

Drug Monograph

[Drug Name](#) | [Mechanism of Action and Pharmacokinetics](#) | [Indications and Status](#) | [Adverse Effects](#) | [Dosing](#) | [Administration Guidelines](#) | [Special Precautions](#) | [Interactions](#) | [Recommended Clinical Monitoring](#) | [Supplementary Public Funding](#) | [References](#) | [Disclaimer](#)

A - Drug Name

avelumab

COMMON TRADE NAME(S): Bavencio™

[back to top](#)

B - Mechanism of Action and Pharmacokinetics

Avelumab is a fully human monoclonal antibody (IgG1) that inhibits the suppressive effects of PD-L1 on cytotoxic T cells, thereby restoring the anti-tumour immune response.

Absorption	Time to reach steady state	4 to 6 weeks (2 to 3 cycles) when administered every 2 weeks
Distribution	<p>Avelumab is distributed mainly in the systemic circulation, with less distribution to the extracellular space.</p> <p>Avelumab exposure increases proportionally to dose in the range of 10-20 mg/kg every 2 weeks.</p>	
Metabolism	<p>Monoclonal antibodies are degraded into small peptides and amino acids via catabolic pathways.</p>	
Elimination	Half-life	6.1 days (terminal)

[back to top](#)

C - Indications and Status

Health Canada Approvals:

- Merkel cell carcinoma (MCC)
- Urothelial carcinoma (UC)

(Includes conditional approvals)

Refer to the product monograph for a full list and details of approved indications.

[back to top](#)

D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following table lists adverse effects that occurred in $\geq 1\%$ of patients in an unresectable locally advanced or metastatic urothelial carcinoma (UC) study, where higher incidences were observed in the avelumab arm. Adverse effects marked with “†” were reported in previously untreated Merkel cell carcinoma. It also includes severe, life-threatening and post-marketing adverse effects from other indications.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (10%) †	E
	Hypotension (2%)	E
	Myocarditis (rare)	E D
Dermatological	Erythema multiforme (rare)	E
	Rash, pruritus (20%) (1% severe)	E
Gastrointestinal	Abdominal pain (13%) †	E
	Anorexia, weight loss (14%)	E
	Constipation (16%)	E
	Diarrhea (17%) (may be severe, 2% colitis)	E D
	Nausea, vomiting (16%)	E
General	Edema (13%)	E
	Fatigue (36%)	E
	Fever, chills (15%)	I

Hematological	Anemia (16%) †	E D
Hepatobiliary	↑ LFTs (5%) (2% severe; 1% autoimmune hepatitis)	E D
	Pancreatitis (rare, in combination with axitinib)	E
Hypersensitivity	Hypersensitivity (2%)	I E
	Infusion related reaction (10%) (may be severe)	I
Immune	Antibody response (4%)	E D
Metabolic / Endocrine	Adrenal insufficiency (2%)	E D
	Hyperglycemia (4%) ; diabetes mellitus (type 1; rare)	E D
	Hyperthyroidism (6%)	E D
	Hypothyroidism (12%)	E D
Musculoskeletal	Musculoskeletal pain (24%)	E
	Other - Rheumatoid arthritis (rare)	E
Nervous System	Guillain-Barre syndrome (rare)	E
	Myasthenia gravis (rare)	E
	Myositis (<1%)	E D
Ophthalmic	Uveitis (rare)	E
Renal	Nephrotoxicity (2%) (nephritis - rare)	E D
Respiratory	Cough, dyspnea (14%)	E
	Pneumonitis (3%)	E D
Urinary	Urinary tract infection (20%)	E

* "Incidence" may refer to an absolute value or the higher value from a reported range.
 "Rare" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
 D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for avelumab include fatigue, musculoskeletal pain, rash/pruritus, diarrhea, anemia, constipation, nausea/vomiting, fever, chills, anorexia/weight loss, cough/dyspnea.

Refer to CCO's [Immune Checkpoint Inhibitor Toxicity Management Guideline](#) for detailed descriptions of Immune-related toxicities and their management.

Presentation of immune-mediated reactions may be different compared to other anti-cancer agents and early diagnosis and appropriate management is critical.

Immune-mediated reactions such as rash, pneumonitis, colitis, hepatitis, nephritis, endocrinopathies and neuropathies were reported in patients who received avelumab and may be severe or fatal.

Anti-drug antibodies have been reported, but did not appear to impact the risk of infusion-related reactions.

[back to top](#)

E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the [hepatitis B virus screening and management](#) guideline.

Avoid the use of corticosteroids or immunosuppressants before starting treatment.

Premedication with an antihistamine and acetaminophen prior to the first 4 infusions is recommended. Consider for subsequent infusions based on clinical judgement and prior infusion reactions.

Adults:

Avelumab 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity

Dosage with Toxicity:

Healthcare professionals should also consult the most recent avelumab product monograph for additional information.

Dose reductions are not recommended for avelumab . Doses may be delayed or discontinued based on toxicity.

Summary of Principles of Management of Immune-Related Adverse Effects (irAEs):

- Immune-related adverse effects (irAEs) are different in their presentation, onset and duration compared to conventional chemotherapy. Patient and provider education is essential.
- Initial irAEs presentation can occur months after completion of treatment and affect multiple organs.
- Dose escalation or reduction is not recommended.

