YERVOY®

(ipilimumab)

Risk Minimisation Information for Healthcare Professionals

Guide for Prescribing

YERVOY® is indicated for the treatment of tumours, as monotherapy or in combination with nivolumab.

Use this Risk Minimisation Guide for treatment of patients with **ipilimumab monotherapy** for advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older.

Use the OPDIVO® (nivolumab) Risk Minimisation Guide for treatment with **ipilimumab in combination with nivolumab**.

Healthcare professionals are asked to report any suspected adverse reactions via www.medicinesauthority.gov.mt/adrportal
Adverse reactions should also be reported to Bristol-Myers Squibb Medical Information at ***00 356 2397***6417or **pv@ammangion.com**

This Guide

- Is provided for healthcare professionals (HCPs) who are involved in the treatment of patients with ipilimumab monotherapy
  (for treatment with ipilimumab in combination with nivolumab, please see the OPDIVO® (nivolumab) Risk Minimisation Guide).
- Is essential to ensure the safe and effective use of ipilimumab and appropriate management of immune-related adverse reactions (irARs).
- Is to be read before prescribing and administering ipilimumab.
- Presents the Patient Information Guide and Patient Alert Card. It is important to review the Patient Information Guide with patients before each treatment cycle to reinforce understanding of side effects and the need to contact a HCP if they develop side effects.

Summary of important information

- Ipilimumab increases the risk of severe immune-related adverse reactions (irARs), which can include diarrhoea, colitis, hepatitis, skin inflammation, neurological adverse reactions, endocrinopathies, inflammation of the eyes, and other irARs.
- These irARs can occur several months after the last dose of ipilimumab and therefore require a longer follow-up of the patient.
- Early diagnosis and appropriate management of irARs are essential to minimise potentially life-threatening complications.
- Suspected adverse reactions must be promptly evaluated to exclude infectious or other alternate aetiologies.
- Based on the severity of symptoms, ipilimumab may need to be withheld or discontinued and systemic high-dose corticosteroid therapy or other immunosuppressant therapy may be required.
- Patients should be informed about the symptoms of these irARs and the importance of reporting them immediately to the treating physician. For this reason, there is a Patient Information Guide and Patient Alert Card.
- Patients should be advised to carry the Patient Alert Card at all times and to show it to the HCP at all medical visits.

Guide for prescribing ipilimumab

Before prescribing ipilimumab and before each infusion, check:

- liver function tests (LFTs)
- thyroid function tests
- for any signs or symptoms of irARs, including diarrhoea and colitis
- if the patient is pregnant, planning to become pregnant, or if she is breastfeeding.

Caution

Ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially life-threatening.

- **Additional information concerning ipilimumab is available in the Summary of Product Characteristics (SmPC) and package leaflet.**

Immune-Related Adverse Reactions

Immune-Related Adverse Reactions (irARs) can occur with ipilimumab, and can include:

- **Colitis**, that can progress to bleeding or bowel perforation.
- **Hepatitis**, that can lead to liver failure.
- **Skin inflammation** that can progress to severe skin reaction (e.g. toxic epidermal necrolysis [TEN], drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome).
- **Neurological** adverse reactions that can result in motor or sensory neuropathy.
- **Endocrinopathies** involving the pituitary, adrenal or thyroid glands that may affect their function.
- **Inflammation of the eyes.**

There were isolated reports of **severe infusion reactions** in clinical trials.

Additional irARs include: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in patients treated with ipilimumab + gp100 peptide vaccine. Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported post-marketing.

Early diagnosis and appropriate management

- Prompt recognition of adverse events and appropriate treatment are essential to minimise life-threatening complications. Systemic high-dose corticosteroids with or without additional immunosuppressive therapy may be required for the management of severe irARs.[1]
- Please refer to the Summary of Product Characteristics (SmPC) for guidelines on treatment and report any suspected adverse reaction to the National Health Authority in accordance with the national reporting system.
- Onset of irARs can occur up to several months after the last dose of ipilimumab.[1]

