SUMMARY OF THE RISK MANAGEMENT PLAN FOR YERVOY® (IPILIMUMAB)

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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 YERVOY® (ipilimumab) 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 YERVOY® (ipilimumab) 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 YERVOY® (ipilimumab).

SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for YERVOY (ipilimumab)

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

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

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

I. The medicine and what it is used for

YERVOY is authorised for treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older. YERVOY in combination with OPDIVO (nivolumab) is authorised for treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older, for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma, for treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine based combination chemotherapy, for the first-line treatment of adult patients with dMMR or MSI-H unresectable or metastatic colorectal cancer, for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma, and for the first-line treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) (see SmPC for the full indication). YERVOY in combination with OPDIVO and chemotherapy is authorised for the first-line treatment of metastatic non-small cell lung cancer in adults. It contains ipilimumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of YERVOY's benefits can be found in YERVOY'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/yervoy

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

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

Together, these measures constitute routine risk minimisation measures.

In the case of YERVOY, 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 Periodic Safety Update Report (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 YERVOY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of YERVOY 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 YERVOY. 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 GI, hepatic, skin, neurologic, endocrine and other irARs) Severe infusion reactions
Important potential risks	Immunogenicity
Missing information	Long-term safety in adolescent patients ≥ 12 years of age Potential PD interaction with systemic immunosuppressants Patients with severe hepatic impairment Patients with severe renal impairment Patients with autoimmune disease

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risks

Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs)	
Evidence for linking the risk to the medicine	**GI irARs (eg, diarrhoea, colitis, GI perforation)** In clinical studies, GI irARs most often presented as diarrhoea, abdominal pain, and/or hematochezia with or without fever. Majority of subjects with GI irARs had mild to moderate (Grade 1 or 2) diarrhoea or colitis which were generally manageable and usually resolved. However, severe or persistent diarrhoea or colitis could occur. Discontinuation of ipilimumab (either temporarily or permanently) was required for subjects with Grade 3-4 events. Late onset GI irARs (more than 30 days after last dose) and fatalities due to GI perforation and hemorrhagic colitis requiring colectomy have been reported. **Hepatic irARs (eg, hepatitis)** Hepatic irARs of any grade reported during the treatment period were less common than those affecting the GI tract and skin and generally resolved. In the clinical studies, hepatic irARs were most often asymptomatic but could be detected by routine laboratory monitoring. Discontinuation of ipilimumab was required in patients with high-grade events. Fatal outcome may occur if not treated promptly and appropriately. **Skin irARs (eg, rash, pruritus, TEN, and DRESS)** Skin irARs during the treatment dosing period were common and consisted primarily of Grade 1-2 rash and pruritus. Skin irARs generally resolved, however can be potentially severe or fatal. **Neurologic irARs (eg, neuropathy)** Neurological manifestations in subjects treated with ipilimumab may include motor and/or sensory neuropathy. Given the difficulty in definitely establishing an inflammatory etiology, alternative etiologies (eg, tumor progression) should be excluded. Fatal Guillain-Barre syndrome and cases of myasthenia gravis have been reported in clinical

