Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) in this indication and the information is provided to assist physicians in prescribing this medicine outside the licence. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine in this new promising indication. As such, this is a scientific opinion and should not be regarded as an indication licensed by the MHRA or a future commitment by the MHRA to license such an indication, nor should it be regarded as an authorisation to sell or supply a medicine for such an indication. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated. However, for other updates of the safety information, please refer to the product information of [brandname (INN)] on the electronic Medicines Compendium (eMC) website: [insert link].

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Avelumab 20 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 20 mg of avelumab.
One vial of 10 mL contains 200 mg of avelumab.

Avelumab is a human monoclonal immunoglobulin G1 (IgG1) antibody directed against the immunomodulatory cell surface ligand protein PD-L1 and produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless to slightly yellow solution. The solution pH is in the range of 5.0–5.6 and the osmolality is between 270 and 330 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Avelumab is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the treatment of cancer.

Posology

The recommended dose of avelumab as monotherapy is 800 mg administered intravenously over 60 minutes every 2 weeks.

Administration of avelumab should continue according to the recommended schedule until disease progression or unacceptable toxicity.

Premedication

Patients have to be premedicated with an antihistamine and with paracetamol prior to the first four 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 physician.

Treatment modifications

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability (see Table 1).

Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1: Guidelines for withholding or discontinuation of avelumab

Treatment-related adverse reaction	Severity*	Treatment modification
Infusion-related reactions	Grade 1 infusion-related reaction	Reduce infusion rate by 50%
	Grade 2 infusion-related reaction	Withhold until adverse reactions recover to Grade 0-1; restart infusion with a 50% slower rate
	Grade 3 or Grade 4 infusion-related reaction	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold until adverse reactions recover to Grade 0-1
	Grade 3 or Grade 4 pneumonitis or recurrent Grade 2 pneumonitis	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 endocrinopathies	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
Other immune-related adverse reactions (including myositis, hypopituitarism, uveitis, 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 • Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue

	• Persistent Grade 2 or Grade 3 immune-mediated 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)

Special populations

Elderly

No dose adjustment is needed for elderly patients (≥65 years) (see sections 5.1 and 5.2).

Paediatric population

To be eligible for the avelumab UC EAMS, patients must be at least 18 years of age. The safety and efficacy of avelumab in children and adolescents below 18 years of age have not been established.

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment (see section 5.2). There are insufficient data in patients with severe renal impairment for dosing recommendations.

Hepatic impairment

No dose adjustment is needed for patients with mild hepatic impairment (see section 5.2). There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations.

Method of administration

Avelumab is for intravenous infusion only. It must not be administered as an intravenous push or bolus injection.

Avelumab has to be diluted with either sodium chloride 9 mg/mL (0.9%) solution for injection or with sodium chloride 4.5 mg/mL (0.45%) solution for injection. It is administered over 60 minutes as an intravenous infusion using a sterile, non pyrogenic, low protein binding 0.2 micrometre in-line or add-on filter.

For instructions on the preparation and administration of the medicinal product, see section 6.6

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, both the EAMS and batch numbers, and the name of the administered product should be clearly recorded in the patient file.

Special populations

Patients with the following conditions were excluded from clinical trials: active cardiovascular disease, active central nervous system (CNS) metastasis; active autoimmune disease (in JAVELIN Bladder 100, patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment were eligible) or a history of autoimmune disease; a history of other malignancies within the last 5 years; a history of prior immunodeficiency or organ transplant requiring immunosuppressive therapy; conditions requiring therapeutic immune suppression, acquired immunodeficiency syndrome (AIDS) or active infection with human immunodeficiency virus (HIV), or hepatitis B or C. In the absence of data, avelumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Infusion-related reactions

Infusion-related reactions, which might be severe, have been reported in patients receiving avelumab (see section 4.8).

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.

For Grade 3 or Grade 4 infusion-related reactions, the infusion should be stopped and avelumab should be permanently discontinued (see section 4.2).

For Grade 1 infusion-related reactions, the infusion rate should be slowed by 50% for the current infusion. For patients with Grade 2 infusion-related reactions, the infusion should be temporary discontinued until Grade 1 or resolved, then the infusion will restart with a 50% slower infusion rate (see section 4.2).

In case of recurrence of Grade 1 or Grade 2 infusion-related reaction, the patient may continue to receive avelumab under close monitoring, after appropriate infusion rate modification and premedication with paracetamol and antihistamine (see section 4.2).

In clinical trials, 98.6% (433/439) of patients with infusion-related reactions had a first infusion-related reaction during the first four infusions, of which 2.7% (12/439) were Grade ≥3. In the remaining 1.4% (6/439) of patients, infusion-related reactions occurred after the first four infusions and all were of Grade 1 or Grade 2. In JAVELIN Bladder 100, infusion-related reactions were reported in 21.5% of patients treated with avelumab (0.9% Grade 3, with no Grade ≥4 infusion-related reactions reported).

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.

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 in 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

Immune-related pneumonitis occurred in patients treated with avelumab. One fatal case has been reported in patients receiving avelumab (see section 4.8).

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.

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).

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 (see section 4.2).

Immune-related hepatitis

Immune-related hepatitis occurred in patients treated with avelumab. Two fatal cases have been reported in patients receiving avelumab (see section 4.8).

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 ≥2 events (initial dose 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper).

Avelumab should be withheld for Grade 2 immune-related hepatitis until resolution and permanently discontinued for Grade 3 or Grade 4 immune-related hepatitis (see section 4.2).

Immune-related colitis

Immune-related colitis has been reported in patients receiving avelumab (see section 4.8).

