Summary of the Risk Management Plan (RMP) V. 6.0, January 2021 for

BAVENCIO®

Avelumabum 200 mg/10 ml

Concentrate for solution for infusion

Marketing Authorization Number 66380

Marketing Authorisation Holder: Merck (Schweiz) AG, Zug

Disclaimer:
The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of **Bavencio** is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of **Bavencio** in Switzerland is the "Arzneimittelinformation/Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.
Merck (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of **Bavencio**.

Summary of the Risk Management Plan

Summary of the Risk Management Plan for Bavencio (avelumab)

This is a summary of the risk management plan (RMP) for Bavencio. The RMP details important risks of Bavencio, how these risks can be minimised, and how more information will be obtained about Bavencio's risks and uncertainties (missing information).

Bavencio's Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Bavencio should be used.

This summary of the RMP for Bavencio should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Bavencio's RMP.

I. The Medicine and What it is used for

Bavencio is authorised as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma and as first-line maintenance treatment for locally advanced or metastatic urothelial carcinoma. In addition, Bavencio in combination with axitinib is approved for the first-line treatment of adult patients with advanced renal cell carcinoma (see Summay of Product Characteristics for the full indication). It contains avelumab as the active substance and it is given as an intravenous infusion.

Further information about the evaluation of Bavencio's benefits can be found in Bavencio's European public assessment report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004338/human_med_002157.jsp&mid=WC0b01ac058001d124

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Bavencio, together with measures to minimise such risks and the proposed studies for learning more about Bavencio's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Bavencio, these measures are supplemented with *additional risk minimization* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR (Periodic Safety Update Report) assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

If important information that may affect the safe use of Bavencio is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Bavencio are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bavencio. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Immune-related pneumonitis • Immune-related hepatitis • Immune-related colitis • Immune-related pancreatitis • Immune-related myocarditis • Immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders) • Other immune-related events (myositis, Guillain-Barré syndrome, uveitis, myasthenia gravis/myasthenic syndrome) • Immune-related nephritis and renal dysfunction • Severe infusion-related reactions (grade ≥ 3)
Important potential risks	• Other immune-related events (encephalitis) • Severe cutaneous reactions • Immunogenicity • Embryofetal toxicity
Missing information	• Safety in patients with autoimmune disease • Safety in patients with HIV, Hepatitis B or C infections • Safety in patients with organ transplants • Long-term treatment • Safety and efficacy in immune compromised patients

II.B Summary of Important Risks

Important identified risk: Immune-related pneumonitis	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set

