Summary of the Risk Management Plan (RMP)
for
BAVENCIO® (Avelumab)

Dosage strength:	200 mg/10 ml
Pharmaceutical Form:	Concentrate for solution for infusion
Marketing Authorisation Number:	66380
Marketing Authorisation Holder	Merck (Schweiz) AG, Chamerstrasse 174, 6300 Zug
Based on EU RMP:	Version 8.0, sign-off date: 01 August 2024

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.

Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for Avelumab (Bavencio)

This is a summary of the Risk Management Plan (RMP) for Bavencio. The RMP details important risks of Bavencio, how these risks can be minimized, 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 (PL) provide an essential information to HCPs 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 authorized as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC) and as first-line maintenance treatment for locally advanced or metastatic urothelial carcinoma (UC). In addition, Bavencio in combination with axitinib is approved for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC; see SmPC 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 EPAR, including in its plain-language summary, available on the EMA 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 Minimize or Further Characterize the Risks

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

Measures to minimize 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 HCPs;
- Important advice on the medicine's packaging;
- The authorized 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 minimize 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 analyzed, including 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 minimize 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.

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

HIV=human immunodeficiency virus

II.B Summary of Important Risks

Important identified risk: Immune-mediated adverse reactions (including immune-mediated pneumonitis, hepatitis, colitis, pancreatitis, myocarditis, endocrinopathies [thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders], nephritis and renal dysfunction and other immune-mediated adverse reactions [myositis, Guillain-Barré syndrome, uveitis, and myasthenia gravis/myasthenic syndrome])	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2082 patients treated with avelumab were evaluated. Immune-mediated adverse reactions of pneumonitis, hepatitis, colitis, pancreatitis, thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorder, nephritis and renal dysfunction and others (myositis, Guillain-Barré syndrome, uveitis) was observed in patients treated with avelumab in these clinical trials. Immune-mediated myocarditis and myasthenia gravis/myasthenic syndrome were not observed in patients treated with avelumab in these clinical trials. A review of the medical literature revealed cases of myocarditis and myasthenia gravis/myasthenic syndrome in association with checkpoint inhibitors including PD L-1 inhibitors suggesting a class effect of myocarditis. <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 advanced RCC (489 patients). Immune-mediated adverse reactions of pneumonitis, hepatitis, colitis, pancreatitis, thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorder, myocarditis, nephritis and renal dysfunction and myasthenia gravis/myasthenic syndrome was observed in patients treated with avelumab in these clinical trials. Immune-mediated myositis, Guillain-Barré syndrome and uveitis were 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-mediated adverse reactions (including pneumonitis, hepatitis, colitis, pancreatitis, myocarditis, endocrinopathies [thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders], nephritis and renal dysfunction and other immune-mediated adverse reactions [myositis, Guillain-Barré syndrome, uveitis, myasthenia gravis/myasthenic syndrome]) has been performed. In patients with pre-existing autoimmune disease, data from observational studies suggest that the risk of immune-related adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.
Risk minimization measures	Routine risk minimization measures

Important identified risk: Immune-mediated adverse reactions (including immune-mediated pneumonitis, hepatitis, colitis, pancreatitis, myocarditis, endocrinopathies [thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders], nephritis and renal dysfunction and other immune-mediated adverse reactions [myositis, Guillain-Barré syndrome, uveitis, and myasthenia gravis/myasthenic syndrome])	
	Guidance for withholding or discontinuing avelumab based on the severity of immune-mediated adverse reactions (including pneumonitis, hepatitis, colitis, pancreatitis, myocarditis, endocrinopathies [thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders], nephritis and renal dysfunction and other immune-mediated adverse reactions [myositis, Guillain-Barré syndrome, uveitis, myasthenia gravis/myasthenic syndrome]) in SmPC section 4.2. *Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advise based on severity included in SmPC section 4.4.* *Warning about an increased risk of immune-mediated adverse reactions in patients with pre-existing autoimmune disease as compared with the risk in patients without pre-existing AID included in SmPC section 4.4. Avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population.* *SmPC section 4.8* *Description of immune-mediated adverse reactions of pneumonitis, hepatitis, colitis, pancreatitis, myocarditis, endocrinopathies (including thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus) and immune-mediated nephritis and renal dysfunction 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, liver, intestines, pancreas, heart, muscles or kidneys, problems with their hormone producing glands, or if they have type 1 diabetes mellitus including acid in the blood produced from diabetes in PL section 2* *PL section 4* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease,* which may increase the risk of immune-mediated adverse reactions, *in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