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 ≥2 events (initial dose of 1 to 2 mg/kg/day prednisone 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 (see section 4.2).

Immune-related pancreatitis

Immune-related pancreatitis has been reported in patients receiving avelumab. Two fatal cases have been reported in patients receiving avelumab in combination with axitinib (see section 4.8).

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 (see section 4.2).

Immune-related myocarditis

Immune-related myocarditis has been reported in patients receiving avelumab. Two fatal cases have been reported in patients receiving avelumab in combination with axitinib (see section 4.8).

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 (see section 4.2).

Immune-related endocrinopathies

Immune-related thyroid disorders, immune-related adrenal insufficiency, and Type 1 diabetes mellitus have been reported in patients receiving avelumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of endocrinopathies. Avelumab should be withheld for Grade 3 or Grade 4 endocrinopathies until resolution (see section 4.2).

Thyroid disorders (hypothyroidism/hyperthyroidism)

Thyroid disorders can occur at any time during treatment (see section 4.8).

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 an anti-thyroid medicinal product, as needed.

Avelumab should be withheld for Grade 3 or Grade 4 thyroid disorders (see section 4.2).

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 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.

Avelumab should be withheld for Grade 3 or Grade 4 symptomatic adrenal insufficiency (see section 4.2).

Type 1 diabetes mellitus

Avelumab can cause Type 1 diabetes mellitus, including diabetic ketoacidosis (see section 4.8).

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 ≥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 (see section 4.8).

Patients should be monitored for elevated serum creatinine prior to and periodically during treatment. 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. Avelumab should be withheld for Grade 2 or Grade 3 nephritis until resolution to Grade ≤1 and permanently discontinued for Grade 4 nephritis.

Other immune-related adverse reactions

Other clinically important immune-related adverse reactions were reported in less than 1% of patients: myositis, hypopituitarism, uveitis, and Guillain-Barré syndrome (see section 4.8).

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 to 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 (see section 4.2).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

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.

Pregnancy

There are no or limited data from the use of avelumab in pregnant women.

Animal reproduction studies have not been conducted with avelumab. However, in murine models of pregnancy, blockade of programmed death ligand 1 (PD-L1) signalling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of avelumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

Human IgG1 immunoglobulins are known to cross the placental barrier. Therefore, avelumab has the potential to be transmitted from the mother to the developing foetus. It is not recommended to use avelumab during pregnancy unless the clinical condition of the woman requires treatment with avelumab.

Breast-feeding

It is unknown whether avelumab is excreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded.

Breast-feeding women should be advised not to breast-feed during treatment and for at least 1 month after the last dose due to the potential for serious adverse reactions in breast-fed infants.

Fertility

The effect of avelumab on male and female fertility is unknown.

Although studies to evaluate the effect of avelumab on fertility have not been conducted, there were no notable effects in the female reproductive organs in monkeys based on 1-month and 3-month repeat-dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Avelumab has negligible influence on the ability to drive and use machines. Fatigue has been reported following administration of avelumab (see section 4.8). Patients should be advised to use caution when driving or operating machinery until they are certain that avelumab does not adversely affect them.

4.8 Undesirable effects

Avelumab is associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of avelumab.

Summary of the safety profile

The safety of avelumab has been evaluated for patients with locally advanced or metastatic UC receiving 10 mg/kg avelumab every 2 weeks in the Phase 3 study B9991001(JAVELIN Bladder 100 study; N=344).

In this patient population, the most common adverse reactions were fatigue (17.7%); pruritus (17.2%), urinary tract infection (UTI; 17.2%); diarrhoea (16.6%); arthralgia (16.3%), asthenia (16.3%), constipation (16.3%); back pain (16.0%); nausea (15.7%); pyrexia (14.8%); decreased appetite (13.7%); cough (12.8%); vomiting (12.5%), hypothyroidism (11.6%), rash (11.6%); anaemia (11.3%); haematuria (10.5%) and infusion-related reaction (IRR; 10.2%). The most common Grade ≥3 treatment-emergent adverse events were urinary tract infection (4.4%), anaemia (3.8%), and fatigue (1.7%).

In JAVELIN Bladder 100, avelumab was generally tolerable, with a manageable safety profile consistent with prior experience in other solid tumours (see the summary of product characteristics [SmPC] of Bavencio®). No new safety concerns were identified in patients with locally advanced or metastatic UC who received maintenance treatment with avelumab.

Serious adverse reactions were immune-related adverse reactions and infusion-related reaction (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions reported for avelumab as monotherapy in patients with solid tumours, including locally advanced or metastatic UC, or metastatic Merkel cell carcinoma are presented in Table 2. In all studies, avelumab was administered at 10 mg/kg every 2 weeks.

These reactions are presented by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2. Adverse reactions in patients treated with avelumab as monotherapy

