

Attachment 1: Product information for AusPAR Bavencio - Avelumab (rch) - Merck Serono Australia Pty Ltd - PM-2016-03575-1-4 FINAL 22 January 2019. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

## **BAVENCIO 200 mg per 10 mL concentrated solution for infusion**

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

### **AUSTRALIAN PRODUCT INFORMATION – AVELUMAB (BAVENCIO™)**

#### **1 NAME OF THE MEDICINE**

BAVENCIO (avelumab) 200 mg per 10 mL concentrated solution for intravenous 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 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 THERAPEUTIC INDICATIONS**

BAVENCIO is indicated for the treatment of adults and paediatric patients 12 years and older with metastatic Merkel Cell Carcinoma (mMCC).

This indication is approved based on tumour response rate, duration of response in a single arm study.

##### **4.2 DOSE AND METHOD OF ADMINISTRATION**

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

##### Premedication

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

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*Dosage*

The recommended dose of BAVENCIO is 10 mg/kg body weight administered intravenously over 60 minutes every 2 weeks.

The administration of BAVENCIO should continue according to the recommended schedule until disease progression or unacceptable toxicity.

*Treatment modifications*

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

**Table 1: Recommended dose modifications of BAVENCIO for the management of adverse reactions**

<b>Adverse Reaction</b>	<b>Severity</b>	<b>Treatment modification</b>
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
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycemia)	Grade 3 or Grade 4 endocrinopathies	Withhold until adverse reactions recover to Grade 0-1

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Adverse Reaction	Severity	Treatment modification
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 myocarditis, myositis, hypopituitarism, uveitis, Guillain-Barré syndrome)	For any of the following: <ul style="list-style-type: none"> <li>Grade 2 or Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above.</li> </ul>	Withhold until adverse reactions recover to Grade 0-1
	For any of the following: <ul style="list-style-type: none"> <li>Life threatening or Grade 4 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)</li> <li>Recurrent Grade 3 immune-related adverse reaction</li> <li>Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks</li> <li>Persistent Grade 2 or Grade 3 immune-mediated adverse reactions lasting 12 weeks or longer</li> </ul>	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.03)

### Special populations

#### *Renal impairment*

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

#### *Hepatic impairment*

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.

### Administration

BAVENCIO is administered over 60 minutes as an intravenous infusion using a sterile, non-pyrogenic, low-protein binding 0.2 µm in-line or add-on filter.

BAVENCIO has to be diluted with either 0.9% or 0.45% sodium chloride solution prior to infusion.

BAVENCIO infusion must not be administered as an intravenous push or bolus injection.

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### *Compatibilities*

BAVENCIO is compatible with either 0.9% or 0.45% sodium chloride solution.

BAVENCIO is compatible with 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 µm.

BAVENCIO must not be mixed with other medicinal products except those mentioned above.

### *Handling instructions*

An aseptic technique for the preparation of the solution for infusion has to be used.

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

An infusion bag of appropriate size (preferable 250 mL) containing either 0.9% or 0.45% sodium chloride solution should be used. The required volume of BAVENCIO has to be withdrawn from the vial(s) and to be transferred to the infusion bag. Any partially used or empty vials have to be discarded.

The diluted solution should be mixed 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 drugs through the same intravenous line.

Administer the infusion as described above.

After administration of BAVENCIO, the line should be flushed with either 0.9% or 0.45% sodium chloride solution.

## **4.3 CONTRAINDICATIONS**

Hypersensitivity to the active substance or to any of the excipients

## **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

### 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.

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 temporarily discontinued until Grade 1 or

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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 4 infusions of which 2.7% (12/439) were Grade  $\geq$  3. In the remaining 1.4% (6/439) of patients, infusion-related reactions occurred after the first 4 infusions and all were of Grade 1 or Grade 2.

#### Immune-related adverse reactions

Most immune-related adverse reactions occurring during treatment with avelumab were reversible and managed with temporary or permanent discontinuation of avelumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of avelumab.

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

Immune-related pneumonitis including fatal outcome has been reported in patients receiving avelumab, see section 4.8.

Patients should be monitored for signs and symptoms of 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  $\geq$  2 events (initial dose of 1 - 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 or Grade 4 or recurrent Grade 2 immune-related pneumonitis, see section 4.2.

