ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Bavencio 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 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 as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).

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 Bavencio is 10 mg/kg body weight administered intravenously over 60 minutes every 2 weeks.

Administration of Bavencio should continue according to the recommended schedule 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.

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.

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 Bavencio

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
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

Treatment-related adverse reaction	Severity*	Treatment modification
Other immune-related adverse reactions (including myocarditis 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 • Persistent Grade 2 or Grade 3 immune-mediate adverse reactions lasting 12 weeks or longer	Permanently discontinue

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

<u>*Special populations*</u>

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

Paediatric population
The safety and efficacy of Bavencio 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.

<u>Method of administration</u>
Bavencio is for intravenous infusion only. It must not be administered as an intravenous push or bolus injection.

Bavencio 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

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 4 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 4 infusions and all were of Grade 1 or Grade 2.

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 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 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 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: 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 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).

Patients excluded from clinical studies
Patients with the following conditions were excluded from clinical trials: active central nervous system (CNS) metastasis; active or a history of 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.

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 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

Summary of the safety profile
Avelumab is most frequently 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" below).

The safety of avelumab has been evaluated in 1,738 patients with solid tumours including metastatic MCC receiving 10 mg/kg every 2 weeks of avelumab in clinical studies. In this 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 decreased (16.6%), and vomiting (16.2%).

The most common Grade ≥ 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 reaction (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions reported for 88 patients with metastatic MCC treated with avelumab 10 mg/kg 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 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 in clinical study EMR100070-003 and adverse reactions from a phase I study (EMR100070-001) in other solid tumours

Frequency	Adverse drug reactions
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*

Frequency	Adverse drug reactions
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*
Nervous system disorders	
Common	Headache, dizziness, neuropathy peripheral
Uncommon	Guillain-Barré 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*
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, constipation, vomiting, abdominal pain
Common	Dry mouth
Uncommon	Colitis*, autoimmune colitis*, enterocolitis*, ileus
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis*, acute hepatic failure*, hepatic failure*, hepatitis*
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
Musculoskeletal and connective tissue disorders	
Very common	Back pain, arthralgia
Common	Myalgia
Uncommon	Myositis*
Renal and urinary disorders	
Uncommon	Tubulo-interstitial 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*
Injury, poisoning and procedural complications	
Very common	Infusion related reaction

* Immune-related adverse reaction based on medical review

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

Description of selected adverse reactions
Data for the following immune-related adverse reactions are based on 1,650 patients in the phase I study EMR100070-001 in other solid tumours and 88 patients in study EMR100070-003 who received avelumab (see section 5.1).

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

Immune-related pneumonitis
Across clinical studies, 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
Across clinical studies, 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
Across clinical studies, 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 endocrinopathies
Thyroid disorders
Across clinical studies, 6% (98/1,738) 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%) 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
Across clinical studies, 0.5% (8/1,738) of patients developed immune-related adrenal insufficiency. Of these patients, there was 1 (0.1%) patient with Grade 3.

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
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, efficacy and safety is uncertain, while the impact of neutralizing antibodies (nAb) is unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 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 $CD8^+$ 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

Merkel cell carcinoma (study EMR100070-003)

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 or a history of central nervous system (CNS) metastasis; active or a history of 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.

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, an updated efficacy analysis was conducted in all 88 patients after a minimum follow-up of 24 months. Patients received a median of 7 doses of avelumab (range: 1 dose to 72 doses), and the median duration of treatment was 17 weeks (range: 2 weeks to 158 weeks).

Of the 88 patients, 65 (74%) were male, the median age was 73 years (range 33 years to 88 years), 81 (92%) patients were Caucasian, and 49 (56%) patients and 39 (44%) patients with an Eastern Cooperative Oncology Group (ECOG) performance status 0 and 1, respectively.

Overall, 52 (59%) patients were reported to have had 1 prior anti-cancer therapy for MCC, 26 (30%) with 2 prior therapies, and 10 (11%) with 3 or more prior therapies. Forty-seven (53%) of the patients had visceral metastases.

Table 3 summarises efficacy endpoints in patients receiving avelumab at the recommended dose for study EMR100070-003, Part A, updated with a minimum follow-up of 24 months.