Important identified risk: Immune-related pneumonitis	
	The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related pneumonitis was observed in patients treated with avelumab in these clinical trials. <u>Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment</u> The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related pneumonitis was observed in patients treated with avelumab in this clinical trial. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was evaluated in the clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related pneumonitis was observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related pneumonitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-related pneumonitis.
Risk minimization measures	Routine risk minimization measures *Guidance for withholding or discontinuing avelumab based on the severity of pneumonitis in SmPC section 4.2* *Warning to monitor for immune-related pneumonitis and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of immune-related pneumonitis observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their lungs in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related hepatitis	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related hepatitis was observed in patients treated with avelumab in these clinical trials. <u>Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment</u> The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related hepatitis was observed in patients treated with avelumab in this clinical trial. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related hepatitis was observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related hepatitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-related hepatitis.
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of hepatitis in SmPC section 4.2* *Warning to monitor for immune-related hepatitis and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of immune-related hepatitis observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their liver in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related colitis	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related colitis was observed in patients treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related colitis was observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related colitis was observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related colitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-related colitis
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of colitis in SmPC section 4.2* *Warning to monitor for immune-related colitis and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of Immune-related colitis observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their intestines in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related pancreatitis	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related pancreatitis was not observed in patients treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related pancreatitis was observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related pancreatitis was observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related pancreatitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-related pancreatitis.
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab due to immune-related pancreatitis in SmPC section 4.2* *Warning to monitor for immune-related pancreatitis and treatment advice in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their pancreas in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related myocarditis	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related myocarditis was not observed in patients treated with avelumab in these clinical trials. A review of the medical literature revealed cases of myocarditis in association with checkpoint inhibitors including PD-L1 inhibitors suggesting a class effect of myocarditis. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related myocarditis was not observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related myocarditis was observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related myocarditis has been performed. There are no known risk factors for patients treated with avelumab developing immune-related myocarditis.
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab due to immune-related myocarditis in SmPC section 4.2* *Warning to monitor for immune-related myocarditis and treatment advice in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have inflammation of their heart in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related endocrinopathies (thyroid disorders)	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related thyroid disorders were observed in patients treated with avelumab in these clinical trials. <u>Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment</u> The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related thyroid disorders were observed in patients treated with avelumab in this clinical trial. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related thyroid disorders were observed in patients treated with avelumab in these clinical trials
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related endocrinopathies, including thyroid disorders, has been performed. There are no known risk factors for patients treated with avelumab developing immune-related endocrinopathies, including thyroid disorders.
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding avelumab based on the severity of endocrinopathies in SmPC section 4.2* *Warning to monitor for changes in thyroid function and signs and symptoms of thyroid disorders and treatment advice in SmPC section 4.4* *SmPC section 4.8* *Description of immune-related endocrinopathies including thyroid disorders observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems with their hormone producing glands in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related endocrinopathies (adrenal insufficiency)	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related adrenal insufficiency was observed in patients treated with avelumab in these clinical trials. <u>Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment</u> The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related adrenal insufficiency was observed in patients treated with avelumab in this clinical trial. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related adrenal insufficiency was observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related endocrinopathies, including adrenal insufficiency, has been performed. There are no known risk factors for patients treated with avelumab developing immune-related endocrinopathies, including adrenal insufficiency.
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding avelumab based on the severity of endocrinopathies in SmPC section 4.2* *Warning to monitor for signs and symptoms of adrenal insufficiency and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of Immune-related endocrinopathies including adrenal insufficiency observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems with their hormone producing glands in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related endocrinopathies (type 1 diabetes mellitus)	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related type 1 diabetes mellitus was observed in patients treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related Type 1 diabetes mellitus was observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related type 1 diabetes mellitus was observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related type 1 diabetes mellitus has been performed. There are no known risk factors for patients treated with avelumab developing immune-related type 1 diabetes mellitus
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding avelumab based on the severity of endocrinopathies in SmPC section 4.2* *Warning to monitor for hyperglycaemia or other signs and symptoms of diabetes and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of immune-related endocrinopathies including type 1 diabetes mellitus observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have type 1 diabetes mellitus including acid in the blood produced from diabetes in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related endocrinopathies (pituitary disorders)	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. An immune-related pituitary disorder was observed in a patient treated with avelumab in these clinical trials. <u>Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment</u> The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related pituitary disorders were not observed in patients treated with avelumab in this clinical trial. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). An AE consistent with an immune-related pituitary disorder was observed in a patient treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related endocrinopathies, including pituitary disorders, has been performed. There are no known risk factors for patients treated with avelumab developing immune-related pituitary disorders.
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to monitor for other immune-related adverse reactions (hypopituitarism) and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems with their hormone producing glands in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Other immune-related events (myositis)	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related myositis was observed in patients treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related myositis was observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related myositis was not observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related myositis has been performed. There are no known risk factors for patients treated with avelumab developing immune-related myositis.
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to monitor for other immune-related adverse reactions (myositis) and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have inflammation of their muscles in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Other immune-related events (Guillain-Barré syndrome)	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Guillain-Barré syndrome was observed in a patient treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Guillain-Barré syndrome was observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Guillain-Barré syndrome was not observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related Guillain-Barré syndrome has been performed. There are no known risk factors for patients treated with avelumab developing Guillain-Barré syndrome.
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to monitor for other immune-related adverse reactions (Guillain-Barré syndrome) and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have an autoimmune disease in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Other immune-related events (uveitis)	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related uveitis was observed in a patient treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related uveitis was observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related uveitis was not observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related uveitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-related uveitis
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to monitor for other immune-related adverse reactions (uveitis) and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have an autoimmune disease in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Other immune-related events (myasthenia gravis/myasthenic syndrome)	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Within the Pooled Safety Set, immune-related myasthenia gravis/myasthenic syndrome were not observed in patients treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related myasthenia gravis/myasthenic syndrome was not observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related myasthenia gravis /myasthenic syndrome was observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related myasthenia gravis /myasthenic syndrome has been performed. There are no known risk factors for patients treated with avelumab developing immune-related myasthenia gravis /myasthenic syndrome.
Risk minimization measures	Routine risk minimization measures: Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2 Warning to adequately evaluate other immune-related adverse reactions (myasthenia gravis/myasthenic syndrome) and treatment advice based on severity included in SmPC section 4.4. SmPC section 4.8 PL section 4. *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Immune-related nephritis and renal dysfunction	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related nephritis and renal dysfunction were observed in a patient treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related nephritis and renal dysfunction were observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related nephritis and renal dysfunction were observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related nephritis and renal dysfunction has been performed. There are no known risk factors for patients treated with avelumab developing immune-related nephritis and renal dysfunction
Risk minimization measures	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of nephritis and renal dysfunction in SmPC section 4.2* *Warning to monitor for immune-related nephritis and renal dysfunction and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of the case of immune-related nephritis observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems with their kidneys in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk: Severe infusion-related reactions (grade ≥ 3)	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Severe infusion-related reactions were observed in patients treated with avelumab in these clinical trials. <u>Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment</u> The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Severe infusion-related reactions (Grade ≥ 3) were observed in patients treated with avelumab in this clinical trial. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Severe infusion-related reactions (grade ≥ 3) were observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with IRRs has been performed. There are no known risk factors for patients treated with avelumab developing IRRs.
Risk minimization measures	Routine risk minimization measures: *Guidance to pre-medicate with an antihistamine and paracetamol prior to the first 4 infusions of avelumab in SmPC section 4.2* *Guidance for withholding or discontinuing avelumab based on the severity of infusion-related reactions in SmPC section 4.2* *Description of infusion-related reactions observed in clinical trials in SmPC section 4.4* *Warning to monitor for infusion-related reactions and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Information that anti-drug antibodies (ADA) positive patients may be at increased risk of infusion-related reactions in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have infusion-related reactions in PL section 2* *Information for the patient that they will receive paracetamol and an antihistamine before at least the first 4 treatments of avelumab in PL section 3* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important potential risk: Other immune-related events (encephalitis)	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. Immune-related encephalitis was not observed in patients treated with avelumab in these clinical trials. <u>Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment</u> The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Immune-related encephalitis was not observed in patients treated with avelumab in this clinical trial. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Immune-related encephalitis was not observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with immune-related encephalitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-related encephalitis.
Risk minimization measures	Routine risk minimization measures: *Warning to monitor for immune-related adverse reactions and treatment advice based on aetiology in SmPC section 4.4* *Information that avelumab works on the immune system and may cause inflammation which may be serious and life-threatening requiring avelumab withdrawal or treatment in PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: None