#### Immune-related hepatitis

Immune-related hepatitis including fatal outcome has 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. Causes other than immune-related hepatitis should be ruled out. Corticosteroids should be administered for Grade  $\geq$  2 events (initial

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dose 1 - 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 immuno-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 - 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 endocrinopathies*

Immune-related thyroid disorders and 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.

#### *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 drug as needed.

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 remains at 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.

#### *Adrenal insufficiency*

Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment. Corticosteroids should be administered (1 - 2 mg/kg/day prednisone i.v. 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, see section 4.2.

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### *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  $\geq 3$  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, 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  $\geq 2$  nephritis. Avelumab should be withheld for Grade 2 or Grade 3 nephritis until resolution to  $\leq$  Grade 1 and permanently discontinued for Grade 4 nephritis.

### *Other 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, 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 remains at Grade 1 or less following corticosteroid taper.

Avelumab should be permanently discontinued for any other Grade 3 immune-related adverse reactions that recur and for any Grade 4 treatment-related adverse reactions except for endocrinopathies controlled with hormone replacement, see section 4.2.

### Patients excluded from clinical studies

Patients with the following conditions were excluded from clinical trials: active central nervous system (CNS) metastasis or treated within 2 months; active or a history of autoimmune disease; a history of other malignancies within the last 5 years except basal or squamous cell carcinoma of the skin or cervical carcinoma in situ; organ transplant; conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C.

### **Paediatric Use**

The safety and efficacy of BAVENCIO have been established in paediatric patients age 12 years and older. Use of BAVENCIO in this age group is supported by evidence from adequate and well-controlled studies of BAVENCIO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of



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avelumab, that drug exposure is generally similar between adults and paediatric patients age 12 years and older for monoclonal antibodies, and that the course of MCC is sufficiently similar in adults and paediatric patients to allow extrapolation of data in adults to paediatric patients. The recommended dose in paediatric patients 12 years of age or greater is the same as that in adults.

The safety and efficacy of BAVENCIO in children less than 12 years of age have not been established.

### **Use in the Elderly**

Clinical studies of BAVENCIO in MCC did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

### **Immunosuppressed/Organ Transplant Patients**

Efficacy and safety have not been studied in immunosuppressed patients or in patients with a history of organ transplantation.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

No interaction studies have been conducted with avelumab in humans.

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

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on 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 male and female reproductive organs in monkeys following IV administration at up to 140 mg/kg weekly for 3 months (yielding 25 times the serum AUC in patients at the recommended clinical dose of 10 mg/kg every two weeks).

### **Use in Pregnancy (Category D)**

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 PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss. 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.

Blockade of PD-L1 signalling has been shown in mouse models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. Therefore,



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potential risks of administering avelumab during pregnancy include increased rates of abortion or stillbirth.

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.

### **Use in Lactation**

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 breastfeed during treatment and for 1 month after the last dose due to the potential for serious adverse reactions in breastfed infants.

### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Avelumab has no or negligible influence on the ability to drive and use machines. Fatigue has been reported following administration of avelumab, see section 4.8.

### **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

#### Summary of the safety profile

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, see Description of selected adverse reactions.

The safety of avelumab has been evaluated in a total of 1738 patients with solid tumours including metastatic MCC receiving 10 mg/kg every 2 weeks of avelumab in clinical studies. In patient population, the most common adverse reactions with avelumab were fatigue (32.4%), nausea (25.1%), diarrhoea (18.9%), decreased appetite (18.4%), constipation (18.4%), infusion-related reactions (17.1%), weight decrease (16.6%), and vomiting (16.2%).

The most common Grade  $\geq 3$  adverse reactions were anaemia (6.0%), dyspnoea (3.9%), and abdominal pain (3.0%). Serious adverse reactions were immune-related adverse reactions and infusion-related reactions, see section 4.4.

#### Tabulated summary of adverse reactions

Adverse reactions reported for 88 patients with mMCC treated with avelumab 10 mg/kg in study 003 and adverse reactions reported for 1,650 patients in a phase I study in other solid tumours are presented in Table 2.