Table 3: Response to avelumab 10 mg/kg every 2 weeks in patients with metastatic MCC in study EMR100070-003 (Part A)*

Efficacy endpoints (Part A) (per RECIST v1.1, IERC)	Results (N=88)
Objective response rate (ORR)	
Response rate, CR+PR** n (%)	29 (33.0%)
(95% CI)	(23.3, 43.8)
Confirmed best overall response (BOR)	
Complete response (CR)** n (%)	10 (11.4%)
Partial response (PR)** n (%)	19 (21.6%)
Duration of response (DOR)[a]	
Median, months	NR
(95% CI)	(18, not estimable)
Minimum, maximum (months)	2.8, 31.8+
≥ 6 months by K-M, (95% CI)	93% (75, 98)
≥ 12 months by K-M, (95% CI)	71% (51, 85)
≥ 24 months by K-M, (95% CI)	67% (46, 81)
Progression-free survival (PFS)	
Median PFS, months	2.7
(95% CI)	(1.4, 6.9)
6-month PFS rate by K-M, (95% CI)	40% (29, 50)
12-month PFS rate by K-M, (95% CI)	29% (19, 39)
24-month PFS rate by K-M, (95% CI)	26% (16, 36)

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

* Efficacy data updated with a minimum follow-up of 24 months (cut-off date 26 September 2017)

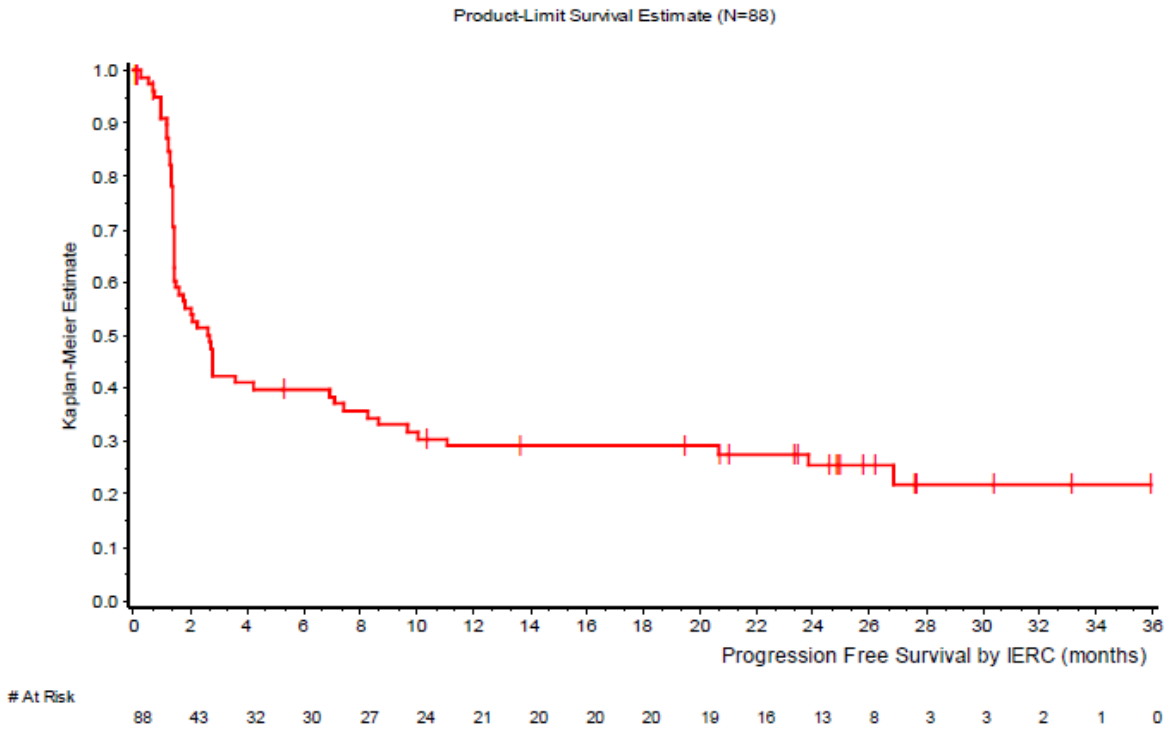
** CR or PR was confirmed at a subsequent tumour assessment

[a] Based on number of patients with confirmed response (CR or PR)

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 (76%) patients with response were reported to have responded within 7 weeks after the first dose of avelumab.

