (3-5%, severe 1%)[1,2,8,11]
	immune-mediated type 1 diabetes mellitus (≤1%)[1,8]
eye	***immune-mediated uveitis*** (<1%)[8,11]
gastrointestinal	*emetogenic potential:* low[12]
	abdominal pain (16-19%, severe 2%)[2,8]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	constipation (17-18%, severe 1%)[2,8]
	diarrhea (6-23%, severe ≤2%)[1,2,8,11]
	immune-mediated colitis (≤2%, severe <1%)[2,8,11]; see paragraph following **Side Effects** table
	immune-mediated diarrhea (≤1%)[1,11]; see paragraph following **Side Effects** table
	intestinal obstruction (≥2%)[8]
	nausea (9-24%, severe 1%)[1,2,8]
	vomiting (13-14%, severe 1%)[2,8]
general disorders and administration site conditions	*extravasation hazard:* none[13]
	chills (2-5%)
	edema, peripheral (16-21%, severe <1%)[2,8]
	fatigue (14-50%, severe 2-7%)[1,2,8,11]
	infusion-related reaction (14-30%, severe <1%)[2,8,11]; see paragraph following **Side Effects** table
	pyrexia (2-16%, severe <1%)[2,8]
hepatobiliary	***immune-mediated hepatitis*** (≤2%, severe ≤1%)[2,11]; has been fatal; see paragraph following **Side Effects** table
immune system	hypersensitivity (2%)
infections and infestations	skin infection (>1%)[1,8]
	urinary tract infection (21%, severe 5%)[8]
investigations	alkaline phosphatase increase (1-36%, severe ≤7%)[2,11]
	ALT increase (19-20%, severe ≤5%)
	amylase increase (8-9%, severe 1-2%)
	AST increase (26-34%, severe 1-3%)
	bilirubin increase (6-10%, severe 1%)
	creatine phosphokinase increase (2-5%, severe ≤1%)[1,2]
	creatinine increase (≤38%, severe 2%)[2,8]
	gamma-glutamyl transferase increase (1-28%, severe ≤12%)[2,8,11]
	hypercholesterolemia (1%, severe 1%)[1]
	lipase increase (1-15%, severe ≤6%)[2,11]
	weight loss (15-19%)[2,8]
metabolism and nutrition	appetite decrease (4-21%, severe 1-2%)[1,2,8,11]
	dehydration (1%, severe <1%)[11]
	hyperglycemia (severe 3-9%)[2,8]
	hypokalemia (10%, severe <1%)
	hyponatremia (1-37%, severe ≤16%)[2,8,11]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypophosphatemia (1%, severe 1%)[11]
musculoskeletal and connective tissue	arthralgia (9-16%, severe ≤1%)[2,8]
	back pain (1%)
	musculoskeletal pain (25-32%, severe 2-3%)[2,8]
	weakness (1-8%, severe 1%)[1,8,11]
nervous system	dizziness (14%)
	headache (10%)
renal and urinary	***immune-mediated nephritis*** (≤1%)[2,8]; see paragraph following **Side Effects** table
	renal failure (≤16%, severe 3%)[2,8]
respiratory, thoracic and mediastinal	cough (11-18%)[2,8]
	dyspnea (11-17%, severe 1-2%)[2,8]
	immune-mediated pneumonitis (1-2%, severe ≤1%)[1,2,8,11]; has been fatal; see paragraph following **Side Effects** table
skin and subcutaneous tissue	***immune-mediated rash*** (1-5%, severe <1%)[1,2,11]; see paragraph following **Side Effects** table
	pruritus (9-10%)[2,8]
	rash (7-22%, severe <1%)[1,2,8,11]
vascular	hypertension (10-13%, severe 5-6%)[2,8]
	hypotension (1%)

Adapted from standard reference[2] unless specified otherwise.

Infusion reactions are reported in up to 30% of patients***.*** Symptoms include flushing, chills, hypotension, dyspnea, wheezing, pyrexia, back pain, abdominal pain, and urticaria. Grade 3 or 4 reactions are uncommon (i.e., <1% incidence). Premedication with an antihistamine plus acetaminophen is recommended for at least the first four doses of avelumab. Subsequent infusions may be administered without premedications depending on the patient's reaction history. For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***. Permanently discontinue avelumab following a severe or life threatening reaction.[2,7,8]

Immune-mediated adverse events are a spectrum of side effects caused by general immunologic enhancement that can occur at any time during avelumab treatment or months after discontinuation. Consider the etiology of any reported diarrhea/colitis, endocrinopathy, hepatitis, myocarditis, nephritis, pneumonitis, rash, and uveitis to be immune-mediated until another etiology is confirmed. Symptoms can be severe or fatal if not recognized and treated quickly. Strongly advise patients to promptly report symptoms and to avoid self-treatment without medical advice. Management of symptoms depends on the severity of the reaction and may require treatment interruption and/or administration of systemic corticosteroids. Corticosteroids should be appropriately tapered following resolution of symptoms to grade 1 or less. Depending on the severity of the initial reaction, avelumab may be restarted following completion of the steroid taper. Based on limited data, immunosuppressants may be administered if adverse reactions are not controlled by corticosteroids. Referral to appropriate medical specialty may be required to manage other immune-mediated complications related to treatment. Antibiotic prophylaxis should be considered for patients on long term corticosteroid treatment (e.g., oral trimethoprim/sulfamethoxazole for the prevention of *Pneumocystis jiroveci* pneumonia).