These reactions are presented by MedDRA system organ class, preferred term, frequency, and grade of severity. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

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**Table 2: Expected adverse reactions in patients treated with avelumab in clinical studies**

Frequency category	Adverse Drug Reactions	Avelumab (N = 1738)	
		All Grades n (%)	Grade ≥ 3 n (%)
	<b>Blood and lymphatic system disorder</b>		
Very common	Anaemia	259 (14.9)	104 (6.0)
	<b>Endocrine disorders</b>		
Common	Hypothyroidism*	88 (5.1)	3 (0.2)
Uncommon	Adrenal insufficiency*	8 (0.5)	1 (0.1)
Uncommon	Hyperthyroidism*,#	7 (0.4)	0
Uncommon	Thyroiditis*,#	2 (0.1)	0
Uncommon	Autoimmune thyroiditis*,#	2 (0.1)	0
Uncommon	Adrenocortical insufficiency acute*,#	1 (0.1)	0
Uncommon	Autoimmune hypothyroidism*,#	2 (0.1)	0
Uncommon	Hypopituitarism*,#	1 (0.1)	0
	<b>Eye disorders</b>		
Uncommon	Uveitis*,#	1 (0.1)	0
	<b>Gastrointestinal disorders</b>		
Very common	Nausea	437 (25.1)	27 (1.6)
Very common	Diarrhoea <sup>a</sup>	329 (18.9)	22 (1.3)
Very common	Constipation	320 (18.4)	17 (1.0)
Very common	Vomiting	281 (16.2)	31 (1.8)
Very common	Abdominal pain	250 (14.4)	52 (3.0)
Uncommon	Colitis*	5 (0.3)	4 (0.2)
Uncommon	Autoimmune colitis*,#	1 (0.1)	0
Uncommon	Enterocolitis*,#	1 (0.1)	0
	<b>General disorders and administration site conditions</b>		
Very common	Fatigue	563 (32.4)	51 (2.9)
Very common	Pyrexia <sup>b</sup>	237 (13.6)	5 (0.3)
Very common	Oedema peripheral	206 (11.9)	8 (0.5)
Common	Chills <sup>#,b</sup>	169 (9.7)	1 (0.1)
	<b>Hepatobiliary disorders</b>		
Uncommon	Autoimmune hepatitis*	5 (0.3)	4 (0.2)
Uncommon	Acute hepatic failure*,#	1 (0.1)	1 (0.1)
Uncommon	Hepatic failure*,#	1 (0.1)	1 (0.1)
Uncommon	Hepatitis*,#	1 (0.1)	1 (0.1)
	<b>Immune system disorders</b>		
Uncommon	Drug hypersensitivity <sup>#,b</sup>	8 (0.5)	0
Uncommon	Hypersensitivity <sup>#,b</sup>	6 (0.3)	0
Uncommon	Anaphylactic reaction <sup>b</sup>	2 (0.1)	2 (0.1)
Uncommon	Type I hypersensitivity <sup>#,b</sup>	1 (0.1)	0
	<b>Injury, Poisoning and Procedural Complications</b>		
Very common	Infusion related reaction <sup>b</sup>	297 (17.1)	10 (0.6)
	<b>Investigations</b>		
Very common	Weight decreased	288 (16.6)	12 (0.7)
Uncommon	Aspartate aminotransferase (AST) increased*,#	10 (0.6)	3 (0.2)
Uncommon	Alanine aminotransferase (ALT) increased*,#	9 (0.5)	4 (0.2)
Uncommon	Blood creatine phosphokinase increased*	5 (0.3)	3 (0.2)

