SUMMARY OF THE RISK MANAGEMENT PLAN FOR OPDIVO® **(NIVOLUMAB)**

Version Number: 11.0

Based on European Union RMP Version 37.1

Document Date: 22-Jan-2025

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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 OPDIVO® (nivolumab) 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 OPDIVO® (nivolumab) in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of OPDIVO® (nivolumab).

SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for OPDIVO (nivolumab).

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

OPDIVO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how OPDIVO should be used.

This summary of the RMP for OPDIVO 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 OPDIVO's RMP.

I. The medicine and what it is used for

OPDIVO is authorized for the treatment of adults and adolescents 12 years of age and older with advanced melanoma (unresectable or metastatic), and the adjuvant treatment of Stage IIB, or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see SmPC for the full indication).

OPDIVO is also authorized for the treatment of adults with advanced melanoma, melanoma after complete resection, advanced or metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), squamous cell cancer of the head and neck (SCCHN), urothelial carcinoma (UC), esophageal squamous cell carcinoma (ESCC), unresectable malignant pleural mesothelioma (MPM), mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (CRC), oesophageal cancer or gastro-oesophageal junction cancer (OC or GEJC), gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma (OAC) muscle invasive urothelial carcinoma (MIUC) (adjuvant treatment), unresectable advanced, recurrent or metastatic OSCC, and resectable NSCLC (neoadjuvant treatment) (see SmPC for the full indication).

It contains nivolumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of OPDIVO’s benefits can be found in OPDIVO’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo.

II. Risks associated with the medicine and activities to minimise or further characterize the risks

Important risks of OPDIVO, together with measures to minimise such risks and the proposed studies for learning more about OPDIVO’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 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 (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In the case of OPDIVO, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR 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 OPDIVO is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of OPDIVO 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 OPDIVO. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin adverse reactions [ARs], and other immune-related adverse reactions [irARs]) Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Risk of GVHD with nivolumab after allogeneic haematopoietic stem cell transplant (HSCT)
Missing information	Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab

List of important risks and missing information

Long-term safety in adolescent patients ≥ 12 years of age

II.B Summary of important risks

Important identified risks

Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)

Evidence for linking the risk to the medicine

Pneumonitis

Immune-related pneumonitis has been reported in subjects with a variety of tumor types and in subjects with and without lung metastases. The majority of cases reported were Grade 1-2 and subjects presented with either asymptomatic radiographic changes (eg, focal ground glass opacities, patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3-4 pulmonary toxicities were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Severe pneumonitis can be life-threatening if not diagnosed early and managed appropriately.

Death due to pulmonary toxicity, including pulmonary embolism, has been reported with nivolumab in combination with ipilimumab.

Colitis

Immune-related colitis has been reported in subjects with a variety of tumor types. The majority of subjects had mild to moderate (Grade 1-2) diarrhea or colitis. Grade 3-4 cases were more common with nivolumab in combination with ipilimumab. Diarrhea/colitis was manageable using the established management guidelines. The majority of cases resolved with drug interruption and, in severe cases, with steroids treatment. Severe or persistent diarrhea and colitis can be life-threatening if not recognized early and managed appropriately.

Hepatitis

Immune-related hepatitis has been reported in subjects with a variety of tumor types. Subjects may be asymptomatic. In clinical studies, hepatotoxicities manifesting as transaminase elevations were detectable with liver function testing and signs and symptoms monitoring. Most were Grade 1-2 transaminase elevation or hepatitis. Immune-related hepatitis can be serious or life-threatening and even fatal if not treated promptly. Subjects with immune-related hepatitis are generally managed clinically with steroid therapy with resolution of the event. Prompt review of blood tests, recognition of signs and symptoms, and implementation of the recommended management guidelines may prevent serious complications.

Nephritis and renal dysfunction

Immune-related nephritis and renal dysfunction have been reported in subjects with a variety of tumor types. Most patients present with asymptomatic increase in serum creatinine. Most were Grade 1-2 severity. Immune-related nephritis and renal dysfunction can be serious or life-threatening. Subjects with immune-related nephritis and renal dysfunction are generally managed clinically with steroid therapy with resolution of the event. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications.

Endocrinopathies

Important identified risks

	Immune-related endocrinopathies have been reported in subjects with a variety of tumor types. Immune-related endocrinopathies have been observed with nivolumab monotherapy and the most common disorder was hypothyroidism with Grade 1-2 severity in majority of the cases. Endocrinopathies were more frequent with nivolumab in combination with ipilimumab. Less frequently observed endocrinopathies included adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis. Patients are typically managed with hormone replacement and/or steroid treatment. Lifelong hormone replacement may be required. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications. **Skin ARs** Immune-related skin ARs have been reported in subjects with a variety of tumor types. Mild to moderate (Grade 1-2) immune-related skin ARs are common with nivolumab monotherapy, while severe (Grade 3-4) immune-related skin ARs are of low frequency with nivolumab monotherapy and more frequent with nivolumab in combination with ipilimumab. Rare cases of SJS and TEN, some with fatal outcome, have been observed. Early detection and timely treatment are key to recovery and to prevent severe complications. **Other irARs** Selected other irARs, which are uncommon but considered important identified risks, include uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, encephalitis, solid organ transplant rejection, and Vogt-Koyanagi-Harada. Other irARs can be serious and life-threatening. Patients are usually clinically managed with steroids and the events generally resolved. Severe (Grade 3-4) immune-related ARs are reported in minority of patients.
Risk factors and risk groups	**Pneumonitis** Interstitial lung disease (ILD) can develop or exacerbate as a consequence of radiotherapy, chemotherapy, or pulmonary resection. Other risk factors for ILD include older age, reduced normal lung on computed tomography scan, smoking history, and concomitant or previous lung infection. **Colitis** Patients with active inflammatory bowel disease. **Hepatitis** Active autoimmune hepatitis, which may also be associated with previous chemotherapy or immunotherapy, such as IL-2 or IFN. **Nephritis and renal dysfunction** Active autoimmune diseases with potential for renal involvement. **Endocrinopathies** Active autoimmune diseases of the endocrine glands may also be associated with previous chemotherapy or immunotherapy, such as IL-2, IFN, or anti-CTLA4. **Skin ARs** Active autoimmune skin disorders. **Other irARs** Active autoimmune diseases may also be associated with previous chemotherapy or immunotherapy, such as IL-2, IFN, or anti-CTLA4.

