Avelumab Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with metastatic Merkel cell carcinoma who have received 1 or more lines of chemotherapy for metastatic disease	C44	00535a	ODMS 01/05/2019
First-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum based chemotherapy	C67	00535b	ODMS 01/09/2022

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Avelumab is administered on day 1 of a 14 day cycle until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Avelumab	800mg	IV infusion	250mL NaCl 0.9% over 60 minutes	Every 14 days
Administer the solution for infusion using a sterile, non-pyrogenic, low-protein binding 0.2 micrometre in-line or add-on filter.					

ELIGIBILITY:

- Indication as above
- ECOG 0-1
- Adequate organ function
- **Merkel cell carcinoma**
  - Histologically proven metastatic merkel cell carcinoma
- **Urothelial carcinoma: First line**
  - Histologically confirmed, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium
  - Completed platinum based chemotherapy in the previous 4 - 10 weeks
  - ≥18 years

EXCLUSIONS:

- Hypersensitivity to avelumab or any of the excipients
- Prior therapy with other immune checkpoint inhibitors
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids)
- Uncontrolled systemic infections such as HIV, Hepatitis B and Hepatitis C
- History of organ transplant

- Untreated, symptomatic CNS metastases
- Pregnancy / breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- Thyroid function test
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV.

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Blood glucose and thyroid function test prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose escalation or dose reduction is not recommended.
- Dosing delay or discontinuation may be required based on individual safety and tolerability

Renal and Hepatic Impairment:

Table 1: Dose modification of avelumab in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dose adjustment is needed for patients with mild or moderate renal impairment. There are insufficient data in patients with severe renal impairment for dosing recommendations	No dose adjustment is needed for patients with mild hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations

Management of adverse events:

Table 2: Dose Modification of avelumab for Adverse Events

Adverse reactions	Severity*	Recommended dose modification
Infusion-related reactions	Grade 1	Reduce infusion rate by 50%
	Grade 2	Withhold until adverse reactions recover to Grade 0-1; restart infusion with a 50% slower rate
	Grade 3 or Grade 4	Permanently discontinue
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grade 0-1
	Grade 3 or Grade 4 or recurrent Grade 2	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN	Withhold until adverse reactions recover to Grade 0-1
	AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN	Permanently discontinue
Colitis	Grade 2 or Grade 3 colitis or diarrhoea	Withhold until adverse reactions recover to Grade 0-1
	Grade 4 colitis or diarrhoea or recurrent Grade 3 colitis	Permanently discontinue
Pancreatitis	Suspected pancreatitis	Withhold
	Confirmed pancreatitis	Permanently discontinue
Myocarditis	Suspected myocarditis	Withhold
	Confirmed myocarditis	Permanently discontinue
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycaemia)	Grade 3 or Grade 4	Withhold until adverse reactions recover to Grade 0-1
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times ULN	Withhold until adverse reactions recover to Grade 0-1
	Serum creatinine more than 6 times ULN	Permanently discontinue
Skin reactions	Grade 3 rash	Withhold until adverse reactions recover to Grade 0-1
	Grade 4 or recurrent Grade 3 rash or confirmed Stevens–Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)	Permanently discontinue
Other immune-related adverse reactions (including myositis, hypopituitarism, uveitis, myasthenia gravis, myasthenic syndrome, Guillain-Barré syndrome)	For any of the following: • Grade 2 or Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above	Withhold until adverse reactions recover to Grade 0-1
	For any of the following: • Life threatening or Grade 4 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy) • Recurrent Grade 3 immune-related adverse reaction	Permanently discontinue

	• Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks • Persistent Grade 2 or Grade 3 immune-mediate adverse reactions lasting 12 weeks or longer	

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.03)

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal **(Refer to local policy).**

PREMEDICATIONS:

Patients have to be premedicated with an antihistamine and with paracetamol prior to the first 4 infusions of avelumab. If the fourth infusion is completed without an infusion-related reaction, premedication for subsequent doses should be administered at the discretion of the clinician

Table 3: Suggested pre-medications prior to avelumab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO at least 30 minutes prior to avelumab infusion
Chlorphenamine	10mg	IV bolus at least 30 minutes prior to avelumab infusion

OTHER SUPPORTIVE CARE:

Women of childbearing potential should be advised to avoid becoming pregnant while receiving avelumab and should use effective contraception during treatment with avelumab and for at least 1 month after the last dose of avelumab.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Infusion-related reactions:** Infusion-related reactions, which might be severe, have been reported in patients receiving avelumab. Patients should be monitored for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. Guidelines for management of infusion–related reactions are in Table 2 above**.**
- **Immune-related adverse reactions:** Most immune-related adverse reactions with avelumab were reversible and managed with temporary or permanent discontinuation of avelumab, administration of corticosteroids and/or supportive care.
    - Based on the severity of the adverse reaction, avelumab should be withheld and corticosteroids administered.

- If corticosteroids are used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement.
- In patients, whose immune-related adverse reactions cannot be controlled with corticosteroid use, administration of other systemic immunosuppressants may be considered.

