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 for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see SmPC for the full indication). 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.

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	GI irARs (eg, diarrhoea, colitis, GI perforation)
	Hepatic irARs (eg, hepatitis)
	Skin irARs (eg, rash, pruritus, TEN, and DRESS)
	Neurologic irARs (eg, neuropathy)
	Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency)
	Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis)
	Severe infusion reactions
Important potential risks	Immunogenicity
	Severe skin drug reactions from concurrent or sequential (in any order) use of ipilimumab and vemurafenib or PD-1/PD-L1 inhibitors
Missing information	Reproductive and lactation data
	Long-term safety in adolescent patients > 12 years of age
	Data in ethnic groups
	Potential PD interaction with systemic immunosuppressants
	Patients with severe hepatic impairment
	Patients with severe renal impairment
	Patients with autoimmune disease
	Long-term safety

II.B Summary of important risks

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

Important identified risks

Gastrointestinal irARs	
Evidence for linking the risk to the medicine	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.
Risk factors and risk groups	Patients with active inflammatory bowel diseases
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring,

Important identified risks

	diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list. Additional risk minimization measures: Patient Information Brochure and Alert Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Hepatic irARs	
Evidence for linking the risk to the medicine	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.
Risk factors and risk groups	Active Autoimmune hepatitis (AIH), which may also be associated with previous chemotherapy or immunotherapy, such as IL-2 or interferon (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 IFN-alpha (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.
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 Brochure and Alert Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important identified risks

Skin irARs	
Evidence for linking the risk to the medicine	Skin irARs during the treatment dosing period were common and consisted primarily of Grade 1-2 rash and pruritus. Skin irARs generally resolved; potentially severe or fatal.
Risk factors and risk groups	Active autoimmune skin disorders
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 Brochure and Alert Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Neurologic irARs	
Evidence for linking the risk to the medicine	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 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.
Risk factors and risk groups	Previous viral or bacterial infection (eg, cytomegalovirus, *Campylobacter jejuni*, *Mycoplasma pneumoniae*, Epstein Barr virus, influenza virus) or previous immunotherapy with IFN-alpha.
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 Brochure and Alert Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Endocrine irARs	
Evidence for linking the risk to the medicine	Severe (Grade 3-4) endocrinopathy 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.
Risk factors and risk groups	Active autoimmune diseases of endocrine glands
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring,

Important identified risks

	diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list. Additional risk minimization measures: Patient Information Brochure and Alert Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Other irARs	
Evidence for linking the risk to the medicine	Selected other irARs which are considered important identified risks include 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	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 Brochure and Alert Card.
Additional pharmacovigilance activities	Additional pharmacovigilance 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 Brochure and Alert Card.
Additional pharmacovigilance 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

Severe Skin Drug Reactions from Concurrent or Sequential (in Any Order) Use of Ipilimumab and Vemurafenib or PD-1/PD-L1 Inhibitors	
Evidence for linking the risk to the medicine	A literature report by Harding described the development of Grade 3 rash within 6 to 8 days in 4 of 13 subjects treated with vemurafenib following ipilimumab treatment. Although there were no instances of life-threatening or fatal adverse skin reactions, the frequency of Grade 3 rash was higher than expected with vemurafenib alone and skin biopsies in 2 subjects were consistent with drug hypersensitivity reaction. The rash resolved within 14 days following discontinuation of vemurafenib, which was then successfully resumed in all subjects at a lower dose. None of the subjects manifested a skin imAR with ipilimumab and vemurafenib was initiated within 28 days of the last dose of ipilimumab, so the proximity of sequential treatment may have contributed to the rash. Successful rechallenge with vemurafenib without subsequent skin toxicity make it difficult to determine with certainty whether rash was mediated by an ongoing immune response. Additionally, there have been 8 cases of TEN with ipilimumab therapy, including a fatal case associated with sequential nivolumab and ipilimumab therapy.This subject experienced a skin adverse reaction with nivolumab raising the possibility that subsequent ipilimumab exacerbated this immune reaction.
Risk factors and risk groups	Caution should be used in melanoma patients when ipilimumab is administered concurrently with vemurafenib or following prior vemurafenib.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4

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
Data in ethnic groups	
Risk minimization measures	Routine risk minimization measures: SmPC Section 5.2
Potential PD interaction with systemic immunosuppressants	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.5

Missing information

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
Long-term Safety	
Risk minimization measures	Routine risk minimization measures: N/A

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.	To further evaluate the efficacy and safety of the combination of nivolumab and ipilimumab compared to nivolumab monotherapy.

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
MAH to sponsor extension of the DMTR to include paediatric subjects and to collect their safety data	To obtain additional safety information in paediatric patients