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Frequency category	Adverse Drug Reactions	Avelumab (N = 1738)	
		All Grades n (%)	Grade ≥ 3 n (%)
Uncommon	Transaminases increased*	2 (0.1)	2 (0.1)
	<b>Metabolism and nutrition disorders</b>		
Very common	Decreased appetite	320 (18.4)	19 (1.1)
Uncommon	Diabetes mellitus*,#	1 (0.1)	1 (0.1)
Uncommon	Type 1 diabetes mellitus*,#	1 (0.1)	1 (0.1)
	<b>Musculoskeletal and connective tissue disorders</b>		
Very common	Back pain	205 (11.8)	24 (1.4)
Very common	Arthralgia	180 (10.4)	18 (1.0)
Uncommon	Myositis*	5 (0.3)	2 (0.1)
	<b>Nervous system disorders</b>		
Uncommon	Guillain-Barre Syndrome*,#	1 (0.1)	1 (0.1)
	<b>Renal and urinary disorders</b>		
Uncommon	Tubulointerstitial nephritis*,#	1 (0.1)	0
	<b>Respiratory, thoracic and mediastinal disorders</b>		
Very common	Cough#	240 (13.8)	2 (0.1)
Very common	Dyspnoea	229 (13.2)	68 (3.9)
Common	Pneumonitis*	21 (1.2)	7 (0.4)
	<b>Skin and subcutaneous tissue disorders</b>		
Common	Rash*,#	40 (2.3)	1 (0.1)
Common	Pruritus*,#	26 (1.5)	0
Common	Rash maculo-papular*,#	20 (1.2)	0
Uncommon	Rash pruritic*,#	7 (0.4)	0
Uncommon	Erythema*,#	5 (0.3)	0
Uncommon	Rash generalised*,#	5 (0.3)	0
Uncommon	Rash erythematous*,#	4 (0.2)	0
Uncommon	Rash macular*,#	3 (0.2)	0
Uncommon	Rash papular*,#	2 (0.1)	0
Uncommon	Dermatitis exfoliative*,#	1 (0.1)	0
Uncommon	Erythema multiforme*,#	1 (0.1)	0
Uncommon	Pemphigoid*,#	1 (0.1)	0
Uncommon	Pruritus generalised*,#	1 (0.1)	0

\* Immune-related adverse reaction based on medical review

# Single or no SAEs

<sup>a</sup> Frequencies presented in the table represents all events of diarrhoea (all causalities) including immune-related diarrhoea: 21 (1.2%); Grade ≥ 3 4 (0.2%); serious 4 (0.2%)

<sup>b</sup> Frequencies presented in the table represents all events (all causalities) including infusion-related adverse reaction based on predefined definition

Pyrexia: 62 (3.6%); Grade ≥ 3 0 (0%), serious: 3 (0.2%)

Chills: 94 (5.4%); Grade ≥ 3 0 (0%), serious 1 (0.1%)

Infusion related reaction: 296 (17.0%), Grade ≥ 3 10 (0.6%), serious: 15 (0.9%)

Drug hypersensitivity: 5 (0.3%), Grade ≥ 3 0 (0%), serious: 0 (0%)

Hypersensitivity: 3 (0.2%), Grade ≥ 3 0 (0%), serious 0 (0%)

Anaphylactic reaction: 1 (0.1%), Grade ≥ 3 1 (0.1%), serious: 1 (0.1%)

Type I hypersensitivity: (0.1%), Grade ≥ 3 0 (0%), serious: 1 (0.1%)

### Description of selected adverse reactions

Data for the following immune-related adverse reactions are based on 1650 patients in study 001 in other solid tumours and 88 patients in study 003, who received avelumab, see section 5.1.

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

#### Immune-related pneumonitis

Across clinical studies, 1.2% (21/1738) 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, 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

Across clinical studies, 0.9% (16/1738) of patients developed immune-related hepatitis. Of these patients there were 2 (0.1%) patients with a fatal outcome, 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 16 patients at the time of data cut-off.

#### Immune-related colitis

Across clinical studies, 1.5% (26/1738) 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) 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.

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### Immune-related endocrinopathies

#### *Thyroid disorders*

Across clinical studies, 5.6% (98/1738) of patients developed immune-related thyroid disorders, of which 90 (5%) patients with hypothyroidism, 7 (0.4%) with hyperthyroidism, and 4 (0.2%) with thyroiditis. Of these patients there were 3 (0.2%) patient 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*

Across clinical studies, 0.5% (8/1738) 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% (2/1738) 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 ( $\geq 40$  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*

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.

### Immune-related nephritis and renal dysfunction

Immune-related nephritis occurred in 0.1% (1/1,738) of patients receiving avelumab leading to permanent discontinuation of avelumab.