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

Figure 1: Updated Kaplan-Meier estimates of progression-free survival (PFS) per RECIST v1.1, IERC (Part A, minimum follow-up of 24 months)



Tumour samples were evaluated for PD-L1 tumour cell expression, and for Merkel cell polyomavirus (MCV) using an investigational immunohistochemistry (IHC) assay. Table 4 summarises the PD-L1 expression and MCV status of patients with metastatic MCC in study EMR100070-003 (Part A).

Table 4: Objective response rates by PD-L1 expression and MCV tumour status in patients with metastatic MCC in study EMR100070-003 (Part A)

	Avelumab ORR (95% CI)
PD-L1 expression at cut-off of 1%	N=74[a]
Positive (n=58)	36.2% (24.0, 49.9)
Negative (n=16)	18.8% (4.0, 45.6)
PD-L1 expression at cut-off of 5%	N=74[a]
Positive (n=19)	57.9% (33.5, 79.7)
Negative (n=55)	23.6% (13.2, 37.0)
IHC-MCV tumour status	N=77[b]
Positive (n=46)	28.3% (16.0, 43.5)
Negative (n=31)	35.5% (19.2, 54.6)

IHC: Immunohistochemistry; MCV: Merkel cell polyomavirus; ORR: objective response rate
[a] Based on data from patients evaluable for PD-L1
[b] Based on data from patients evaluable for MCV by immunohistochemistry (IHC)

The clinical utility of PD-L1 as a predictive biomarker in MCC has not been established.

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.

The prespecified interim analysis for Part B included 39 patients who received at least one dose of avelumab and 29 patients with a minimum 13 weeks of follow-up at the time of the data cut-off (cut-off date 24 March 2017).

Of the 39 patients, 30 (77%) were male, the median age was 75 years (range: 47 to 88 years), 33 (85%) were Caucasian, and 31 (79%) and 8 (21%) had an ECOG performance status of 0 and 1 respectively. The efficacy endpoints were based on 29 patients with 13 weeks of follow-up. The objective response rate (ORR) was 62.1% (95% CI: 42.3, 79.3) with 4 (14%) of patients reported to have a complete response and 14 (48%) to have a partial response. The median duration of response was not estimable (95% CI: 4 months, not estimable) with a minimum of 1.2 months to a maximum of 8.3 months duration. Analysis of progression-free survival (PFS) was based on 39 patients who received at least one dose of avelumab, with median PFS of 9.1 months (95% CI: 1.9, not estimable) and estimated 3-month PFS rate by Kaplan-Meier of 67% (95% CI: 48, 80).

A subsequent interim analysis for Part B was conducted with 74 patients who received at least one dose of avelumab and 39 patients with at least 6 months of follow-up at the time of the data cut-off (cut-off date 26 September 2017). Of the 74 patients, 51 (69%) were male, the median age was 74 years (range: 47 to 89 years), 49 (66%) were Caucasian, and 51 (69%) and 23 (31%) had an ECOG performance status of 0 and 1, respectively.

Table 5 summarises the subsequent interim analysis of efficacy endpoints including an estimate of the 6-month rates by Kaplan-Meier for DOR and PFS, in patients receiving avelumab at the recommended dose for study EMR100070-003, Part B.

Table 5: Subsequent interim analysis of response to avelumab 10 mg/kg every 2 weeks in patients with metastatic MCC in study EMR100070-003 (Part B)*

Efficacy endpoints (Part B) (per RECIST v1.1, IERC)	**Results**
Objective response rate (ORR)	(N=39)
Response rate, CR+PR** n (%)	20 (51.3%)
(95% CI)	(34.8,67.6)
Confirmed best overall response (BOR)	(N=39)
Complete response (CR)** n (%)	7 (17.9%)
Partial response (PR)** n (%)	13 (33.3%)
Duration of response (DOR)[a]	(N=39)
Median, months	11.3
(95% CI)	(5.6, not estimable)
Minimum, maximum (months)	1.2, 13.8
≥ 3 months by K-M, (95% CI)	84% (59, 95)
≥ 6 months by K-M, (95% CI)	73% (46, 88)
Progression-free survival (PFS)	(N=74)
Median PFS, months	4.2
(95% CI)	(2.9, 12.7)
3-month PFS rate by K-M, (95% CI)	61% (48, 73)
6-month PFS rate by K-M, (95% CI)	46% (32, 59)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan-Meier