Frequency	Adverse reactions
Infections and infestations	
Very common	Urinary tract infection
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Lymphopenia
Uncommon	Thrombocytopenia, eosinophilia*
Immune system disorders	
Uncommon	Drug hypersensitivity, hypersensitivity, anaphylactic reaction, Type I hypersensitivity
Endocrine disorders	
Common	Hypothyroidism†
Uncommon	Adrenal insufficiency†, hyperthyroidism†, thyroiditis†, autoimmune thyroiditis†, adrenocortical insufficiency acute†, autoimmune hypothyroidism†, hypopituitarism†
Metabolism and nutrition disorders	
Very common	Decreased appetite
Uncommon	Diabetes mellitus†, Type 1 diabetes mellitus†, hyperglycaemia†
Nervous system disorders	
Common	Headache, dizziness, neuropathy peripheral
Uncommon	Guillain-Barré Syndrome†, Miller Fisher syndrome†
Eye disorders	
Uncommon	Uveitis†
Cardiac disorders	
Rare	Myocarditis†
Vascular disorders	
Common	Hypertension, hypotension
Uncommon	Flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Pneumonitis†
Uncommon	Interstitial lung disease†
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, constipation, vomiting, abdominal pain
Common	Dry mouth
Uncommon	Colitis†, autoimmune colitis†, enterocolitis†, ileus, autoimmune pancreatitis†, enteritis†, proctitis†
Rare	Pancreatitis†
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis†, acute hepatic failure*, hepatic failure†, hepatitis†, hepatotoxicity†
Skin and subcutaneous tissue disorders	
Common	Rash†, pruritus†, rash maculo-papular†, dry skin

Uncommon	Rash pruritic†, erythema†, rash generalised†, psoriasis†, rash erythematous†, rash macular†, rash papular†, dermatitis exfoliative†, erythema multiforme†, pemphigoid†, pruritus generalised†, eczema, dermatitis, vitiligo†, purpura†, dermatitis psoriasiform†, drug eruption†, lichen planus†
Musculoskeletal and connective tissue disorders	
Very common	Back pain, arthralgia
Common	Myalgia
Uncommon	Myositis†, arthritis†, polyarthritis†, oligoarthritis†, rheumatoid arthritis†
Renal and urinary disorders	
Uncommon	Tubulo-interstitial nephritis†, renal failure†, nephritis†
General disorders and administrative site conditions	
Very common	Fatigue, pyrexia, oedema peripheral
Common	Asthenia, chills, influenza-like illness
Uncommon	Systemic inflammatory response syndrome†
Investigations	
Very common	Weight decreased
Common	Gamma-glutamyltransferase increased, blood alkaline phosphatase increased, amylase increased, lipase increased, blood creatinine increased
Uncommon	Alanine aminotransferase (ALT) increased†, aspartate aminotransferase (AST) increased†, blood creatine phosphokinase increased†, transaminases increased†, blood thyroid-stimulating hormone increased†, thyroxine free decreased†
Injury, poisoning and procedural complications	
Very common	Infusion-related reaction

* Reaction only observed from study EMR 100070-003 (Part B) after the data cut-off of the pooled analysis, hence frequency estimated

† Immune-related adverse reaction based on medical review

Description of selected adverse reactions

Data for immune-related adverse reactions for avelumab as a monotherapy are based on 1,650 patients in the Phase I study EMR100070-001 in solid tumours and 88 patients in study EMR100070-003.

The management guidelines for these adverse reactions are described in section 4.4.

Immune-related pneumonitis

In patients treated with avelumab as monotherapy, 1.2% (21/1,738) of patients developed immune-related pneumonitis. Of these patients, there was 1 (0.1%) patient with a fatal outcome, 1 (0.1%) patient with Grade 4, and 5 (0.3%) patients with Grade 3 immune-related pneumonitis.

The median time to onset of immune-related pneumonitis was 2.5 months (range: 3 days to 11 months). The median duration was 7 weeks (range: 4 days to more than 4 months).

Avelumab was discontinued in 0.3% (6/1,738) of patients due to immune-related pneumonitis. All 21 patients with immune-related pneumonitis were treated with corticosteroids and 17 (81%) of the 21 patients were treated with high-dose corticosteroids for a median of 8 days (range: 1 day to 2.3 months). Immune-related pneumonitis resolved in 12 (57%) of the 21 patients at the time of data cut-off.

Immune-related hepatitis

In patients treated with avelumab as monotherapy, 0.9% (16/1,738) of patients developed immune-related hepatitis. Of these patients, there were 2 (0.1%) patients with a fatal outcome, and 11 (0.6%) patients with Grade 3 immune-related hepatitis.

The median time to onset of immune-related hepatitis was 3.2 months (range: 1 week to 15 months). The median duration was 2.5 months (range: 1 day to more than 7.4 months).

Avelumab was discontinued in 0.5% (9/1,738) of patients due to immune-related hepatitis. All 16 patients with immune-related hepatitis treated with corticosteroids and 15 (94%) of the 16 patients received high-dose corticosteroids for a median of 14 days (range: 1 day to 2.5 months). Immune-related hepatitis resolved in 9 (56%) of the 16 patients at the time of data cut-off.

Immune-related colitis

In patients treated with avelumab as monotherapy, 1.5% (26/1,738) of patients developed immune-related colitis. Of these patients, there were 7 (0.4%) patients with Grade 3 immune-related colitis.

The median time to onset of immune-related colitis was 2.1 months (range: 2 days to 11 months). The median duration was 6 weeks (range: 1 day to more than 14 months).

Avelumab was discontinued in 0.5% (9/1,738) of patients due to immune-related colitis. All 26 patients with immune-related colitis were treated with corticosteroids and 15 (58%) of the 26 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Immune-related colitis resolved in 18 (70%) of 26 patients at the time of data cut-off.

Immune-related pancreatitis

In patients treated with avelumab as monotherapy, immune-related pancreatitis occurred in less than 1% (1/4,000) of patients across clinical trials in multiple tumour types.

Immune-related myocarditis

In patients treated with avelumab as monotherapy, immune-related myocarditis occurred in less than 1% (5/4,000) of patients across clinical trials in multiple tumour types.

