

# Risk Minimisation Information for Healthcare Professionals

## Guide for Prescribing

---

YERVOY<sup>®</sup> (ipilimumab), as monotherapy,  
is indicated for the treatment of patients with  
unresectable or metastatic melanoma<sup>1</sup>

### This guide

---

- Is provided for healthcare professionals 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 together with the Australian Product Information/New Zealand Data Sheet before prescribing and administering ipilimumab.
- Includes information on 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 healthcare professional if they develop side effects.

# Summary of important information

---

- Ipilimumab can cause severe and life-threatening immune-related adverse reactions (irARs), which can affect the gastrointestinal tract, liver, skin, nervous system, endocrine system, eyes and other organs.
- 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 potential 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 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 a Patient Alert Card.
- Patients should be advised to carry the Patient Alert Card at all times and to show it to healthcare professionals 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 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.<sup>1</sup>

Before prescribing ipilimumab, and before each infusion, check:

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

### Caution

Treatment with ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially life-threatening.<sup>1</sup>

Caution should be used when considering the use of YERVOY in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy.

**For more information, please consult the approved YERVOY Product Information (PI) [AU] or YERVOY Data Sheet (DS) [NZ] available upon request from the BMS Medical Information department by calling 1800 067 567 [AU] / 0800 167 567 [NZ] or at [www.tga.gov.au](http://www.tga.gov.au) [AU] / [www.medsafe.govt.nz](http://www.medsafe.govt.nz) [NZ].**

# Severe and life-threatening immune-related adverse reactions

---

Immune-related adverse reactions (irARs) can occur with ipilimumab and can include:

- **Gastrointestinal irARs** that can progress to bleeding or bowel perforation (e.g. diarrhoea or colitis)
- **Hepatic irARs** that can lead to liver failure (e.g. hepatitis)
- **Skin irARs** that can progress to severe skin reaction (toxic epidermal necrolysis [TEN], drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome)
- **Neurological irARs** adverse reactions that can result in motor or sensory neuropathy
- **Endocrinopathies** involving the pituitary, adrenal or thyroid glands, that may affect their function
- **Eye-related irARs**, e.g. uveitis, iritis, conjunctivitis, blepharitis, episcleritis, scleritis, Vogt-Koyanagi-Harada (VKH) syndrome
- **Other irARs**, e.g. nephritis, pneumonitis, meningitis, pericarditis, haemolytic anaemia, myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis
- **Severe infusion reactions.**

## Early diagnosis and appropriate management

---

- Prompt recognition of adverse events and appropriate treatment are essential to minimise life-threatening complications. Management of irARs may require withholding or permanent discontinuation of ipilimumab in addition to the use of systemic high dose corticosteroids with or without additional immunosuppressive therapy. Dose reduction is not recommended.<sup>1</sup>
- Onset of irARs can occur up to several months after the last dose of ipilimumab.<sup>1</sup>
- Please refer to the YERVOY prescribing information for guidelines on treatment. For further details on reporting a suspected adverse reaction, please refer to the TGA website [www.tga.gov.au/hp/problem.htm](http://www.tga.gov.au/hp/problem.htm) [AU] or to <http://www.medsafe.govt.nz/profs/adverse/reactions.asp> [NZ].

**If you report a suspected YERVOY-related adverse drug reaction to TGA or Medsafe, BMS would appreciate receiving a copy:**

Bristol-Myers Squibb Australia Pty Ltd.  
Pharmacovigilance Department  
**Email:** [medinfo.australia@bms.com](mailto:medinfo.australia@bms.com)