#### *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). Based on data available, including the low incidence of immunogenicity, the impact of ADA on pharmacokinetics, safety, and efficacy is uncertain, while the impact of neutralising antibodies (nAb) is unknown.

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## 4.9 OVERDOSE

There are limited experiences with overdose with avelumab in clinical studies.

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.

Contact the Poisons Information Centre (telephone 131 126) for advice on the management of overdose.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

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

#### Mechanism of action

PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells and can contribute to the inhibition of the anti-tumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Avelumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand 1 (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<sup>+</sup> T-cells, resulting in the restoration of anti-tumour T-cell responses. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth.

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

#### Clinical trials

##### Merkel cell carcinoma (study 003)

The efficacy and safety of avelumab was investigated in the study EMR100070-003 with two parts. Part A was a single-arm, multi-centre study conducted in patients with histologically confirmed metastatic MCC, whose disease had progressed on or after chemotherapy administered for distant metastatic disease, with a life expectancy of more than 3 months. Part B included patients with histologically confirmed metastatic MCC who were treatment-naïve to systemic therapy in the metastatic setting.

Patients with active central nervous system (CNS) metastasis or treated less than 2 months prior to enrolment, active or a history of any autoimmune disease, a history of other malignancies within the last 5 years, organ transplant, conditions requiring therapeutic immune suppression or active infection with HIV or hepatitis B or C, were excluded.



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Patients received avelumab at a dose of 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than two weeks, and no need for salvage therapy could continue treatment.

Tumour response assessments were performed every 6 weeks, as assessed by an Independent Endpoint Review Committee (IERC) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

For Part A, the major efficacy outcome measure was confirmed best overall response (BOR); secondary efficacy outcome measures included duration of response (DOR), and progression-free survival (PFS).

For Part A, efficacy was evaluated after a minimum of 18 months follow-up after the last patient initiated treatment. Patients received a median of 7 doses of avelumab (range: 1 dose to 61 doses), and the median duration of treatment was 17 weeks (range: 2 weeks to 132 weeks).

Of the 88 patients, 65 (73.9%) were male, the median age was 72.5 years (range 33 years to 88 years), 81 (92.0%) patients were Caucasian, and 49 (55.7%) patients and 39 (44.3%) patients with an ECOG performance status 0 and 1, respectively.

Overall, 52 (59.1%) of the patients were reported to have had 1 prior anti-cancer therapy for MCC, 26 (29.5%) with 2 prior therapies, 10 (11%) with 3 or more prior therapies. Forty-seven (53.4%) of the patients had visceral metastases.

Reported with minimum of 18 months follow-up, the ORR was 33.0% (95% CI: 23.3, 43.8), consisting of 10 complete responses and 19 partial responses in avelumab-treated patients. Of 29 patients with objective responses, duration ranged from 2.8 to 24.9+ months. Twenty patients (69%) had ongoing responses at the cut-off date of the analysis.

The median time to response was 6 weeks (range: 6 weeks to 36 weeks) after the first dose of avelumab. Twenty-two out of 29 (75.9%) patients with a response responded within 7 weeks after the first dose of avelumab.

Responses were observed in patients regardless of PD-L1 expression and/or Merkel cell polyomavirus status.

Table 3 summarises efficacy endpoints in patients receiving avelumab at the recommended dose for study EMR100070-003 Part A.