Immune-related endocrinopathies

Thyroid disorders
In patients treated with avelumab as monotherapy, 6% (98/1,738) of patients developed immune-related thyroid disorders, including 90 (5%) patients with hypothyroidism, 7 (0.4%) with hyperthyroidism, and 4 (0.2%) with thyroiditis. Of these patients, there were 3 (0.2%) patients with Grade 3 immune-related thyroid disorders.

The median time to onset of thyroid disorders was 2.8 months (range: 2 weeks to 13 months). The median duration was not estimable (range: 1 day to more than 26 months).

Avelumab was discontinued in 0.1% (2/1,738) of patients due to immune-related thyroid disorders. Thyroid disorders resolved in 7 (7%) of the 98 patients at the time of data cut-off.

Adrenal insufficiency
In patients treated with avelumab as monotherapy, 0.5% (8/1,738) of patients developed immune-related adrenal insufficiency. Of these patients, there was 1 (0.1%) patient with Grade 3 immune-related adrenal insufficiency.

The median time to onset of immune-related adrenal insufficiency was 2.5 months (range: 1 day to 8 months). The median duration was not estimable (range: 2 days to more than 6 months).

Avelumab was discontinued in 0.1% (2/1,738) of patients due to immune-related adrenal insufficiency. All 8 patients with immune-related adrenal insufficiency were treated with corticosteroids, 4 (50%) of the 8 patients received high-dose systemic corticosteroids (≥ 40 mg prednisone or equivalent) followed by a taper for a median of 1 day (range: 1 day to 24 days). Adrenal insufficiency resolved in 1 patient with corticoid treatment at the time of data cut-off.

Type 1 diabetes mellitus

In patients treated with avelumab as monotherapy, Type 1 diabetes mellitus without an alternative aetiology occurred in 0.1% (2/1,738) of patients including two Grade 3 reactions that led to permanent discontinuation of avelumab.

The median time to onset of Type 1 diabetes mellitus was 1.9 months (range: 1.1 months to 7.3 months).

Avelumab was discontinued in 0.2% (1/489) of patients due to Type 1 diabetes mellitus. All 5 patients with Type 1 diabetes mellitus were treated with insulin. Type 1 diabetes mellitus did not resolve in any of the patients at the time of data cut-off.

Immune-related nephritis and renal dysfunction

In patients treated with avelumab as monotherapy, immune-related nephritis occurred in 0.1% (1/1,738) of patients receiving avelumab leading to permanent discontinuation of avelumab.

The median time to onset of immune-related nephritis was 1.2 months (range: 2.9 weeks to 1.8 months). The median duration was 1.3 weeks (range: more than 4 days to 1.3 weeks).

Immune-related nephritis did not lead to discontinuation of avelumab in any patient. All 2 patients with immune-related nephritis were treated with high-dose corticosteroids for a median of 1.1 weeks (range: 3 days to 1.9 weeks). Immune-related nephritis resolved in 1 (50%) of the 2 patients at the time of data cut-off.

Immunogenicity

Of 1,738 patients treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks, 1,627 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 96 (5.9%) tested positive. In ADA-positive patients, there may be an increased risk for infusion-related reactions (about 40% and 25% in ADA ever-positive and ADA never-positive patients, respectively). A new ADA method with improved sensitivity and drug tolerance for evaluating treatment-emergent ADA in patients treated with avelumab as monotherapy was used for JAVELIN Bladder 100. Of the 344 patients treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks plus best supportive care (BSC), 325 were evaluable for treatment-emergent ADA and 62 (19.1%) tested positive. Based on data available including the low incidence of immunogenicity, the impact of ADA on pharmacokinetics, efficacy and safety is uncertain, the impact of neutralising antibodies (nAb) is unknown.

Of the 480 patients with at least one valid ADA result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily, 453 were evaluable for treatment-emergent ADA and 66 (14.6%) tested positive. The new ADA method with improved sensitivity was used in the renal cell carcinoma population. Overall, there was no evidence of altered pharmacokinetic profile, increased incidence of infusion reactions or effects on efficacy with anti-avelumab antibody development.

Reporting of suspected adverse reactions

All observed or volunteered adverse reactions regardless of causal relationship with the EAMS products must be reported as described in Section 14 of the EAMS Treatment Protocol. Adverse events (serious and non-serious) are reported to Merck from the time the patient has taken the first dose of EAMS product administered, until withdrawal or the end of EAMS. Adverse events occurring after the active reporting period has ended should be reported to the Merck if the responsible physician becomes aware of them and believes they have at least a reasonable possibility of being related to EAMS. Adverse events (serious and non-serious) should be reported to Merck on an EAMS adverse event report form.

The contact details for reporting adverse events are:
Email: ICSR_UKI@merckgroup.com
Telephone: 0208 818 7373

4.9 Overdose

Three patients were reported to be overdosed with 5% to 10% above the recommended dose of avelumab. The patients had no symptoms, did not require any treatment for the overdose, and continued on avelumab therapy.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions. The treatment is directed to the management of symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, monoclonal antibodies, ATC code: L01XC31.

Mechanism of action

Avelumab is a human IgG1 monoclonal antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells, resulting in the restoration of anti-tumour T-cell responses.

Avelumab has also shown to induce natural killer (NK) cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC).

Clinical efficacy and safety

Locally advanced or metastatic urothelial carcinoma (JAVELIN Bladder 100)

The efficacy and safety of avelumab was demonstrated in JAVELIN Bladder 100, a randomised, multicentre, open-label study conducted in 700 patients with unresectable, locally advanced or metastatic UC whose disease had not progressed with first-line platinum-based induction chemotherapy. Patients with autoimmune disease or a medical condition that required immunosuppression were excluded.