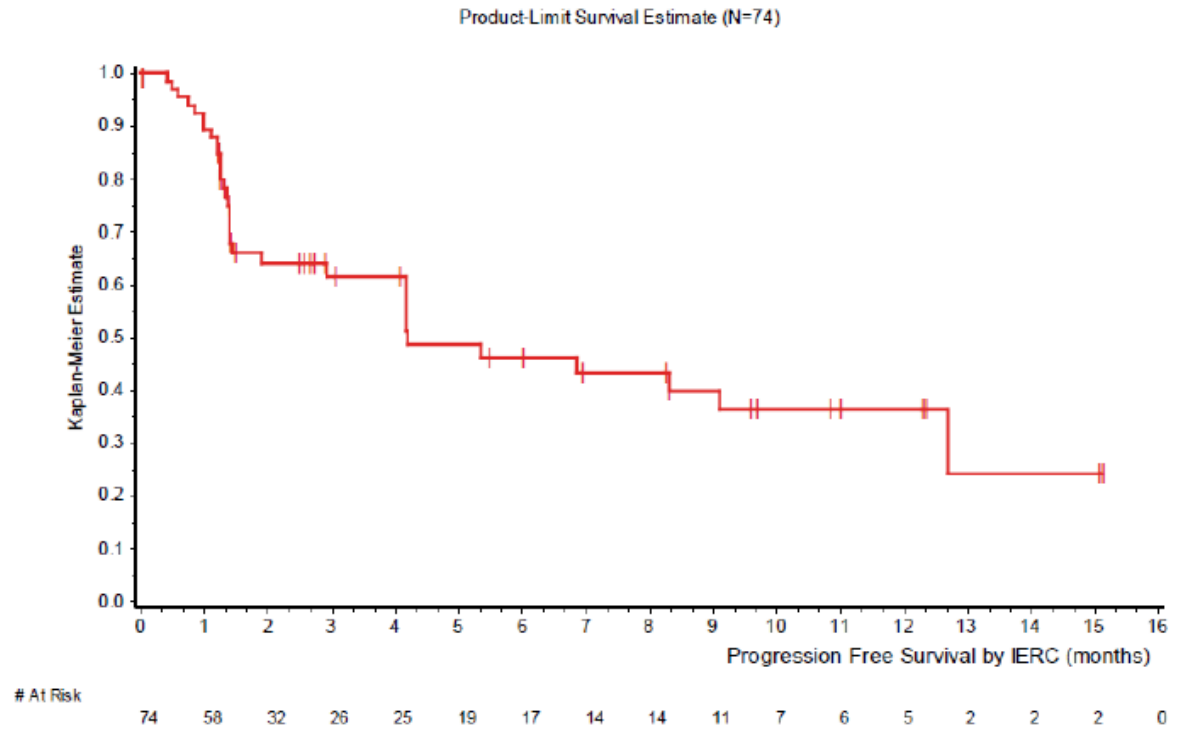
* Efficacy data (cut-off date 26 September 2017) included 39 patients with a minimum follow-up of 6 months for ORR, BOR and DOR analyses, and 74 patients included in the PFS analysis.

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

[a] Based on number of patients with confirmed response (CR or PR)

Figure 2 presents the Kaplan-Meier curve for PFS from the subsequent interim analysis with 74 patients enrolled into Part B who received at least one dose of avelumab prior to the data cut-off.

Figure 2: Updated Kaplan-Meier estimates of progression-free survival (PFS) per RECIST v1.1, IERC (Part B, N=74)*



* Updated progression-free survival data include 74 patients enrolled into Part B who received at least one dose of avelumab.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Bavencio in all subsets of the paediatric population for the treatment of Merkel cell carcinoma (see section 4.2 for information on paediatric use).

Conditional approval
This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

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 supplemental analysis, avelumab CL was found to decrease over time: the largest mean maximal reduction (% coefficient of variation [CV%]) from baseline value with different tumour types was approximately 32.1% (CV 36.2%).