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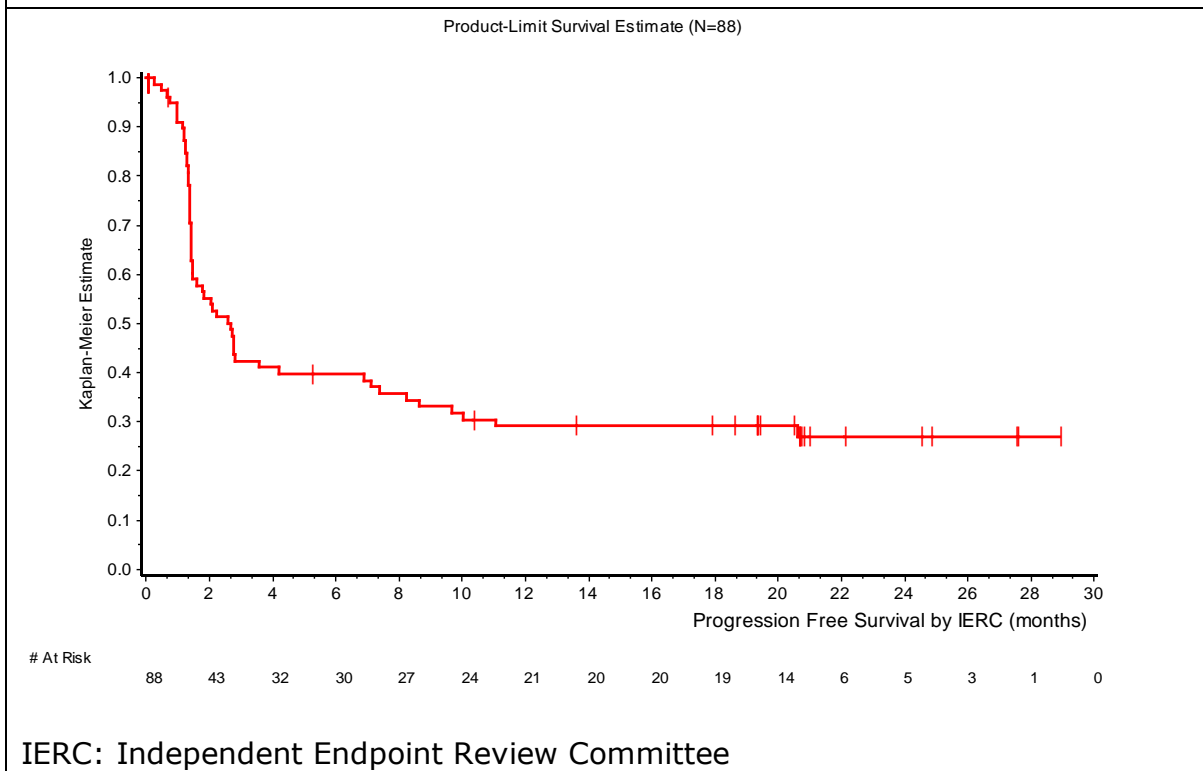
**Table 3: Response to avelumab 10 mg/kg every 2 weeks in patients with mMCC in study 003 (Part A)**

<b>Efficacy Endpoints (per RECIST v1.1, IERC)</b>	<b>Results (N = 88)</b>
Objective Response Rate (ORR) Response Rate, CR+PR* n (%) (95% CI)	29 (33.0%) (23.3, 43.8)
Confirmed Best Overall Response (BOR) Complete Response (CR)* n (%) Partial Response (PR)* n (%)	10 (11.4%) 19 (21.6%)
Duration of Response (DOR) <sup>a</sup> Median, months (95% CI) Minimum, Maximum ≥ 6 months by K-M, (95% CI) ≥ 12 months by K-M, (95% CI)	NR (18.0, not estimated) 2.8+, 24.9+ 93% (75, 98) 71% (51, 85)
Progression-free Survival (PFS) Median PFS, months (95% CI) 6-month PFS rate by K-M, (95% CI) 12-month PFS rate by K-M (95% CI)	2.7 (1.4, 6.9) 40% (29, 50) 29% (19, 39)
CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier; NR: Not reached; +denotes a censored value * CR or PR was confirmed at a subsequent tumour assessment <sup>a</sup> Based on number of subjects with confirmed response (CR or PR)	

The Kaplan-Meier curve of PFS of the 88 patients with mMCC (Part A) is presented in Figure 1.

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**Figure 1: Kaplan-Meier estimates of progression-free survival (PFS) per RECIST v1.1, IERC (Part A)**



For Part B, the major efficacy outcome measure was durable response, defined as objective response (complete response (CR) or partial response (PR)) with a duration of at least 6 months; secondary outcome measures included BOR, DOR, PFS, and OS.

For Part B, prespecified interim analysis of efficacy was conducted after 29 patients had at least 13 weeks of follow-up as of the data cut-off date. There were 39 patients who received at least one dose. Of those, 30 (77%) were males, the median age was 75 years (range: 47 years to 88 years), 33 (85%) patients were Caucasian, and 31 (79%) patients and 8 (21%) patients had an ECOG performance status 0 and 1, respectively. Twenty-nine patients had at least 13 weeks of follow-up at the time of the data cut-off.