Important potential risk: Severe cutaneous reactions	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. A severe cutaneous reaction was observed in a patient treated with avelumab in these clinical trials. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Severe cutaneous reactions (immune-related rash) were observed in patients treated with avelumab in this clinical trial. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Severe immune-related cutaneous reactions were observed in patients treated with avelumab in these clinical trials.
Risk factors and risk groups	No analysis of specific risk factors associated with severe cutaneous reactions (immune-related rash) has been performed. There are no known risk factors for patients treated with avelumab developing severe cutaneous reactions.
Risk minimization measures	Routine risk minimization measures: *Warning to monitor for immune-related adverse reactions and treatment advice based on aetiology in SmPC section 4.4* *SmPC section 4.8* *Information that avelumab works on the immune system and may cause inflammation which may be serious and life-threatening requiring avelumab withdrawal or treatment in PL section 4* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

Important potential risk: Immunogenicity	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). Of the 1738 patients treated with avelumab in these studies, 1627 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 96 (5.9%) tested positive including 41 (2.5%) patients who tested positive for neutralizing antibodies (nAb). Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Of the 344 patients treated with avelumab in this study, 325 were evaluable for treatment-emergent ADA and 62 (19.1%) tested positive. Avelumab in Combination with Axitinib in RCC The safety of Avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Of the 480 patients treated with avelumab in combination with axitinib in these studies, 453 (94.4%) were evaluable for treatment-emergent ADA and 66 (14.6%) had a treatment-emergent ADA. Results for neutralizing antibody (nAb) are not yet available.
Risk factors and risk groups	None identified
Risk minimization measures	Routine risk minimization measures: *Information that treatment-emergent ADA were observed in clinical trials and that there may be an increased risk for infusion-related reactions in ADA positive patients but the impact of ADA on pharmacokinetics, efficacy and safety is uncertain and the impact of neutralizing antibodies (nAb) is unknown in SmPC section 4.8* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