Randomisation was stratified by best response to chemotherapy (complete response [CR]/partial response [PR] versus stable disease [SD]) and site of metastasis (visceral versus non-visceral) at the time of initiating first-line induction chemotherapy. Patients were randomised (1:1) to receive either avelumab 10 mg/kg intravenous infusion every 2 weeks plus BSC or BSC alone.

Treatment with avelumab continued until Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression of disease by blinded independent central review (BICR) assessment or unacceptable toxicity. Administration of avelumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at baseline, 8 weeks after randomisation, then every 8 weeks up to 12 months after randomisation, and every 12 weeks thereafter until documented confirmed disease progression based on BICR assessment per RECIST v1.1.

Demographic and baseline characteristics were generally well balanced between the avelumab + BSC and the BSC alone arms. Baseline characteristics were a median age of 69 years (range: 32 to 90), 66% of patients were 65 years or older, 77% were male, 67% were white, and the Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0 (61%) or 1 (39%) for both arms.

For first-line induction chemotherapy, 56% of patients received cisplatin plus gemcitabine, 38% of patients received carboplatin plus gemcitabine and 6% of patients received cisplatin plus gemcitabine and carboplatin plus gemcitabine (i.e. these patients received one or more cycles of each combination). Best response to first-line induction chemotherapy was CR or PR (72%) or SD (28%). Sites of metastasis prior to chemotherapy were visceral (55%) or non-visceral (45%). Fifty-one percent of patients had PD-L1-positive tumours. Six percent of patients in the avelumab + BSC arm and 44% of patients in the BSC alone arm received another PD-1/PD-L1 checkpoint inhibitor after discontinuation of treatment.

The primary efficacy outcome measure was overall survival (OS) in all randomised patients and in patients with PD-L1-positive tumours. Progression-free survival (PFS) based on BICR assessment per RECIST v1.1 was an additional efficacy outcome measure. Efficacy outcomes were measured from time of randomisation after 4 to 6 cycles of platinum-based induction chemotherapy.

Efficacy results are presented below.

Table 3: Efficacy results from JAVELIN Bladder 100 (study B9991001)

Efficacy endpoints	**Avelumab + BSC (N=350)**	**BSC (N=350)**
OS		
Events (%)	145 (41.4)	179 (51.1)
Median in months (95% CI)	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)
Hazard ratio (95% CI)	0.69 (0.556, 0.863)	
Two-sided p-value*	0.0010	
12-month OS rate by K-M (95% CI)†	71.3% (66.0, 76.0)	58.4% (52.7, 63.7)
18-month OS rate by K-M (95% CI) †	61.3% (55.4, 66.7)	43.8% (37.8, 49.7)
PFS‡		
Events (%)	225 (64.3)	260 (74.3)
Median in months (95% CI)	3.7 (3.5, 5.5)	2.0 (1.9, 2.7)
Hazard ratio (95% CI)	0.62 (0.519, 0.751)	
Two-sided p-value*	<0.0001	

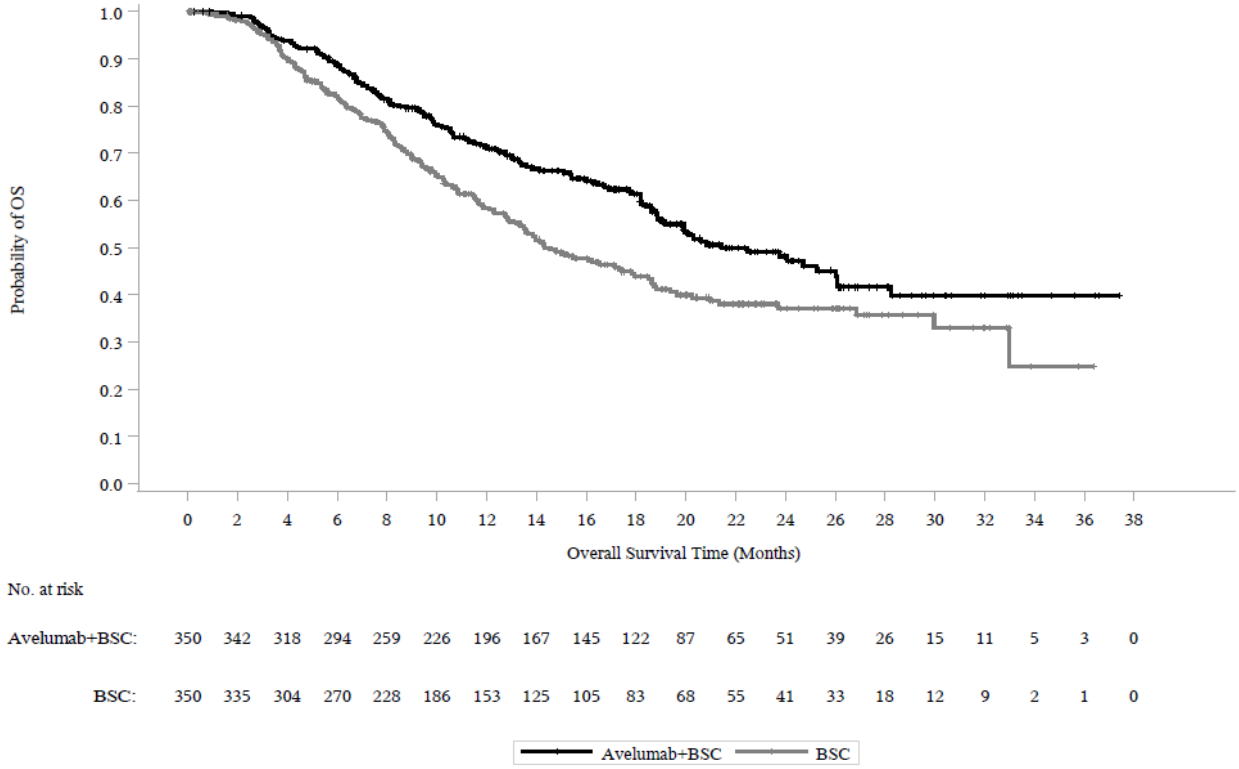
Abbreviations: BSC = best supportive care; CI = confidence interval; K-M = Kaplan-Meier; OS = overall survival; PFS = progression-free survival

