Risk Minimisation Information for Healthcare Professionals

Guide for Prescribing

YERVOY® (ipilimumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma[1]

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to www.medicinesauthority.gov.mt/adrportal

This Guide

- Is provided for healthcare professionals (HCPs) who are involved in the treatment of patients on ipilimumab.
- 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 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.
- Early diagnosis and appropriate management of irARs are essential to minimise life-threatening complications.
- Suspected adverse reactions must be promptly evaluated to exclude infectious or other alternate aetiologies.
- Based on the severity of symptoms, ipilimumab should be withheld or discontinued and systemic high-dose corticosteroid 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 HCP at all medical visits.

Guide for prescribing ipilimumab

Ipilimumab is a medicine designed to help the immune system to fight tumours by increasing the activity of T-cells. It is a fully human, monoclonal IgG1 antibody and it works by blocking CTLA-4 (cytotoxic T lymphocyte associated antigen 4), a molecule on T-cells that acts as a natural brake on the immune response[1].

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 trial

Additional irARs: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in particular conditions. Cases of Vogt-Koyanagi-Harada 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 reaction	Severity	Treatment modification
Gastrointestinal (diarrhoea, colitis)	Grade 1 or 2	Patient may remain on ipilimumab. Symptomatic treatment and close monitoring are advised. If symptoms recur or persist for 5-7 days withhold ipilimumab and initiate corticosteroids (e.g. methylprednisolone) 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 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 IV corticosteroids (e.g. methylprednisolone 2 mg/kg/day or equivalent). 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.
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 returns to Grade 1 or resolve, ipilimumab may be resumed
	Grade 4 skin rash or Grade 3 pruritus	Permanently discontinue ipilimumab and start systemic high-dose IV corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day or equivalent). 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.
Neurological (Guillain-Barré syndrome, myasthenia gravis-like symptoms, muscle weakness, sensory 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 IV corticosteroids (e.g. methylprednisolone 2 mg/kg/day)
	Grade 3 or 4 (Motor) neuropathy	Permanently discontinue ipilimumab, regardless of causality

Immune related reaction	Severity	Recommended treatment modification
Endocrinopathies (hypophysitis, hypopituitarism, adrenal insufficiency, hypothyroidism)	Signs of adrenal crisis	Administer 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 to initiate 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. If symptoms are controlled, start corticosteroid taper based on clinical judgement. Tapering should occur over a period of at least 1 month to avoid reaction recurrence.
Other irAR (uveitis, eosinophilia, lipase elevation, glomerulonephritis, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, pneumonitis	Grade 3 or 4	Permanently discontinue ipilimumab and start systemic high-dose IV corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day)
	Ipilimumab related uveitis, iritis, episcleritis	Consider corticosteroid eye drops as medically indicated

Grades according to NCI-CTCAE v4

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 immune-related reactions (except for Grade 3-4 endocrinopathies controlled with hormone replacement)
- ≥ 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 dose of ipilimumab

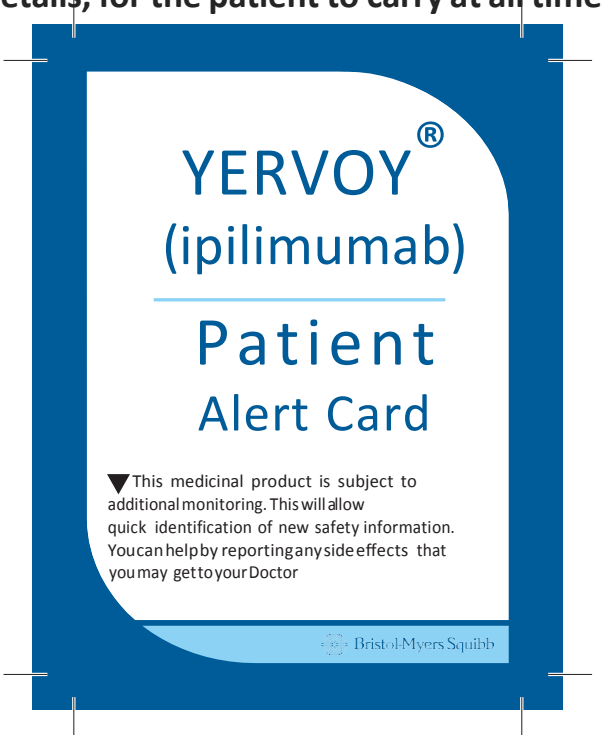
Withhold ipilimumab dose in patients with the following irARs:

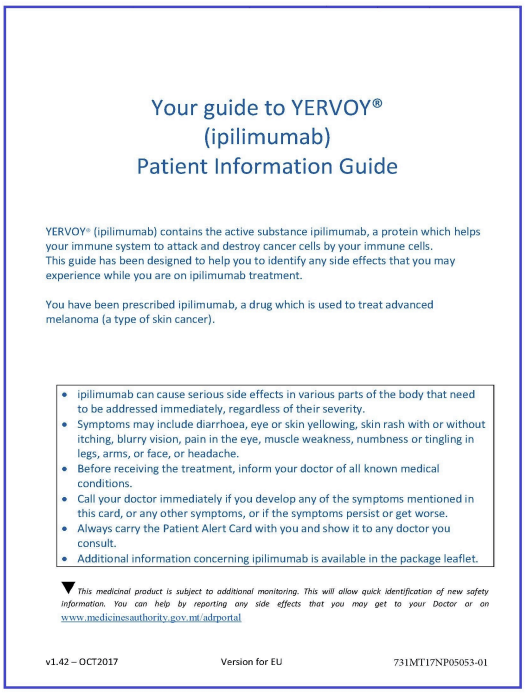
- Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs
- Grade 2 elevations in AST, ALT, or total bilirubin
- Moderate to severe (Grade 3) skin rash or widespread/intense pruritus
- Severe endocrinological adverse reactions not adequately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

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.**





Your guide to YERVOY®
(ipilimumab)
Patient Information Guide

YERVOY® (ipilimumab) contains the active substance ipilimumab, a protein which helps your immune system to attack and destroy cancer cells by your immune cells.
This guide has been designed to help you to identify any side effects that you may experience while you are on ipilimumab treatment.

You have been prescribed ipilimumab, a drug which is used to treat advanced melanoma (a type of skin cancer).

- ipilimumab can cause serious side effects in various parts of the body that need to be addressed immediately, regardless of their severity.
- Symptoms may include diarrhoea, eye or skin yellowing, skin rash with or without itching, blurry vision, pain in the eye, muscle weakness, numbness or tingling in legs, arms, or face, or headache.
- Before receiving the treatment, inform your doctor of all known medical conditions.
- Call your doctor immediately if you develop any of the symptoms mentioned in this card, or any other symptoms, or if the symptoms persist or get worse.
- Always carry the Patient Alert Card with you and show it to any doctor you consult.
- Additional information concerning ipilimumab is available in the package leaflet.

▼*This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects that you may get to your Doctor or on* www.medicinesauthority.gov.mt/adrportal

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Checklist for patient's visit (first or following)

FIRST VISIT

- **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 and to seek immediate medical attention should any adverse reaction occur or worsen**
- **Inform the patient that they may experience growth of existing tumours or develop new tumours**
- **Check** appropriate laboratory tests
- **Check** for signs and symptoms of irARs

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

YERVOY® (ipilimumab) for advanced (unresectable or metastatic) melanoma

To learn more about YERVOY™, please visit www.YERVOY.country
or call 00 356 23976505 for Medical Information