Table 4: Management of immune related adverse reactions

Adverse reaction	Withhold/ discontinue	Recommended action -1st occurrence
Immune-related pneumonitis Patients should be monitored for signs and symptoms of immune-related pneumonitis and causes other than immune-related pneumonitis should be ruled out.		
Grade 2 Grade 3 or Grade 4 or recurrent Grade 2	Withhold until resolution Permanently discontinue	Suspected pneumonitis should be confirmed with radiographic imaging. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).
Immune-related colitis Patients should be monitored for signs and symptoms of immune-related colitis and causes other than immune-related colitis should be ruled out.		
Grade 2 or Grade 3 Grade 4 or recurrent Grade 3	Withhold until resolution Permanently discontinue	Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper).
Immune-related hepatitis Patients should be monitored for changes in liver function and symptoms of immune-related hepatitis and causes other than immune-related hepatitis should be ruled out.		
Grade 2 Grade 3 or Grade 4	Withhold until resolution Permanently discontinue	Corticosteroids should be administered for Grade ≥ 2 events (initial dose 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper)
Immune-related pancreatitis Patients should be monitored for signs and symptoms of immune-related pancreatitis. In symptomatic patients, obtain gastroenterology consultation and laboratory investigations (including imaging) to ensure the initiation of appropriate measures at an early stage.		
Suspected immune-related pancreatitis Confirmed immune-related pancreatitis	Withhold until resolution Permanently discontinue	Corticosteroids should be administered for immune-related pancreatitis (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper).
Immune-related myocarditis Patients should be monitored for signs and symptoms of immune-related myocarditis. In symptomatic patients, obtain		

cardiologic consultation and laboratory investigations to ensure the initiation of appropriate measures at an early stage.		
Suspected immune-related myocarditis Confirmed immune-related myocarditis	Withhold until resolution Permanently discontinue	Corticosteroids should be administered for immune-related myocarditis (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper). If no improvement within 24 hours on corticosteroids, additional immunosuppression (e.g., mycophenolate, infliximab, anti-thymocyte globulin) should be considered.
Immune-related endocrinopathies Immune-related thyroid disorders, immune-related adrenal insufficiency, and Type 1 diabetes mellitus have been reported in patients receiving avelumab. Patients should be monitored for clinical signs and symptoms of endocrinopathies.		
Thyroid disorders: *(hypothyroidism/hyperthyroidism)* Grade 3 or 4	 Withhold until resolution	Hypothyroidism should be managed with replacement therapy and hyperthyroidism with anti-thyroid medicinal product as needed
Adrenal insufficiency Grade 3 or Grade 4 symptomatic	Withhold	Corticosteroids should be administered (1 to 2 mg/kg/day prednisone intravenously or oral equivalent) for Grade ≥ 3 adrenal insufficiency followed by a taper until a dose of less than or equal to 10 mg/day has been reached.
Type 1 diabetes mellitus **Grade ≥ 3 hyperglycaemia**	 Withhold	Avelumab can cause Type 1 diabetes mellitus, including diabetic ketoacidosis. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Initiate treatment with insulin for Type 1 diabetes mellitus Antihyperglycaemics should be administered. Treatment with avelumab should be resumed when metabolic control is achieved on insulin replacement therapy
Immune-related nephritis and renal dysfunction Grade 2 or 3 nephritis **Grade 4**	 Withhold until resolution to ≤ Grade 1 Permanently discontinue	 Corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) should be administered for Grade ≥ 2 nephritis..
Other immune-related adverse reactions Other clinically important immune-related adverse reactions were reported in less than 1% of patients: myositis, hypopituitarism, uveitis, myasthenia gravis, myasthenic syndrome and Guillain-Barré syndrome.		

DRUG INTERACTIONS:

- No interaction studies have been conducted with avelumab.
- Avelumab is primarily metabolised through catabolic pathways, therefore, it is not expected that avelumab will have pharmacokinetic drug-drug interactions with other medicinal products.

- Current drug interaction databases should be consulted for more information.

SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

HCP Guide - Important safety information to minimise the risk of immune-related adverse reactions – FAQs:
https://www.hpra.ie/img/uploaded/swedocuments/460fee39-40bf-4f56-b969-ef3f58512de9.pdf

Information for patients:

Patient brochure:
https://www.hpra.ie/img/uploaded/swedocuments/b2be5fcd-fe84-4492-9be7-5f85999c9840.pdf
Patient alert card:
https://www.hpra.ie/img/uploaded/swedocuments/af89f4ed-df98-4667-bb57-6ba8745b8fc3.pdf

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3. Powles T et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2020 Sep 24;383(13):1218-1230. doi: 10.1056/NEJMoa2002788. Epub 2020 Sep 18. PMID: 32945632.
4. Powles T, Park SE, Voog E, et al. Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Long-term follow-up results from the JAVELIN Bladder 100 trial. Presented at: ASCO-GU 2022; February 17-19, 2022; Abstract 487
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
6. Avelumab (Bavencio®) 20 mg/mL concentrate for solution for infusion Summary of Product characteristics. Last updated 26/04/2022. Accessed July 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	10/04/2019		Dr Deirdre O'Mahony
2	09/07/2019	Updated immune related adverse reactions to include pancreatitis as per SPC update	Dr Deirdre O'Mahony
3	14/02/2020	Updated dosing posology as per SmPC update to flat dosing. Updated dose modification and adverse events for pancreatitis and myocarditis as per SmPC update	Dr Deirdre O'Mahony
4	20/10/2020	Added support resources	Prof Maccon Keane
5	28/04/2021	Reviewed. Updated Table 2 (Dose modification for adverse events) as per SPC update. Updated Table 5 (management of immune related adverse effects) as per SPC update. Updated support resources.	Prof Maccon Keane
6	01/09/2022	Addition of new indication.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.