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 ($t_{½}$) 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 for1 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

Bavencio 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. Bavencio 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 Bavencio 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 Bavencio, 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. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1214/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Merck Serono SA
Succursale de Corsier-sur-Vevey
Chemin du Fenil - Zone Industrielle B,
1804 Corsier-sur-Vevey
Switzerland

Name and address of the manufacturer(s) responsible for batch release

Merck Serono S.p.A.
Via Delle Magnolie 15 (loc. frazione Zona Industriale)
70026 - Modugno (BA)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Bavencio in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of certain important identified risks of avelumab, including immune-related pneumonitis, hepatitis, colitis, thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, nephritis and renal dysfunction, myocarditis, myositis, hypopituitarism, uveitis, Guillain-Barre syndrome and infusion related reactions, and how to manage them.

The MAH shall ensure that in each Member State where Bavencio is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Bavencio have access to/are provided with the following educational package:
- Healthcare Professional / Frequently Asked Question Brochure
- Patient Information Brochure
- Patient Alert Card

The physician educational material should contain:
- The Summary of Product Characteristics
- Healthcare professionals brochure

The healthcare professional / Frequently Asked Question brochure shall contain the following key elements:
- Relevant information (e.g. seriousness, severity, frequency, time to onset, reversibility as applicable) of the following safety concerns associated with the use of Bavencio:
    - Immune-Related Pneumonitis
    - Immune-Related Hepatitis
    - Immune-Related Colitis
    - Immune-Related Endocrinopathies (diabetes mellitus, thyroid disorders, adrenal insufficiency)
    - Immune-related nephritis and renal dysfunction
    - Other immune-related adverse reactions including myocarditis, myositis, hypopituitarism, uveitis and Guillain-Barre Syndrome
    - Infusion-Related Reactions
- Description of the signs and symptoms of immune-related adverse reactions.
- Details on how to minimise the safety concerns through appropriate monitoring and management.
- Reminder to distribute the patient brochure with the patient alert card to all patients receiving treatment with Bavencio and to advise them to carry the patient alert card at all times and show it to any healthcare professional who may treat them.
- Reminder to educate patients/caregivers about the symptoms of immune-related adverse reactions and of the need to report them immediately to the physician.

The patient educational material should contain
- The package leaflet
- Patient Information brochure
- Patient Alert Card

The Patient Information brochure shall contain the following key messages:
- Brief introduction to the tool and its purpose
- Brief introduction to Bavencio treatment
- Recommendation to consult the package leaflet

- Information that avelumab can cause serious side effects during or after treatment, that need to be treated right away and warning message on the importance of being aware of signs and symptoms while receiving avelumab treatment
- Reminder of the importance to consult their doctor before any change of treatment or in case of side effect

The Patient Alert Card shall contain the following key messages:

- Brief introduction to avelumab (indication and purpose of this tool)
- Description of the main signs and symptoms of the following safety concerns and reminder of the importance of notifying their treating physician immediately if symptoms occur, persist or worsen:
    - Immune-Related Pneumonitis
    - Immune-Related Hepatitis
    - Immune-Related Colitis
    - Immune-Related Endocrinopathies (diabetes mellitus, thyroid disorders, adrenal insufficiency)
    - Immune-related nephritis and renal dysfunction
    - Other immune-related adverse reactions including myocarditis, myositis, hypopituitarism, uveitis and Guillain-Barre Syndrome
    - Infusion-Related Reactions
- Warning message for patients on the importance of consulting their doctor immediately in case they develop any of the listed signs and symptoms and on the important not attempting to treat themselves.
- Reminder to carry the Patient Alert Card at all times and to show it to all healthcare professionals that may treat them.
- The card should also prompt to enter contact details of the physician and include a warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Bavencio.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy for chemotherapy-naïve treated patients, the MAH should submit the final results of study EMR 100070-003 - Part B.	30th January 2020

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bavencio 20 mg/mL concentrate for solution for infusion
avelumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: Mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

200 mg/10 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after dilution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1214/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bavencio 20 mg/mL sterile concentrate
avelumab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/10 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Bavencio 20 mg/mL concentrate for solution for infusion
avelumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bavencio is and what it is used for

Bavencio contains the active substance avelumab, a monoclonal antibody (a type of protein) that attaches to a specific target in the body called PD-L1.