* p-value based on stratified log-rank

† CIs are derived using the log-log transformation with back transformation to untransformed scale

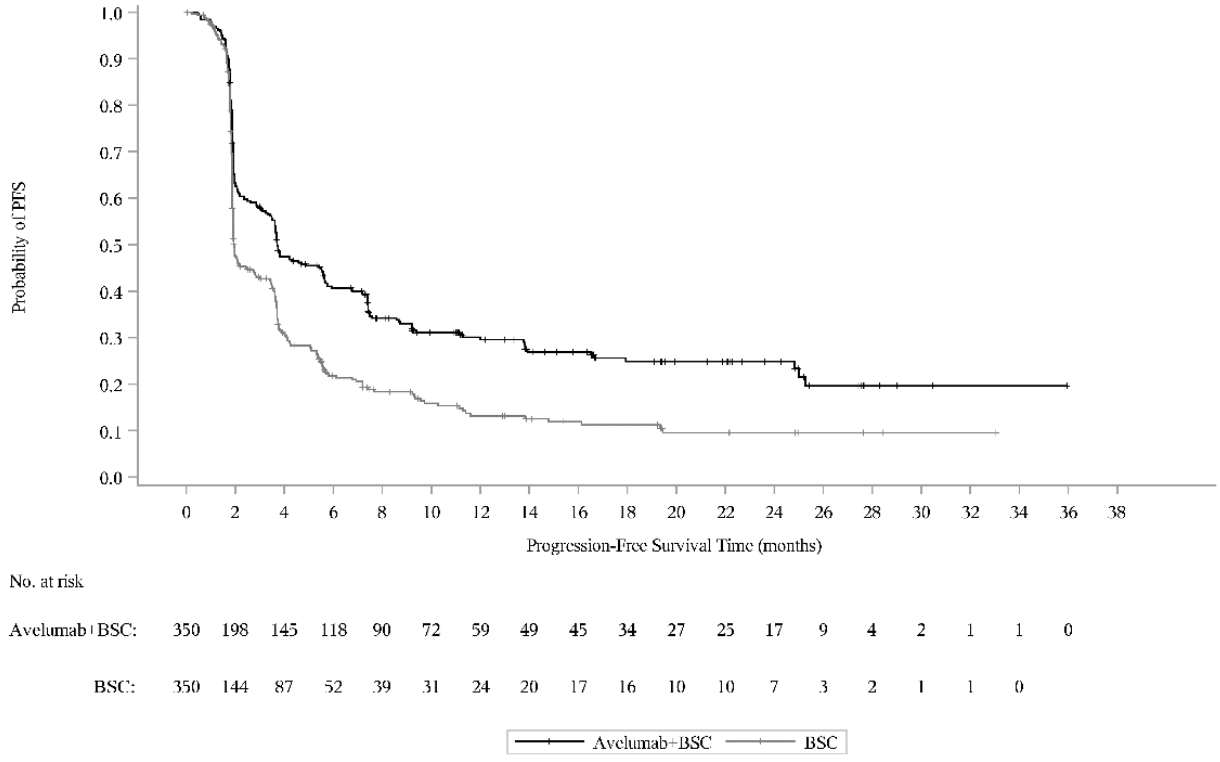
‡ based on BICR assessment per RECIST v1.1

Figure 1: Kaplan-Meier estimates for overall survival (OS) – Full analysis set



Abbreviations: BSC = best supportive care; OS = overall survival

Figure 2: Kaplan-Meier estimates for progression-free survival (PFS) based on BICR assessment per RECIST v1.1 – Full analysis set