Immune-Related Adverse Reactions and Treatment Modifications

Immune-related reaction	Severity	Treatment modification
Gastrointestinal (diarrhoea, colitis)	Grade 1 or 2	Patient may remain on ipilimumab. Symptomatic treatment (e.g. loperamide, fluid replacement) and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days withhold ipilimumab and initiate corticosteroids (e.g. prednisone at 1 mg/kg orally once daily). If resolution to Grade 0-1 or return to baseline occurs, ipilimumab may be resumed.
	Grade 3 or 4	Permanently discontinue ipilimumab and start immediately IV corticosteroids (e.g. methylprednisolone 2 mg/kg/day). If symptoms are controlled, start corticosteroids taper based on clinical judgement. Tapering should occur over a period of at least 1 month to avoid recurrence of reaction.
Hepatotoxicity	Grade 2 transaminase or total bilirubin elevation	Withhold ipilimumab and monitor LFTs until resolution. Upon improvement, ipilimumab may be resumed.
	Grade 3 or 4 transaminase or total bilirubin elevation	Permanently discontinue ipilimumab and start immediately IV corticosteroids (e.g. methylprednisolone 2 mg/kg/day or equivalent). Monitor LFTs until normalisation. If symptoms are controlled, start corticosteroids taper based on clinical judgement. Tapering should occur over a period of at least 1 month to avoid recurrence of reaction. Manage LFT elevations during taper with an increased corticosteroid dose and slower taper.
Skin (rash, pruritus, TEN, DRESS)	Grade 1 or 2 skin rash or Grade 1 pruritus	Patient may remain on ipilimumab. Symptomatic treatment (e.g. antihistamines) is advised. If symptoms persist for 1-2 weeks and do not improve with topical corticosteroids, initiate oral corticosteroids (e.g. prednisone 1 mg/kg/day or equivalent).
	Grade 3 skin rash or Grade 2 pruritus	Withhold ipilimumab. If symptoms return to Grade 1 or resolve, ipilimumab may be resumed.
	Grade 4 skin rash or Grade 3 pruritus	Permanently discontinue ipilimumab and start immediately systemic high-dose IV corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day). If symptoms are controlled, start corticosteroids taper based on clinical judgement. Tapering should occur over a period of at least 1 month to avoid recurrence of reaction.

Grade definition according to NCI CTCAE v.4

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Hepatobiliary disorders	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
ALT/AST increase	> ULN-3.0 ×ULN	> 3.0-5.0 × ULN	> 5.0-20.0 × ULN	> 20.0 × ULN	
Bilirubin increase	> ULN-1.5 × ULN	> 1.5-3.0 × ULN	> 3.0-10.0 × ULN	> 10.0 × ULN	
Allergic reaction	Transient flushing or rash, drug fever < 38°C (< 100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Rash acneiform	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Toxic Epidermal Necrolysis				Skin sloughing covering ≥30% Body Surface Area (BSA) with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
DRESS	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Immune-Related Adverse Reactions and Treatment Modifications

Immune-related reaction	Severity	Recommended treatment modification
Neurological (Guillain-Barré syndrome, myasthenia gravis-like symptoms, muscle weakness, sensory neuropathy, motor neuropathy)	Grade 2 neuropathy	Withhold ipilimumab if likely related to ipilimumab. If symptoms resolve to baseline, ipilimumab may be resumed.
	Grade 3 or 4 (Sensory) neuropathy	Permanently discontinue ipilimumab if suspected to be related to ipilimumab. Treat according to guidelines for sensory neuropathy, and start immediately IV corticosteroids (e.g. methylprednisolone 2 mg/kg/day).
	Grade 3 or 4 (Motor) neuropathy	Permanently discontinue ipilimumab, regardless of causality.
Endocrinopathies (hypophysitis, hypopituitarism, adrenal insufficiency, hypothyroidism)	Signs of adrenal crisis	Administer immediately IV corticosteroids with mineralocorticoid activity, and evaluate the patient for presence of sepsis or infections.
	Signs of adrenal insufficiency (no crisis)	Consider further investigations (including laboratory and imaging assessment). Consider assessing endocrine function before initiation of corticosteroid therapy.
	Abnormal pituitary imaging or endocrine function lab tests	Withhold ipilimumab and start short course of corticosteroids (e.g. dexamethasone 4 mg every 6 hours or equivalent). Appropriate hormone replacement should be started. Long-term hormone replacement therapy may be necessary. If symptoms are controlled, treatment with ipilimumab may be resumed and corticosteroid taper should occur over a period of at least 1 month to avoid reaction recurrence.