Important identified risks

	trials of ipilimumab. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy should be evaluated, and noninflammatory causes such as disease progression, infections, metabolic disorders, and medications should be excluded. **Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)** Severe (Grade 3-4) endocrinopathy has been reported in minority of patients. Patients with hypophysitis and hypopituitarism typically presented with headache or fatigue, which may be incorrectly attributed to underlying malignancy. Diagnosis requires laboratory confirmation. Endocrinopathy can be serious or life-threatening. Patients are usually clinically managed with steroids and/or hormone replacement therapy. Long-term hormone replacement may be required. **Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)** Selected other irARs which are considered important identified risks include, for example, pneumonitis, nephritis, and non-infectious myocarditis. Severe (Grade 3-4) irARs reported in minority of patients. Other irARs can be serious and life-threatening. Patients are usually clinically managed with steroids and the events generally resolved.
Risk factors and risk groups	**GI irARs (eg, diarrhoea, colitis, GI perforation)** Patients with active inflammatory bowel diseases **Hepatic irARs (eg, hepatitis)** AIH, which may also be associated with previous chemotherapy or immunotherapy, such as IL-2 or IFN. In addition to female gender, genetic factors appear to confer a predisposition for the incidence of AIH. The HLAs DR3, DR4, and DR7 have been associated with AIH. Moreover, there is evidence to suggest that susceptibility to AIH, the severity and clinical outcome may vary according to genetic polymorphisms for the cytokines TNF-α and TGF- β1. Certain therapies, including long-term therapy with IFNα, have been reported to induce hepatocellular injury that mimics AIH. There is mounting evidence that IFN therapy (α,β) may exacerbate or initiate certain autoimmune diseases. The frequency of IFN-α associated autoimmune diseases has been reported to range from 4% to 19%. Among patients with chronic myeloid leukemia, IFN-α2a associated autoimmunity has been reported to be as high as 28%. The frequency of AIH is unknown. It was reported to occur in 2% (1 of 46) of chronic myeloid leukemia patients treated at one institution (detected after 38 months on therapy). and there are case reports of AIH following IFN-beta therapy for multiple sclerosis and following IFN-α therapy for malignant melanoma. **Skin irARs (eg, rash, pruritus, TEN, and DRESS)** Active autoimmune skin disorders **Neurologic irARs (eg, neuropathy)** Previous viral or bacterial infection (eg, cytomegalovirus, *Campylobacter jejuni*, *Mycoplasma pneumoniae*, Epstein Barr virus, influenza virus) or previous immunotherapy with IFN-alpha.

Important identified risks

	Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency) Active autoimmune diseases of endocrine glands **Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)** Active autoimmune diseases
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring, diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list. Additional risk minimization measures: Patient Information Guide and Alert Card.
Additional PV activities	None
Severe Infusion Reactions	
Evidence for linking the risk to the medicine	As with any other intravenous administered drugs, infusion-related reactions can occur with ipilimumab. Likely systemic infusion reactions were defined as any event from the list that occurred within 48 hours after the subject received study treatment. Premedications were not required prior to ipilimumab administration during clinical trials with ipilimumab. Severe infusion reactions can be potentially serious if associated with severe hypersensitivity reaction or anaphylaxis. No fatal events of infusion-related reactions were reported.
Risk factors and risk groups	Infusion reactions may be observed during treatment with any injectable protein including ipilimumab, which is a fully-human IgG1 anti-CTLA-4 monoclonal antibody.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4, and 4.8 Additional risk minimization measures: Patient Information Guide and Alert Card.
Additional PV activities	None

Important potential risks

Immunogenicity	
Evidence for linking the risk to the medicine	Anti-ipilimumab antibodies could lead to immune complex formation with the drug and result in hypersensitivity, leading to immediate or delayed reactions after infusion. In addition, the anti-ipilimumab antibodies may increase the clearance of the drug or it may neutralize its ability to bind to its biological target CTLA4, which in turn will reduce the efficacy of ipilimumab. No life threatening or fatal outcomes have been reported.
Risk factors and risk groups	The risk factors for immunogenicity are largely unknown.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 5.1

Missing information

Long-term safety in adolescent patients ≥ 12 years of age	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2, 4.4, 4.8, and 5.2
Additional pharmacovigilance activity	Long-term follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated paediatric patients enrolled in the DMTR (CA184557). See section II.C of this summary for an overview of the post-authorisation development plan.
Potential PD interaction with systemic immunosuppressants	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.5
Patients with severe renal impairment	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 and 4.5
Patients with severe hepatic impairment	
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2 and 5.2
Patients with autoimmune disease	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorization of YERVOY in combination with nivolumab in RCC:

Planned and ongoing post-authorization efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorization	
Final clinical study report for 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 (CA2098Y8)	To further evaluate the efficacy and safety of the combination of nivolumab and ipilimumab compared to nivolumab monotherapy.
Final clinical study report for 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 (CA2098HW).	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.

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
Long-term follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated paediatric patients enrolled in the DMTR (CA184557)	To assess safety and long-term outcomes in children and adolescents.