

## Avelumab (Urothelial)

### Indication

Maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy

(TA788)

### ICD-10 codes

C43

### Regimen details

Day	Drug	Dose	Route
1	Avelumab	800mg	IV infusion

### Cycle frequency

14 days

### Number of cycles

Continued until unacceptable toxicity or disease progression.

### Administration

Avelumab is administered in 250mL sodium chloride 0.9% over 60 minutes. It should be given via a sterile, non pyrogenic, low protein binding 0.2micron filter.

Patients should be monitored for infusion related reactions including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. For Grade 1 reactions, decrease the infusion rate to 50% and closely monitor. For Grade 2 infusion-related reactions, the infusion should be temporary discontinued until Grade 1 or resolved, then restart at a 50% slower infusion rate. If Grade 1-2 reactions, subsequent infusions may be given with premedication as below. For Grade 3 or Grade 4 infusion-related reactions, the infusion should be stopped and avelumab should be permanently discontinued.

### Pre-medication

Patients should receive an antihistamine (e.g chlorphenamine 10mg IV) and paracetamol 500mg-1g PO prior to the first 4 infusions. If these are completed without infusion related reactions, premedication for subsequent doses should be given at the consultant's discretion.

### Emetogenicity

This regimen has low emetogenic potential

### Additional supportive medication

Loperamide if required.

### Extravasation

Avelumab is neutral (Group 1)

### Investigations – pre first cycle

Investigation	Validity period (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days
Thyroid function	14 days
Calcium	14 days
Glucose	14 days
Cortisol	14 days

### Investigations – pre subsequent cycles

Investigation	Validity period (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFT	7 days
Calcium	As clinically indicated
Thyroid function*	7 days
Glucose*	7 days
Cortisol*	7 days

\* every cycle for the first 24 weeks, then every other cycle.

### Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Haemoglobin	> 90 g/L
Neutrophils	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 75 \times 10^9/L$
Creatinine Clearance (CrCl)	$\geq 30\text{mL}/\text{min}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
ALT/AST	$< 1.5 \text{ ULN}$
Alkaline Phosphatase	$< 5 \times \text{ULN}$

### Dose modifications

Dose reductions or escalations are not recommended. Doses should be delayed until an adverse reaction resolves to  $\leq$  grade 1.

### Toxicity

Immune related toxicities may affect any organ system and should be considered for any new symptoms. Grade 1 toxicities should be managed symptomatically with close monitoring. Specific management guidelines for immune-related adverse reactions are described in full in the summary of product characteristics

- **Haematological toxicity**

Discuss with consultant if:

Haemoglobin	$\leq 90 \text{ g/L}$
Neutrophils	$< 1.0 \times 10^9/L$
Platelets	$< 75 \times 10^9/L$

- **Renal impairment**

No modifications are required for patients with mild or moderate renal impairment. There is insufficient data regarding administration in severe renal impairment.

Note: worsening renal failure can be a sign of toxicity and so investigation of the cause of worsening renal impairment should be considered before go ahead.

- **Hepatic impairment**

No modifications are required for patients with mild hepatic impairment. There is insufficient data regarding administration in moderate-severe hepatic impairment.

Note: worsening hepatic function can be a sign of toxicity and so investigation of the cause of hepatic impairment should be considered before go ahead.

- **Other toxicities**

**Immune-related adverse reactions**

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. 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 could not be controlled with corticosteroid use, administration of other systemic immunosuppressants may be considered.

**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. Suspected pneumonitis should be confirmed with radiographic imaging e.g. high resolution CT. Corticosteroids should be administered for Grade  $\geq 2$  events (initial dose of 1 to 2 mg/kg/day prednisolone or equivalent, followed by a corticosteroid taper). Avelumab should be withheld for Grade 2 immune-related pneumonitis until resolution, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 immune-related pneumonitis.

**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. Corticosteroids should be administered for Grade  $\geq 2$  events (initial dose 1 to 2 mg/kg/day prednisolone or equivalent, followed by a corticosteroid taper). Avelumab should be withheld for Grade 2 immune-related hepatitis (ALT/AST 3-5 x ULN or Bilirubin 1.5-3 x ULN) until resolution and permanently discontinued for Grade 3 or Grade 4 immune-related hepatitis (ALT/AST  $> 5$  x ULN or Bilirubin  $> 3$  x ULN).