Table 4 summarises efficacy endpoints in patients receiving avelumab at the recommended dose for study EMR100070-003, Part B.

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**Table 4: Response to avelumab 10 mg/kg every 2 weeks in patients with metastatic MCC in study EMR100070-003 (Part B)**

<b>Efficacy endpoints (Part B) (per RECIST v1.1, IERC)</b>	<b>Results</b>
Objective response rate (ORR) Response rate, CR+PR* n (%) (95% CI)	(N=29) 18 (62.1%) (42.3, 79.3)
Confirmed best overall response (BOR) Complete response (CR)* n (%) Partial response (PR)* n (%)	(N=29) 4 (13.8%) 14 (48.3%)
Duration of response (DOR) <sup>a</sup> Median, months (95% CI) Minimum, maximum ≥ 3 months by K-M, (95% CI)	(N=18) NR (4.0, not estimable) 1.2+, 8.3+ 93% (61, 99)
Progression-free survival (PFS) Median PFS, months (95% CI) 3-month PFS rate by K-M, (95% CI)	(N=39) 9.1 (1.9, not estimable) 67% (48, 80)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier; NR: Not reached; +denotes a censored value

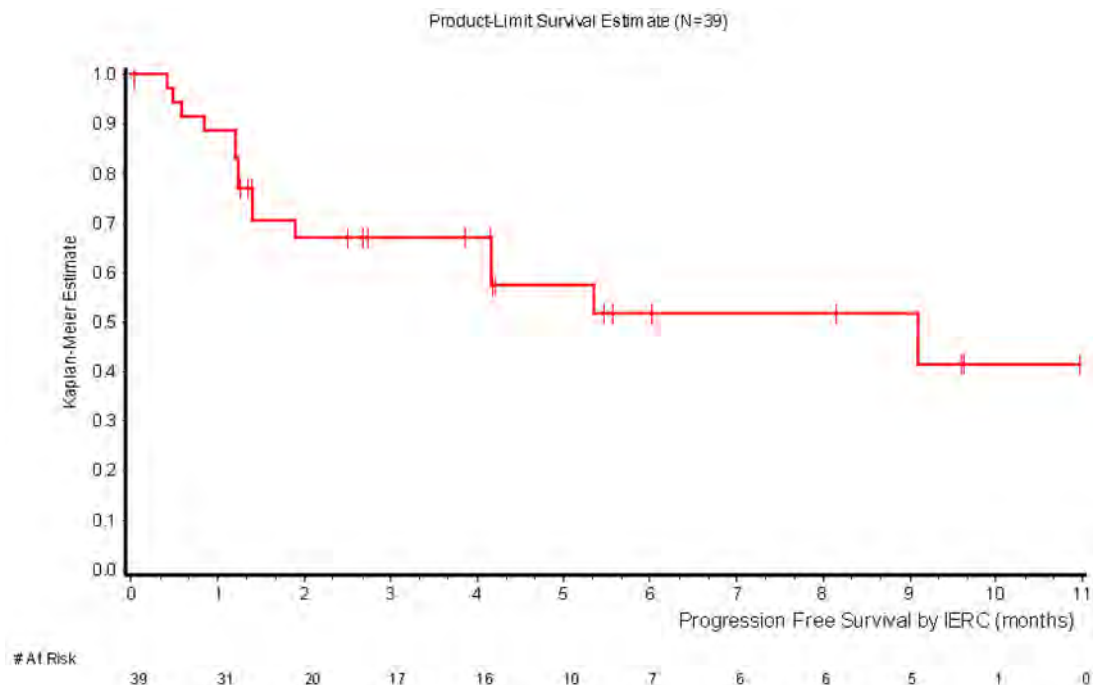
\* CR or PR was confirmed at a subsequent tumour assessment

<sup>a</sup> Based on number of patients with confirmed response (CR or PR)

Figure 2 presents the Kaplan-Meier curve for PFS for the 39 patients enrolled into Part B who received at least one dose of study drug prior to the data cut-off for the interim analysis.