Important identified risks

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimisation measures: Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice See section II.C of this summary for an overview of the post-authorisation development plan.
Severe infusion reactions	
Evidence for linking the risk to the medicine	As with any other intravenous administered drugs, infusion-related reactions can occur with nivolumab. Premedications were generally not required prior to nivolumab administration during clinical trials with nivolumab. Severe infusion reactions were uncommon but can lead to discontinuation.
Risk factors and risk groups	None.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8 Additional risk minimisation measures: None
Additional pharmacovigilance activities	• CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice • See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risks

Embryofetal toxicity	
Evidence for linking the risk to the medicine	Contraception is required for women of childbearing potential (WOCBP). Preclinical study suggested potential risk of third trimester fetal loss and premature birth with increased neonatal mortality if exposed to nivolumab during pregnancy.
Risk factors and risk groups	Exposure during pregnancy.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3
Additional pharmacovigilance activities	None
Immunogenicity	
Evidence for linking the risk to the medicine	No increased risk of hypersensitivity or infusion reaction in patients with positive anti-drug antibodies (ADA) vs negative ADA subjects. No life threatening or fatal outcomes have been reported. Low rates of immunogenicity have been observed and no impact has been observed on safety or efficacy even following prolonged dose interruptions and rechallenge.
Risk factors and risk groups	Occurrence of immunogenicity is dependent on several factors related to drugs of interest and patient characteristics, such as drug characteristics, processing, doses, and route of administration, and patients' age, genetic factors, immune status, disease status, concomitant medications.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8

Important potential risks

Additional pharmacovigilance activities	None

Evidence for linking the risk to the medicine	In patients treated with nivolumab post allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting.
Risk factors and risk groups	Patients who have previously undergone allogeneic HSCT prior to nivolumab therapy.
Risk minimisation measures	SmPC Section 4.4 provides warnings of the increased risk of severe GVHD and death in patients who have had prior allogeneic HSCT. Related information is found in SmPC Section 4.8 Undesirable effects
Additional pharmacovigilance activities	None

Missing information

Patients with severe hepatic and/or renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2
Patients with autoimmune disease	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4
Patients already receiving systemic immunosuppressants before starting nivolumab	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5
Long-term safety in adolescent patients ≥ 12 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8
Additional pharmacovigilance activity	Additional pharmacovigilance activity: Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the Dutch Melanoma Treatment Registry (DMTR) (CA184557). 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

The following studies are conditions of the marketing authorisation:

Planned and ongoing post-authorisation efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorisation	
Final clinical study report for CA2098Y8: a randomized, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels.	To further evaluate the efficacy and safety of the combination of nivolumab and ipilimumab compared to nivolumab monotherapy.
Final clinical study report for CA209577: A randomized study evaluating the efficacy and safety of nivolumab vs. placebo in the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer.	To further evaluate the efficacy and safety of OPDIVO compared to placebo in the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer.
Final clinical study report for CA209274: A Phase III study evaluating the efficacy and safety of nivolumab vs. placebo in the adjuvant treatment of adult patients with high risk invasive urothelial carcinoma, in all randomised patients and all randomised patients with tumour cell PD-L1 expression ≥ 1%.	To further evaluate the efficacy of OPDIVO compared to placebo in the adjuvant treatment of adult patients with high risk invasive urothelial carcinoma, in all randomised patients with tumour cell PD-L1 expression ≥ 1%.
Final clinical study report for CA209816: A randomized, Phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early-stage NSCLC.	To further characterize the efficacy of nivolumab as neoadjuvant treatment of adults with NSCLC
Final clinical study report for CA20976K: A Phase 3, randomized, double-blind study to evaluate the use of adjuvant immunotherapy with nivolumab versus placebo after complete resection of Stage IIB/C melanoma in adults and adolescent subjects ≥ 12 years old.	To further characterize the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma.
Final clinical study report for CA2098HW: A Phase 3 randomized clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with MSI-H or dMMR mCRC.	To further characterize the efficacy of the combination regimen of nivolumab and ipilimumab as first-line treatment in adult patients with MSI-H/dMMR unresectable or metastatic colorectal cancer.
Efficacy studies which are Specific Obligations	
None	NA

II.C.2 Other studies in post-authorisation development plan

Category 3 ongoing and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice
CA184557: Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR.	To assess safety and long-term outcomes in children and adolescents.