Bavencio is used to treat adults with Merkel cell carcinoma (MCC)**, a rare type of skin cancer**, when it is metastatic (has spread to other parts of the body).

PD-L1 is found on the surface of MCC cells, and helps protect tumour cells from the immune system (the body's natural defences). Bavencio binds to PD-L1, and blocks this protective effect, allowing the immune system to attack the tumour cells.

2. What you need to know before you use Bavencio

Do not use Bavencio
if you are allergic to avelumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Blood tests and weight checks:
Your doctor will check your general health before and during treatment with Bavencio.
You will have blood tests during your treatment and your doctor will monitor your weight before and during treatment.

Talk to your doctor before receiving Bavencio:
It may cause side effects (see section 4). Please note that in some cases symptoms may be delayed, and may develop after your last dose. If you suffer from any of these you should **seek urgent medical attention:**
- infusion-related reactions;
- problems due to inflammation of your lungs (pneumonitis);

- inflammation of your liver (hepatitis);
- inflammation of your intestines (colitis), diarrhoea (watery, loose or soft stools) or more bowel movements than usual;
- problems with your hormone producing glands (the thyroid, adrenal and pituitary glands) that may affect how these glands work;
- Type 1 diabetes, including acid in the blood produced from diabetes (diabetic ketoacidosis);
- problems with your kidneys;
- inflammation of your muscles (myositis);
- inflammation of your heart (myocarditis).

If you experience any of these symptoms when taking Bavencio **do not** try to treat them on your own with other medicines. Your doctor may
- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of Bavencio,
- or stop your treatment with Bavencio altogether.

Check with your doctor or nurse before you receive Bavencio if:
- you have an autoimmune disease (a condition where the body attacks its own cells);
- you have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS);
- you have ever had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV);
- you receive medicines to suppress your immune system;
- you have had an organ transplant.

Children and adolescents
Bavencio has not been studied in children and adolescents below 18 years of age.

Other medicines and Bavencio
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy
Bavencio can cause harm to your unborn baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

You must not use Bavencio if you are pregnant unless your doctor specifically recommends it.

If you are a woman who could become pregnant, you must use effective contraceptives while you are being treated with Bavencio and for at least 1 month after your last dose.

Breast-feeding
If you are breast-feeding, tell your doctor.

Do not breast-feed while receiving Bavencio and for at least 1 month after your last dose.

It is unknown if Bavencio passes into your breast milk. A risk to the breast-fed child cannot be excluded.

Driving and using machines
Do not drive or use machines after you have received Bavencio if you are not feeling well enough. Tiredness is a very common side effect of Bavencio and can affect your ability to drive or to use machines.

Bavencio has a low sodium content
Bavencio contains less than 1 mmol sodium (23 mg) in each dose and therefore is essentially sodium-free.

3. How to use Bavencio

You will receive Bavencio in a hospital or clinic, under the supervision of an experienced doctor.

How much Bavencio you will receive
The amount of Bavencio you will receive will be based on your body weight. The recommended dose is 10 mg of avelumab per kilogram of your body weight.

Depending on your dose, the appropriate amount of Bavencio will be added to an infusion bag containing a sodium chloride solution before use. More than one vial of Bavencio may be necessary to obtain the required dose.

How you will receive Bavencio
You will receive Bavencio as an infusion (a drip) into a vein (intravenously) over a period of 1 hour, every 2 weeks. Your doctor will decide how many treatments you need.

Before you receive Bavencio
For at least the first 4 treatments, you will receive paracetamol and an antihistamine before being given Bavencio, to help to prevent possible side effects related to the infusion. Depending on how your body responds to treatment, your doctor may decide to continue giving you these medicines before all of your Bavencio treatments.

If you miss a dose of Bavencio
It is very important for you to keep all your appointments to receive Bavencio. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop receiving Bavencio
Do not stop treatment with Bavencio unless you have discussed this with your doctor. Stopping your treatment may stop the effect of the medicine.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some side effects may happen weeks or months after your last dose.

Bavencio acts on your immune system and may cause inflammation in parts of your body (see section 2). Inflammation may cause serious damage to your body and some inflammatory conditions may lead to death and need treatment or withdrawal of Bavencio.

Seek urgent medical attention if you experience inflammation in any part of your body or if you have any of the following signs or symptoms, or if they get worse.