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Figure 2: Kaplan-Meier estimates of progression-free survival (PFS) per RECIST v1.1, IERC (Part B)



## 5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of avelumab have been determined by non-compartmental analyses and a population PK analysis in which patients received avelumab up to 20 mg/kg were studied while the majority of them received dose of 10 mg/kg every 2 weeks, which equates to the recommended avelumab dose.

### 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 an antibody, avelumab is not expected to bind to plasma proteins in a specific manner.

### Elimination

Based on a population pharmacokinetic analysis from 1629 patients, the value of total systemic clearance (CL) is 0.59 L/day.

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 ( $t_{1/2}$ ) at the recommended dose is 6.1 days based on the population PK analysis.

### Linearity/non-linearity

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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.

#### 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, n = 623), moderate (GFR 30 to 59 mL/min, n = 320) or severe (GFR 15 to 29 mL/min, n = 4) renal impairment and patients with normal (GFR greater than or equal to 90 mL/min, n = 671) renal function.

#### Hepatic impairment

No clinically important differences in the clearance of avelumab were found between patients with mild hepatic impairment (bilirubin less than or equal to the ULN and AST greater than ULN or bilirubin between 1 and 1.5 times ULN, n = 217), or moderate hepatic impairment (bilirubin between 1.5 and 3 times ULN, n = 4), and normal hepatic function (bilirubin and AST less than or equal to ULN, n = 1388) in a population PK analysis.

Avelumab has not been studied in patients with severe hepatic impairment (bilirubin greater than 3 times ULN).

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

No studies have been conducted to assess the genotoxic potential of avelumab. As a large protein molecule, avelumab is not expected to interact directly with DNA or other chromosomal material.

#### **Carcinogenicity**

No studies have been conducted to assess the carcinogenic potential of avelumab.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

mannitol

glacial acetic acid

polysorbate 20

sodium hydroxide

water for injections

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## 6.2 INCOMPATIBILITIES

This medicine must not be mixed with other medicines except those mentioned in section 4.2.

## 6.3 SHELF LIFE

### Unopened vial

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging. After opening

BAVENCIO should be diluted and infused immediately.

### After preparation of infusion

BAVENCIO does not contain a preservative. The diluted solution should be infused immediately, unless dilution has taken place in controlled and validated aseptic conditions.

If BAVENCIO is not used immediately, store the diluted solution of BAVENCIO, either:

- At room temperature and room light for up to 8 hours. This includes room temperature storage of the infusion in the infusion bag and the duration of infusion.
- At 2°C to 8°C (Refrigerate. Do not freeze) for up to 24 hours at the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze or shake the diluted solution.

## 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.

Product is for single use in one patient only. Discard any residue.

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

## 6.5 NATURE AND CONTENTS OF CONTAINER

10 mL of concentrated solution for intravenous infusion in a 16 mL vial (Type I glass) with a halobutyl rubber stopper and an aluminium seal fitted with a removable plastic cap.

Pack size of 1 vial.

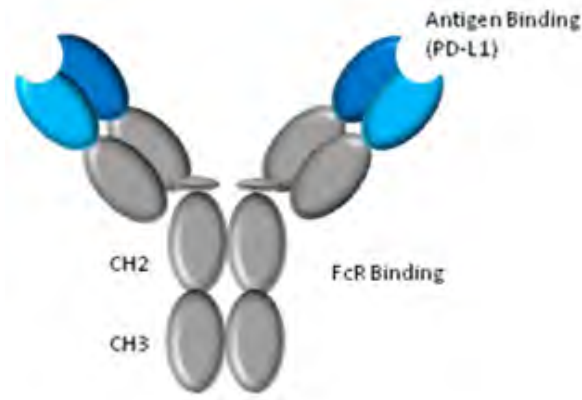
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

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## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure



### CAS number

1537032-82-8

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

## 8 SPONSOR

Merck Serono Australia Pty Ltd  
Unit 3- 4, 25 Frenchs Forest Road East  
French Forest NSW 2086  
Merck Medical Information: 1800 633 463

ALSO DISTRIBUTED BY:

Pfizer Australia Pty Ltd  
38 – 42 Wharf Road  
West Ryde  
NSW 2114

## 9 DATE OF FIRST APPROVAL

3 January 2018