- If no other cause can be identified (such as infection), any new symptom should be considered immune-related and prompt treatment initiated.
- Organ-specific system-based toxicity management is recommended.

Refer to CCO's Immune [Checkpoint Inhibitor Toxicity Management Guideline](#) for detailed descriptions of Immune-related toxicities and their management.

Infusion-related reactions:

Toxicity Grade	Action
1	Slow infusion rate by 50%
2	Interrupt infusion until \leq grade 1; restart at 50% lower infusion rate.
≥ 3	Discontinue

Dosage with Hepatic Impairment:

Refer to CCO's [Immune Checkpoint Inhibitor Toxicity Management Guideline](#) for detailed descriptions for immune-related hepatic toxicity management.

Hepatic impairment	Avelumab dose
Mild (bilirubin \leq ULN and AST $>$ ULN OR bilirubin 1-1.5 x ULN)	no change
Moderate (bilirubin 1.5-3 x ULN)	
Severe (bilirubin $>$ 3 x ULN)	no data

Dosage with Renal Impairment:

Refer to CCO's [Immune Checkpoint Inhibitor Toxicity Management Guideline](#) for detailed descriptions for immune-related renal toxicity management.

Creatinine clearance (ml/min)	Avelumab dose
≥ 60	no change
30-59	
15-29	

Dosage in the elderly:**Metastatic Merkel Cell Carcinoma:**

Differences in safety or efficacy between patients aged 65 and older compared to younger patients have not been evaluated

Locally Advanced or Metastatic Urothelial Carcinoma:

No overall differences in safety or efficacy were reported between elderly patients and younger patients. There is limited safety data in patients ≥ 75 years of age in maintenance treatment after first-line platinum-based chemotherapy.

Children:

Safety and efficacy in pediatric patients have not been established.

[back to top](#)

F - Administration Guidelines

- DO NOT administer as an IV push or bolus.
- Dilute avelumab with 0.9% or 0.45% saline solution (preferably 250 mL) prior to infusion. It must not be mixed with other products or diluents.
- Mix the diluted solution by gentle inversion; do not shake.
- Infuse over 60 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 micrometer in-line or add-on filter.
- Do not co-administer with other drugs through the same IV line; flush the line with 0.9% or 0.45% saline after administration.
- Avelumab is compatible with polyethylene, polypropylene and ethylene vinyl acetate infusion bags, glass bottles, polyvinyl chloride infusion sets and in-line filters with polyethersulfone membranes and pore sizes of 0.2 micrometer.
- Avelumab vials should be stored at 2-8°C; do not freeze.
- Store in the original container and protect from light.

[back to top](#)

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any components of the formulation.

Other Warnings/Precautions:

- Use with caution and monitor closely in patients with pre-existing conditions such as colitis, hepatic impairment, respiratory or endocrine disorders, such as hypo or hyperthyroidism or diabetes mellitus.
- Avelumab may cause fatigue; patients should be advised not to drive or operate machinery/tools until they are sure of feeling well.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Crosses placental barrier: Yes
- Fetotoxicity: Likely
Avelumab may cause fetal harm and is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 month** after the last dose.
- Excretion into breast milk: Likely
Breastfeeding is not recommended during treatment and for at least **1 month** after the last dose.
- Fertility effects: Unknown

[back to top](#)

H - Interactions

No formal pharmacokinetic drug-drug interaction studies have been conducted. Avelumab is mainly metabolized through catabolic pathways; it is not expected that avelumab will have drug-drug interactions with other medications.

Use of systemic corticosteroids or immunosuppressants should be avoided prior to starting avelumab because of the potential for interference with avelumab's efficacy. They can be used to treat immune-mediated reactions after starting the drug.

Acetaminophen may affect the response to immune checkpoint inhibitors. Further clinical studies are needed to determine the exact mechanism and the appropriate clinical management (Bessedé et al, 2022).

[back to top](#)

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the [hepatitis B virus screening and management](#) guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, before each dose and as clinically indicated

Liver function tests	Baseline, before each dose and as clinically indicated; frequent with severe toxicity
Renal function tests	Baseline, periodically during treatment and as clinically indicated; frequent with severe toxicity
Thyroid function tests	Baseline and before each dose, or at least once monthly
Blood glucose	Baseline, periodically during treatment and as clinically indicated
Clinical toxicity assessment for infusion-related reactions, fatigue, immune-mediated reactions, including GI, skin, respiratory, neurologic, cardiac, ophthalmic and endocrine toxicities	At each visit and as clinically indicated

Grade toxicity using the current [NCI-CTCAE \(Common Terminology Criteria for Adverse Events\) version](#)

[back to top](#)

J - Supplementary Public Funding

New Drug Funding Program ([NDFP Website](#))

- Avelumab - Metastatic Merkel Cell Carcinoma
- Avelumab - Maintenance Treatment for Unresectable Locally Advanced or Metastatic Urothelial Carcinoma

[back to top](#)

K - References

Avelumab (Bavencio®) product monograph, EMD Serono, January 2021.

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Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol.* 2016 Oct;17(10):1374-1385.

Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol* 2018;19:51–64.

Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med* . 2020 Sep 24;383(13):1218-30.

April 2024 Updated Pregnancy and Lactation section

[back to top](#)

L - Disclaimer

Refer to the [New Drug Funding Program](#) or [Ontario Public Drug Programs](#) websites for the most up-to-date public funding information.

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[back to top](#)