- Signs of infusion-related reactions such as **shortness of breath or wheezing**, **chills or shaking**, **bumpy rash or skin wheals**, **flushing**, **low blood pressure (**dizziness, fatigue, nausea) **fever**, **back pain**, and **abdominal pain**. This is very common.

- Signs of inflammation of the lungs (pneumonitis) may be **breathing difficulties** or **cough**. This is common.

- Signs of inflammation of the liver (hepatitis) may include **yellowing of your skin** (jaundice) or the **whites of your eyes**, **severe nausea or vomiting**, **pain on the right side of your stomach area** (abdomen), **drowsiness**, **dark urine** (tea coloured), **bleeding or bruising more easily than normal**, **feeling less hungry than usual**, **tiredness** or **abnormal liver function tests**. This is uncommon.

- Signs of inflammation of the intestines (colitis) may include **diarrhoea** (loose stools) or **more bowel movements than usual**, **blood in your stools or dark, tarry, sticky stools**, or **severe stomach (abdomen) pain** or **tenderness**. This is uncommon.

- Signs of inflammation of the hormone producing glands (the thyroid, adrenal and pituitary glands) may include **extreme tiredness**, **rapid heart beat**, **increased sweating**, **changes in mood or behaviour**, such as irritability or forgetfulness, **feeling cold**, **very low blood pressure (**fainting, dizziness, fatigue, nausea), **weight change** or **headache**. This is uncommon.

- Signs of type 1 diabetes may include **feeling more hungry** or **thirsty than usual**, **needing to urinate more often**, **weight loss**, and **feeling tired**. This is uncommon.

- Signs of inflammation of the kidney may include **abnormal kidney function tests**, **urinating less than usual**, **blood in your urine**, or **swelling in your ankles**. This is uncommon.

- Signs of inflammation of the muscles (myositis) may include **muscle pain** or **weakness**. This is uncommon.

- Signs of inflammation of the heart (myocarditis) may include **trouble breathing**, **dizziness** or **fainting**, **fever**, **chest pain** and **chest tightness** or **flu like symptoms**. This is rare.

Do not try to treat yourself with other medicines.

Other side effects
The following side effects have been reported in clinical trials with avelumab:

Very common (may affect more than 1 in 10 people)
- Decrease in the number of red blood cells
- Nausea, loose stools, constipation, vomiting
- Belly pain, back pain, joint pain
- Feeling tired or weak
- Fever
- Swelling in the arms, feet or legs
- Weight loss, feeling less hungry

Some side effects may not have symptoms and may only be discovered through blood tests.

Common (may affect up to 1 in 10 people)
- Decrease in the number of white blood cells
- Underactive thyroid gland
- Increases or decreases in blood pressure
- Feeling cold
- Dryness in the mouth
- Skin rash, itching

Uncommon (may affect up to 1 in 100 people)
- Decrease in the number of platelets in the blood
- Overactive thyroid gland
- Redness in the skin
- Abdominal pain
- Red, itchy, scaly patches on the skin
- Sepsis
- Decreased secretion of hormones produced by adrenal glands
- Underactive pituitary gland
- Inflammation of the eye
- Increased liver enzymes in the blood
- Type 1 diabetes
- Guillain-Barré Syndrome (an immune system disorder that causes nerve inflammation and can result in pain, numbness, muscle weakness and difficulty walking)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bavencio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

Do not store any unused portion of the concentrate or of the diluted infusion solution for reuse.

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

6. Contents of the pack and other information

What Bavencio contains

The active substance is avelumab.

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

The other ingredients are mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, water for injections (see section 2 “Bavencio has a low sodium content”).

What Bavencio looks like and contents of the pack
Bavencio is a clear, colourless to slightly yellow concentrate for solution for infusion (sterile concentrate).

The pack size is 1 glass vial per carton.

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Gustav Mahlerplein 102
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The Netherlands

Manufacturer
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Via Delle Magnolie 15 (loc. frazione Zona Industriale)
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Handling instructions

Preparation and administration
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. Bavencio 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 Bavencio should be withdrawn from the vial(s) and be 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 infusion using a sterile, non-pyrogenic, low-protein binding 0.2 micrometre in-line or add-on filter.

After administration of Bavencio, 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.

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