Grade definition according to NCI CTCAE v.4					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Guillain Barré syndrome (nervous system disorders, general)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Myasthenia gravis-like symptoms (nervous system disorders, general)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Hypophysitis (endocrine disorders, general)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalisation indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypopituitarism (endocrine disorders, general)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalisation indicated	Life-threatening consequences; urgent intervention indicated	Death

Immune-Related Adverse Reactions and Treatment Modifications

Immune-related reaction	Severity	Recommended treatment modification
Other irAR (uveitis, eosinophilia, lipase elevation, glomerulonephritis, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, pneumonitis, VKH syndrome)	Grade 3 or 4	Permanently discontinue ipilimumab and may require immediate systemic high-dose corticosteroid therapy.
	Ipilimumab related uveitis, iritis, episcleritis	Consider corticosteroid eye drops as medically indicated.

Grade definition according to NCI CTCAE v.4					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	
Iritis (eye disorders, general)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately sight-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	
Eosinophilia (immune system disorders, general)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	
Glomerulonephritis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or non-invasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Creatinine increased	> 1-1.5 × baseline; >ULN-1.5 × ULN	> 1.5-3.0 × baseline; >1.5-3.0 × ULN	> 3.0 baseline; > 3.0-6.0 × ULN	> 6.0 × ULN	
Haemolysis	Laboratory evidence of haemolysis only (e.g. direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of haemolysis and >=2 gm decrease in haemoglobin	Transfusion or medical intervention indicated (e.g. steroids)	Life-threatening consequences; urgent intervention indicated	Death
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	
Multi-organ failure			Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)	Death
VKH syndrome (immune disorders, general; see also uveitis)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

When to permanently discontinue ipilimumab

Permanently discontinue ipilimumab in patients with the following irARs:

- Grade 3 or 4 diarrhoea or colitis
- Grade 3 or 4 elevation in AST, ALT, or total bilirubin
- Grade 4 skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or Grade 3 pruritus
- Grade 3 or 4 motor or sensory neuropathy
- Grade 3 or 4 immune-related reactions (except for Grade 3-4 endocrinopathies controlled with hormone replacement therapy or Grade 3 skin rash)
- ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy
- Severe infusion reactions

Management of these adverse reactions may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related (see SmPC).

When to withhold a dose of ipilimumab

Withhold ipilimumab dose in patients with the following irARs:

- Grade 2 diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs
- Grade 2 elevations in AST, ALT, or total bilirubin
- Grade 3 skin rash or Grade 2 widespread/intense pruritus regardless of aetiology
- Grade 3 or 4 endocrinological adverse reactions not adequately controlled by hormone replacement therapy or immunosuppressive therapy
- Grade 2 unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)
- Other Grade 2 adverse reactions (except moderate infusion reactions with close monitoring)

Patient Information Guide and Patient Alert Card

It is important to distribute a Patient Information Guide to any patient receiving ipilimumab treatment for the first time or asking for a new copy. You can use the Patient Information Guide to discuss ipilimumab treatment.

The Patient Information Guide will help the patients understand their treatment and how to act should they experience adverse reactions (e.g. irARs). Moreover, **it includes a Patient Alert Card, with contact details, for the patient to carry at all times.**

Patient Information Guide
and

Patient Alert Card Image Here

Checklist for patient's visit (first or following)

FIRST VISIT

- **Check** for signs and symptoms of irARs and for any previous clinical conditions
- **Check** appropriate laboratory tests
- **Distribute** the Patient Information Guide and discuss the treatment with the patient. Fill in the Patient Alert Card and inform the patient to carry it at all times
- **Inform the patient not to treat their own symptoms, even if mild, and to seek immediate medical attention should any adverse reaction occur or worsen as some can worsen rapidly if not treated**
- **Inform the patient that they may experience growth of existing tumours or develop new tumours during the treatment and this does not mean that the therapy is ineffective**

ANY FOLLOWING VISIT

- **Check** appropriate laboratory tests
- **Check** for signs and symptoms of irARs
- **Remind the patient not to treat their own symptoms**
- **Remind the patient to contact you immediately should they experience even a mild adverse reaction, as some can worsen rapidly if not treated**
- **Remind** the patient that early diagnosis and appropriate management are essential to minimise life-threatening complications

1. YERVOY® Summary of Products Characteristics.

To learn more about YERVOY®, please visit www.YERVOY.country
or call 00 356 23976505 for Bristol-Myers Squibb Medical Information