**Drug Monograph**



## A - Drug Name

# avelumab

**COMMON TRADE NAME(S):** Bavencio™

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## 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 | Avelumab is distributed mainly in the systemic circulation, with less distribution to the extracellular space.<br><br>Avelumab exposure increases proportionally to dose in the range of 10-20 mg/kg every 2 weeks. | |
| Metabolism | Monoclonal antibodies are degraded into small peptides and amino acids via catabolic pathways. | |
| Elimination | Half-life | 6.1 days (terminal) |

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## C - Indications and Status

**Health Canada Approvals:**

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

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

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## D - Adverse Effects

**Emetogenic Potential:** Minimal

**Extravasation Potential:** None

The following table lists adverse effects that occurred in ≥ 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 |
| | Sarcoidosis (rare) - disease flare | E |

| | | |
|---|---|---|
| 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.

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## 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 ≤ 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 ≤ 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.

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## 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$^{o}$C; do not freeze.
- Store in the original container and protect from light.

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## G - Special Precautions

### Contraindications:

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

### Other Warnings/Precautions:

- Patients with pre-existing autoimmune disease (AID) were excluded from clinical trials. Data from post-marketing suggest that there are risks of immune-related reactions in patients with pre-existing AID. Consider the risks versus the benefit of giving avelumab in these patients.
- 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

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## 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 (Bessede et al, 2022).

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## 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

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## 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

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## K - References

Bessede A, Marabelle A, Guegan JP, et al. Impact of acetaminophen on the efficacy of immunotherapy in cancer patients. Ann Oncol 2022;33(9):909-15.

D'Angelo SP, Lebbé C, Mortier L, et al. First-line avelumab in a cohort of 116 patients with metastatic Merkel cell carcinoma (JAVELIN Merkel 200): primary and biomarker analyses of a phase II study. J Immunother Cancer 2021 Jul;9(7):e002646.

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.

Product monograph: Avelumab (Bavencio®), EMD Serono, August 6, 2024.

**January 2025** Updated Adverse effects and Warnings sections

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## 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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