Important potential risk: Embryofetal toxicity	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and in a large Phase I trial EMR10007-001 in patients with various solid tumors (1650 patients). A total of 1738 patients treated with avelumab were evaluated. There were no cases of avelumab exposure during pregnancy in these studies. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the fetus throughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that administration of avelumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). There were no cases of avelumab exposure during pregnancy in this clinical trial. Avelumab in Combination with Axitinib in RCC Embryofetal toxicity was not observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. There was 1 case of paternal exposure timing unspecified when the wife of a male patient in clinical trial B9991003 became pregnant while he was receiving avelumab in combination with axitinib. This event of exposure during pregnancy was not associated with an AE in the mother or fetus/child. A healthy baby was born at 36 weeks.
Risk factors and risk groups	Pregnant women
Risk minimization measures	Routine risk minimization measures: *Guidance for women of childbearing to avoid becoming pregnant and to use effective contraception during treatment and for at least 1 month after the last dose in SmPC section 4.6* *Guidance that avelumab is not recommended for use during pregnancy unless the woman requires treatment in SmPC section 4.6* *Information that there are no or limited data in pregnant women in SmPC section 4.6* *Information that blockade of PD-L1 signalling has been shown to disrupt tolerance to the fetus and result in increased fetal loss in murine models of pregnancy in SmPC section 5.3* *Guidance for the patient to seek advice before taking avelumab if they are pregnant, think they may be pregnant or are planning to have a baby in PL section 2* *Warning for the patient not to use avelumab if they are pregnant unless their doctor specifically recommends it in PL section 2* *Guidance for a woman to use effective contraceptives while they are being treated and for at least 1 month after their last dose in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

Missing information: Safety in patients with autoimmune disease	
Risk minimization measures	Routine risk minimization measures: *Information that patients with active or a history of autoimmune disease were excluded from clinical trials in SmPC section 4.4* *Information that patients with active or a history of autoimmune disease were excluded from Study EMR100070-003 in SmPC section 5.1* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: None

Missing information: Safety in patients with HIV, Hepatitis B or C infections	
Risk minimization measures	Routine risk minimization measures: *Information that patients with conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from clinical trials in SmPC section 4.4* *Information that patients with conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from Study EMR100070-003 in SmPC section 5.1* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS) in PL section 2* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have ever had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV) in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

Missing information: Safety in patients with organ transplants	
Risk minimization measures	Routine risk minimization measures: *Information that patients with an organ transplant were excluded from clinical trials in SmPC section 4.4* *Information that patients with an organ transplant were excluded from Study EMR100070-003 in SmPC section 5.1* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have had an organ transplant in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

Missing information: Long-term treatment	
Risk minimization measures	Routine risk minimization measures: *Legal status (prescription only medicine)* Additional risk minimization measures: None

Missing information: Safety and efficacy in immune compromised patients	
Risk minimization measures	Routine risk minimization measures: *Information that patients with active or a history of autoimmune disease, organ transplant, conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from clinical trials in SmPC section 4.4* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: Non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070_0031) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations.

II.C.2 Other Studies in the Post-Authorisation Development Plan

Study short name: Non-interventional cohort registry study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070_0031)

Rationale and study objectives:

The study will evaluate the efficacy and safety of avelumab in immune compromised patients in addition to other objectives, by using real-world data. Within this context, the study aims to:

1) describe patient characteristics (including co-morbidities and concomitant medications),

2) estimate background rates of potential safety events (including immune mediated events),

3) describe treatment patterns, and

4) characterize disease outcomes (effectiveness and safety).

Objectives related to effectiveness/ safety outcomes will also be assessed in the sub-group of immune compromised patients treated with avelumab, and an exploratory objective (due to expected limited sample size) will compare these outcomes in immune compromised patients with the ones in immune competent patients.