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Permanently discontinue avelumab for:
- life-threatening (grade 3 or 4) reactions; excluding endocrinopathies controlled with replacement hormones,
- persistent grade 2 or 3 reactions that do not improve to grade 0 or 1, or
- recurrent grade 2 or 3 reactions.[2,14]

For further information on management of immune-mediated adverse reactions, see BC Cancer Protocol SCIMMUNE ***Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitors Immunotherapy*.**

Immune-mediated ***colitis*** may present as severe abdominal pain, diarrhea, black/tarry stools, or stools with blood or mucous. Withhold avelumab for grade 2 or greater colitis and administer systemic corticosteroids. Initiate corticosteroid taper upon symptom resolution. Avelumab may be restarted when symptoms have resolved to grade 0 or 1. Permanently discontinue avelumab for grade 4 or recurrent grade 3 colitis.[2,8]

Immune-mediated ***endocrinopathies*** may present as nonspecific symptoms such as fatigue, nausea, headache, vision changes.
Commonly reported endocrinopathies are outlined below:
- ***adrenal insufficiency*** (e.g., dehydration, hypotension, electrolyte imbalances),
- autoimmune thyroid disease, including ***hyper-*** and ***hypothyroidism***, ***thyroiditis***,
- ***hypopituitarism***, and
- ***type 1 diabetes mellitus*** and ***diabetic ketoacidosis***.[2,14]

Monitor blood glucose and thyroid function at baseline and periodically during therapy. Symptomatic endocrinopathies may require treatment interruption, corticosteroids, and/or replacement hormones as clinically indicated. Withhold avelumab for grade 3 or 4 endocrinopathies until symptoms resolve to grade 0 or 1.[2,14]

Immune-mediated ***hepatitis*** has been observed and is sometimes fatal. Liver function tests should be monitored at baseline and during therapy as indicated. Monitor patients for clinical signs and symptoms of hepatotoxicity. Withhold avelumab for AST/ALT greater than 3 times ULN or total bilirubin greater than 1.5 times ULN and administer systemic corticosteroids. Upon symptom resolution, corticosteroid taper may be initiated. Avelumab may be restarted once symptoms have resolved to grade 0 or 1. Permanently discontinue avelumab for AST/ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN.[2]

Immune-mediated ***nephritis*** has been observed. Monitor for changes in renal function and urine volume or colour. Withhold avelumab for grade 2 or greater nephritis and administer systemic corticosteroids. Initiate corticosteroid taper upon symptom resolution. Avelumab may be restarted when symptoms have resolved to grade 0 or 1. Permanently discontinue avelumab for grade 4 nephritis.[2]

Immune-mediated ***pneumonitis*** has been reported and is sometimes fatal. Monitor for shortness of breath, chest pain, and new or worsening cough. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Withhold avelumab for grade 2 or greater pneumonitis and administer systemic corticosteroids. Initiate corticosteroid taper upon symptom resolution. Avelumab may be restarted when symptoms have resolved to grade 0 or 1. Permanently discontinue avelumab for grade 3 or 4 reactions and recurrent grade 2 reactions.[2,14]

Other less common, but clinically significant, immune-mediated toxicities associated with avelumab include: ***erythema multiforme***, ***exfoliative dermatitis***, ***Guillain-Barré syndrome***, ***myocarditis*** (has been fatal), ***myositis***, ***pemphigoid***, ***sepsis***, and ***uveitis***.[2,8,11]

INTERACTIONS: none known[2]

SUPPLY AND STORAGE:

***Injection*:** EMD Serono Canada supplies avelumab in 200 mg preservative-free, single use vials in a concentration of 20 mg/mL. Refrigerate. Protect from light.[2]

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: flush line with NS or 0.45% sodium chloride after administration[2]

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[2]
Intermittent infusion	***over 60 min***; administer with a 0.2 micron filter[2,15]
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.

***Adults*:**

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

Intravenous:

Cycle Length: ***2 weeks***[1,2,11,15]: ***10 mg/kg IV for one dose on day 1*** (total dose per cycle 10 mg/kg)

2 weeks[5,6,16]: 800 mg IV for one dose on day 1 (total dose per cycle 800 mg)

Concurrent radiation: no information found

Dosage in renal failure[2]: no adjustment required

Dosage in hepatic failure[2,8]:

Bilirubin		AST	Dose
≤ ULN	and	> ULN	no adjustment required
1 to 3 x ULN		-	no adjustment required
> 3 x ULN		-	no information found

Dosage in dialysis: no information found

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Children: safety and efficacy has not been established

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