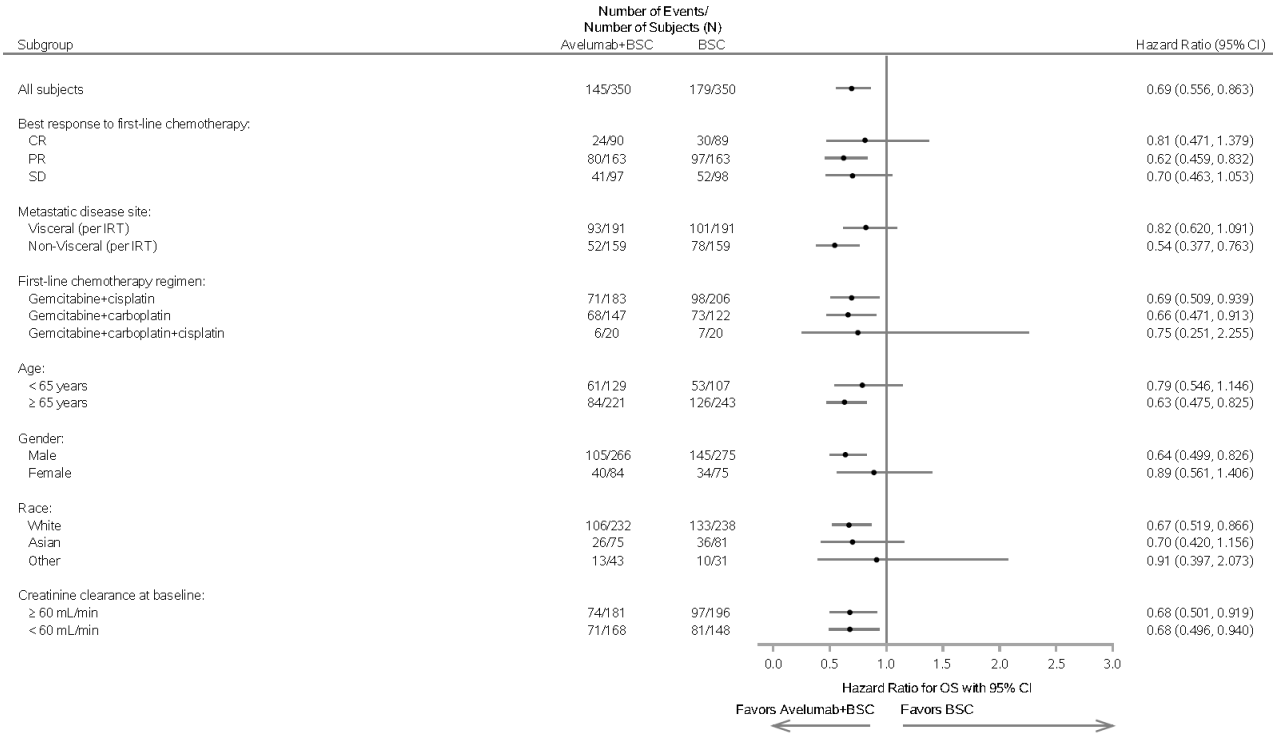


Abbreviations: BICR = blinded independent central review; BSC = best supportive care; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors

In addition, a statistically significant improvement in OS was demonstrated in patients with PD-L1-positive tumours (n=358, 51%) for avelumab + BSC compared with BSC alone (hazard ratio [HR] 0.56; 95% confidence interval [CI]: 0.40, 0.79; two-sided p=0.0007). The median OS was not reached (95% CI: 20.3 months, not reached) in the avelumab + BSC arm, and 17.1 months (95% CI: 13.5, 23.7) in the BSC alone arm. Patients with PD-L1-positive tumours assigned to avelumab + BSC also had an improvement in PFS, with a 44% reduction of the risk of progression or death compared with those assigned to BSC alone (HR: 0.56; 95% CI: 0.431, 0.728; one-sided p<0.0001). The median PFS for avelumab + BSC was 5.7 months (95% CI: 3.7, 7.4), and for BSC alone was 2.1 months (95% CI: 1.9, 3.5). In an exploratory analysis of patients with PD-L1-negative tumours (n=271, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18) and the PFS hazard ratio was 0.63 (95% CI: 0.47, 0.84) for patients randomised to avelumab + BSC compared with BSC alone.

Consistent results were observed across pre-specified subgroups, including best response to first-line induction chemotherapy, and sites of metastasis, as shown in Figure 3.

Figure 3: Forest plot of overall survival (OS) by subgroups – Full analysis set



Abbreviations: BSC = best supportive care; CR =complete response; IRT = interactive response technology; PR = partial response; SD = stable disease

Patient reported outcomes (PROs)
PROs of physical and emotional disease-related symptoms, treatment side effects, and function and well-being were collected using the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Bladder Symptom Index (FBlSI-18). No detrimental effects were observed when adding avelumab maintenance therapy to BSC compared to BSC alone as measured by FBlSI-18 during treatment period.

5.2 Pharmacokinetic properties

Avelumab pharmacokinetics (PK) was assessed using a population PK approach for avelumab as monotherapy and avelumab in combination with axitinib.

Based on a population PK analysis for avelumab as monotherapy and in combination with axitinib, there are no expected clinically meaningful differences in exposure of avelumab between settings administered every 2 weeks at 800 mg or 10 mg/kg.

Distribution

Avelumab is expected to be distributed in the systemic circulation and to a lesser extent in the extracellular space. The volume of distribution at steady state was 4.72 L.

Consistent with a limited extravascular distribution, the volume of distribution of avelumab at steady state is small. As expected for an antibody, avelumab does not bind to plasma proteins in a specific manner.

Elimination

Based on a population pharmacokinetic analysis from 1,629 patients, the value of total systemic clearance (CL) is 0.59 L/day. In the population PK analysis in patients with UC, avelumab CL did not change with median (range) maximal change from the baseline value of -0.74% (-48.3% - 154%).

Steady-state concentrations of avelumab were reached after approximately 4 to 6 weeks (2 to 3 cycles) of repeated dosing at 10 mg/kg every 2 weeks, and systemic accumulation was approximately 1.25-fold.

The elimination half-life (t½) at the recommended dose is 6.1 days based on the population PK analysis.

Linearity/non-linearity

The exposure of avelumab increased dose-proportionally in the dose range of 10 mg/kg to 20 mg/kg every 2 weeks.

Special populations

A population pharmacokinetic analysis suggested no difference in the total systemic clearance of avelumab based on age, gender, race, PD-L1 status, tumour burden, renal impairment and mild or moderate hepatic impairment.

Total systemic clearance increases with body weight. Steady-state exposure was approximately uniform over a wide range of body weights (30 to 204 kg) for body weight normalised dosing.