AID=autoimmune disease, aRCC=advanced renal cell carcinoma, mMCC=metastatic merkel cell carcinoma, PD L-1=programmed death ligand 1, PL=package leaflet, SmPC=summary of product characteristics, UC=urothelial carcinoma

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 (Part A), B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients) and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. Severe infusion-related reactions were observed in patients treated with avelumab in these clinical trials. <u>Avelumab in Combination with Axitinib in RCC</u>

Important identified risk: Severe infusion-related reactions (Grade ≥ 3)	
	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 infusion-related reactions has been performed. There are no known risk factors for patients treated with avelumab developing infusion-related reactions.
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 antibody (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*

MCC=metastatic merkel cell carcinoma, PL=package leaflet, PD-L1=programmed death ligand 1, RCC= renal cell carcinoma, SmPC=summary of product characteristics

Important potential risk: Other immune-mediated events (encephalitis)	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. Immune-mediated encephalitis was not observed in patients treated with avelumab in these clinical trials. <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 advanced RCC (489 patients). Immune-mediated 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-mediated encephalitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-mediated encephalitis.
Risk minimization measures	Routine risk minimization measures:

Important potential risk: Other immune-mediated events (encephalitis)	
	Warning to monitor for immune-mediated adverse reactions and treatment advice based on etiology 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

MCC=metastatic merkel cell carcinoma, PL=package leaflet, RCC= renal cell carcinoma, SmPC=summary of product characteristics

Important potential risk: Severe cutaneous reactions	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. Severe cutaneous reaction (immune-mediated rash) was observed in patients treated with avelumab in these clinical trials. <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 advanced RCC (489 patients). Severe immune-mediated cutaneous reactions (immune-mediated rash) 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-mediated 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-mediated adverse reactions and treatment advice based on etiology 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*

MCC=metastatic merkel cell carcinoma, PL=package leaflet, RCC= renal cell carcinoma, SmPC=summary of product characteristics

Important potential risk: Immunogenicity	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001 and EMR100070-003 The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients). Of the 1,738 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 advanced RCC (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 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 nAb is unknown in SmPC section 4.8* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

ADA=anti-drug antibodies, MCC=metastatic merkel cell carcinoma, nAB= neutralizing antibody, RCC= renal cell carcinoma, SmPC=summary of product characteristics, UC=urothelial carcinoma

Important potential risk: Embryofetal toxicity	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2082 patients treated with avelumab were evaluated. There were no cases of avelumab exposure during pregnancy in these studies. The programmed death 1/programed death ligand 1 pathway is thought to be involved in maintaining tolerance to the fetus throughout pregnancy. Blockade of programed death ligand 1 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 in Combination with Axitinib in RCC

Important potential risk: Embryofetal toxicity	
	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 adverse event 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 programed death ligand 1 signaling 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*

MCC=metastatic merkel cell carcinoma, PL=package leaflet, RCC= renal cell carcinoma, SmPC=summary of product characteristics, UC=urothelial carcinoma

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 human immunodeficiency virus (HIV), or hepatitis B or C were excluded from clinical trials in SmPC section 4.4. A warning is included that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population.* *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 and B9991001 in SmPC section 5.1* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have HIV infection or acquired immunodeficiency 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 or hepatitis C in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

PL=package leaflet, SmPC=summary of product characteristics

Important potential risk: Embryofetal toxicity	
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 human immunodeficiency virus (HIV), or hepatitis B or C were excluded from clinical trials in SmPC section 4.4. A warning is included that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population. 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 Study EMR100070-003 and B9991001 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
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-authorization development plan.

PL=package leaflet, SmPC=summary of product characteristics

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

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

II.C.2 Other Studies in the Post-Authorization 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.