**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. Corticosteroids should be administered for Grade  $\geq 2$  events (initial dose of 1 to 2 mg/kg/day prednisolone or equivalent followed by a corticosteroid taper). Avelumab should be withheld for Grade 2 or Grade 3 immune-related colitis until resolution, and permanently discontinued for Grade 4 or recurrent Grade 3 immune-related colitis.

**Immune-related pancreatitis**

Immune-related pancreatitis has been reported in patients receiving avelumab. 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. 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). Avelumab should be withheld in the

event of suspected immune-related pancreatitis. Avelumab should be permanently discontinued if immune-related pancreatitis is confirmed.

### **Immune-related myocarditis**

Immune-related myocarditis has been reported in patients receiving avelumab. 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. 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. Avelumab should be withheld in the event of suspected immune-related myocarditis. Avelumab should be permanently discontinued if immune-related myocarditis is confirmed.

### **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. Avelumab should be withheld for Grade 3 or Grade 4 endocrinopathies until resolution.

### **Thyroid disorders (hypothyroidism/hyperthyroidism)**

Thyroid disorders can occur at any time during treatment. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Hypothyroidism should be managed with replacement therapy and hyperthyroidism with anti-thyroid medicinal product, as needed. Avelumab should be withheld for Grade 3 or Grade 4 thyroid disorders.

### **Adrenal insufficiency**

Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment. Corticosteroids should be administered (1 to 2 mg/kg/day prednisolone intravenously or oral equivalent) for Grade  $\geq 3$  adrenal insufficiency followed by a taper until a dose of less than or equal to 10 mg/day has been reached. Avelumab should be withheld for Grade 3 or Grade 4 symptomatic adrenal insufficiency.

### **Type 1 diabetes mellitus**

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. Avelumab should be withheld and anti-hyperglycaemics in patients with Grade  $\geq 3$  hyperglycaemia should be administered. Treatment with avelumab should be resumed when metabolic control is achieved on insulin replacement therapy.

### **Immune-related nephritis and renal dysfunction**

Avelumab can cause immune-related nephritis. Patients should be monitored for elevated serum creatinine prior to and during treatment. Corticosteroids (initial dose of 1 to 2 mg/kg/day prednisolone or equivalent followed by a corticosteroid taper) should be administered for Grade  $\geq 2$  nephritis (Serum creatinine  $> 1.5 \times$  ULN). Avelumab should be withheld for Grade 2 or Grade 3 nephritis (Serum creatinine  $1.5-6 \times$  ULN) until resolution to  $\leq$  Grade 1 and permanently discontinued for Grade 4 nephritis (Serum creatinine  $>6 \times$  ULN).

### **Other immune-related adverse reactions**

Other clinically important immune-related adverse reactions were reported in less than 1% of patients: myocarditis including fatal cases, myositis, hypopituitarism, uveitis and Guillain-Barré syndrome. For suspected immune-related adverse reactions, ensure adequate evaluation to confirm aetiology or to rule out other causes. Based on the severity of the adverse reaction, avelumab should be withheld and corticosteroids be administered. Avelumab should be resumed when the immune-related adverse reaction returns to Grade 1 or less following corticosteroid taper. Avelumab should be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for Grade 4 immune-related adverse reaction.

**Adverse effects** - for full details consult product literature/ reference texts

- **Serious side effects**

Myocarditis  
Pneumonitis  
Hepatitis  
Nephritis  
Colitis  
Pancreatitis  
Infusion related reactions

- **Frequently occurring side effects**

Anaemia  
Hypothyroidism  
Reduced appetite  
Headache, dizziness  
Hypertension, hypotension  
Cough, dyspnoea  
Nausea, vomiting  
Constipation  
Arthralgia

- **Other side effects**

Uveitis  
Rash

**Significant drug interactions** – for full details consult product literature/ reference texts

No interaction studies have been conducted.

Avelumab is primarily metabolised through catabolic pathways, therefore, it is not expected that avelumab will have pharmacokinetic drug-drug interactions with other medicinal products.

**Additional comments**

Nil

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**References**

- National Institute for Health and Care Excellence. NICE TA788. Accessed 7 November 2022 via [www.nice.org.uk](http://www.nice.org.uk)
- Summary of Product Characteristics Avelumab (Merck-Pfizer) accessed 7 November 2022 via [www.medicines.org.uk](http://www.medicines.org.uk)
- Powles, T. et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2020; 383:1218-1230

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