Renal impairment

No clinically important differences in the clearance of avelumab were found between patients with mild (glomerular filtration rate (GFR) 60 to 89 mL/min, Cockcroft-Gault Creatinine Clearance (CrCL); n=623), moderate (GFR 30 to 59 mL/min, n=320) and patients with normal (GFR ≥90 mL/min, n=671) renal function.

Avelumab has not been studied in patients with severe renal impairment (GFR 15 to 29 mL/min).

Hepatic impairment

No clinically important differences in the clearance of avelumab were found between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin between 1 and 1.5 times ULN, n=217) and normal hepatic function (bilirubin and AST ≤ ULN, n=1,388) in a population PK analysis. Hepatic impairment was defined by National Cancer Institute (NCI) criteria of hepatic dysfunction.

Avelumab has not been studied in patients with moderate hepatic impairment (bilirubin between 1.5 and 3 times ULN) or severe hepatic impairment (bilirubin > 3 times ULN).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity in Cynomolgus monkeys administered intravenously doses of 20, 60 or 140 mg/kg once a week for 1 month and 3 months, followed by a 2-month recovery period after the 3-month dosing period. Perivascular mononuclear cell cuffing was observed in the brain and spinal cord of monkeys treated with avelumab at ≥20 mg/kg for 3 months. Although there was no clear dose-response relationship, it cannot be excluded that this finding was related to avelumab treatment.

Animal reproduction studies have not been conducted with avelumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk that administration of avelumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

No studies have been conducted to assess the potential of avelumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with avelumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the female reproductive organs. Many of the male monkeys used in these studies were sexually immature and thus no explicit conclusions regarding effects on male reproductive organs can be made.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Glacial acetic acid
Polysorbate 20
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
2 years

After opening
From a microbiological point of view, once opened, the medicinal product should be diluted and infused immediately.

After preparation of infusion
Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 20°C to 25°C and room light. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the diluted solution should be infused immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL of concentrate in a vial (Type I glass) with a halobutyl rubber stopper and an aluminium seal fitted with a removable plastic cap.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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 with pore sizes of 0.2 micrometre.

Handling instructions
An aseptic technique for the preparation of the solution for infusion should be used.

The vial should be visually inspected for particulate matter and discoloration. Avelumab is a clear, colourless to slightly yellow solution. If the solution is cloudy, discoloured, or contains particulate matters, the vial should be discarded.

An infusion bag of appropriate size (preferably 250 mL) containing either sodium chloride 9 mg/mL (0.9%) solution for injection or with sodium chloride 4.5 mg/mL (0.45%) solution for injection should be used. The required volume of avelumab should be withdrawn from the vial(s) and transferred to the infusion bag. Any partially used or empty vials have to be discarded.

The diluted solution should be mixed by gently inverting the bag in order to avoid foaming or excessive shearing of the solution.

The solution should be inspected to ensure it is clear, colourless, and free of visible particles. The diluted solution should be used immediately once prepared.

Do not co-administer other medicinal products through the same intravenous line. Administer the solution for infusion using a sterile, non-pyrogenic, low-protein binding 0.2 micrometre in-line or add-on filter as described in section 4.2.

After administration of avelumab, the line should be flushed with either sodium chloride 9 mg/mL (0.9%) solution for injection or with sodium chloride 4.5 mg/mL (0.45%) solution for injection.

Do not freeze or shake the diluted solution. If refrigerated, allow the diluted solution in the intravenous bags to come to room temperature prior to use.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Merck Serono Limited
5 New Square
Bedfont Lakes Business Park
Feltham
Middlesex
TW14 8HA

8. EAMS NUMBER

11648/0003

9. DATE OF SCIENTIFIC OPINION

01/09/2020

Additional information

Healthcare professionals will be provided with the following documents to give to patients to help minimise the risk of immune-related adverse reactions:

- Treatment protocol – Information for patients
- Patient information brochure, directed at patients, containing key information on immune-mediated side effects with avelumab
- An Alert Card, a wallet size card to be completed and given to each patient and carried with them

The Patient Information Brochure is designed to highlight the key immune related adverse events and their symptoms.

Patients should be advised to always carry the Patient Alert Card, with them and show it at all medical visits to other healthcare professionals.

- Please direct the patient to complete all relevant sections of the card, including contact information for the prescriber, patient, and any caregiver who plays a role in helping the patient. This card can be especially helpful in visits to emergency healthcare facilities, where the patient may be unknown.
- Please take a moment to ensure patients understand how to use the Alert Card. Show that it contains summary information about treatment and how to appropriately manage adverse reactions. Emphasise to patients the importance of completing the card and carrying it while on treatment.
- Most importantly, patients should be reminded that if they do experience an adverse reaction, they should seek medical attention immediately and undergo prompt treatment.

EAMS registration

To register a patient with the EAMS, healthcare professionals will need to register on the Clinigen Cliniport portal: https://cliniport.co.uk

Contact details for Clinigen Cliniport portal:

Telephone: 01932 824 100

Email: ukcustomerservice@clinigengroup.com

Once registered they will be able to complete a Patient Access Form, drug supply information and agreement on their responsibilities within the EAMS. Further information and documentation are available within the Clinigen Cliniport EAMS portal. Merck/Pfizer will be able to arrange the required training on adverse event reporting and risk minimisation for immune related toxicities. To gain access to this training please contact either EAMS-UC@merckgroup.com or EAMS-UC@pfizer.com

Contact information

Contact details for reporting adverse events

Email: ICSR_UKI@merckgroup.com
Telephone: 0208 818 7373

Contact details for Medical Information

Email: medinfo.uk@merckgroup.com

Contact details for Clinigen Cliniport portal:

Telephone: 01932 824 100
Email: ukcustomerservice@clinigengroup.com