# Treatment modifications

IMMUNE-RELATED REACTION	SEVERITY	TREATMENT MODIFICATIONS
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 corticosteroid therapy (e.g. prednisone 1 mg/kg orally once daily or equivalent). 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 corticosteroid therapy immediately (e.g. methylprednisolone 2 mg/kg/day). If symptoms are controlled, start corticosteroid taper based on clinical judgement. Tapering should occur over a period of at least 1 month to avoid recurrence of reaction. <i>For patients with corticosteroid-refractory diarrhoea or colitis, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered (e.g. 5 mg/kg infliximab) <b>unless contraindicated</b>. Infliximab must not be used if gastrointestinal perforation or sepsis is suspected. Refer to the Product Information for infliximab.</i>
Hepatotoxicity	Grade 2 transaminase elevation or total bilirubin elevation	Withhold ipilimumab and monitor LFTs until resolution. If LFTs levels improve ipilimumab may be resumed.
	Grade 3 or 4 transaminase or total bilirubin elevation	Permanently discontinue ipilimumab and start IV corticosteroid therapy immediately (e.g. methylprednisolone 2 mg/kg/day or equivalent). Once symptoms have resolved and LFTs show sustained improvement or return to baseline, start corticosteroid taper. Tapering should occur over a period of at least 1 month to avoid recurrence of reaction. Elevations in LFTs during taper may be managed with an increase in the dose of corticosteroid and a slower taper. <i>For patients with significant LFT elevations that are refractory to corticosteroid therapy, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered (e.g. mycophenolate mofetil). Refer to the Yervoy PI for more information.</i>
Skin (rash, pruritus, DRESS, TEN)	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 mild (Grade 1) or resolve, ipilimumab may be resumed.
	Grade 4 skin rash (including SJS and TEN) or Grade 3 pruritus	Permanently discontinue ipilimumab and start systemic high-dose IV corticosteroid therapy immediately (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 immediately (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 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 initiating corticosteroid therapy.
	Abnormal pituitary imaging or endocrine function laboratory tests	Withhold ipilimumab and start short course of corticosteroid therapy (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 recurrence of reaction.
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 or equivalent).
	Ipilimumab related uveitis, iritis, episcleritis	Consider corticosteroid eye drops as medically indicated.
Infusion reactions	Mild or moderate	Patients with mild or moderate infusion reaction may receive ipilimumab with close monitoring.
	Severe	Ipilimumab infusion must be discontinued and appropriate medical therapy administered.

Grades according to NCI-CTCAE v4

## When to withhold a dose of ipilimumab

---

YERVOY should be administered 3-weekly either for all 4 doses OR be completed within 16 weeks from the first dose, whichever occurs earlier. Detailed guidelines for the management of immune related adverse reactions are described in PRECAUTIONS. Not adhering to the dose withholding guidelines may increase the risk of severe adverse events.

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 regardless of aetiology
- Severe endocrinological adverse reactions not adequately controlled by hormone replacement therapy or high-dose 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.

## When to permanently discontinue ipilimumab

---

YERVOY should be permanently discontinued in patients who:

- experience severe or life-threatening adverse reactions
- experience adverse events (Grade 2 protracted, Grade 3 or Grade 4) that are not responsive to corticosteroids and/or require additional immunosuppressive therapy such as TNF-alpha inhibitors.

YERVOY should be discontinued in patients who are unable to complete a full course of YERVOY (4 doses) within 16 weeks from administration of first dose. Any future re-induction in such patients should not be undertaken if they experienced an adverse event fulfilling the criteria for permanent discontinuation described above.

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
- Adverse reactions that are not responsive to corticosteroids and/or require additional immunosuppressive therapy such as TNF-alpha inhibitors
- Grade 2 protracted, Grade 3 or Grade 4 adverse reactions of any kind
- 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 YERVOY prescribing information).

# Patient Information Guide and Alert Card

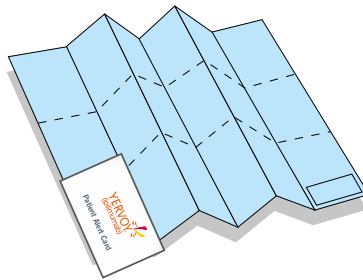
---

**All patients prescribed ipilimumab should receive a Patient Information Guide. It is important to distribute a Patient Information Guide to any patient receiving ipilimumab treatment for the first time or those who require a new copy. You can use the Patient Information Guide to discuss ipilimumab treatment.**

The Patient Information Guide will help patients understand their treatment and what to do if they experience adverse reactions (e.g. irARs). **It also includes a Patient Alert Card, with contact details, for patients to carry at all times.**



Patient Information Guide



Patient Alert Card

# Checklist for patient visits (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, even if these are mild, and to seek immediate medical attention should any adverse reaction occur or worsen, as some symptoms can worsen rapidly if not treated.
- Inform the patient that they may experience growth of existing tumours or develop new tumours, and that this does not necessarily mean that the treatment is ineffective.
- Conduct appropriate laboratory tests.
- Check for signs and symptoms of conditions that are in the WARNINGS and PRECAUTIONS or CONTRAINDICATIONS sections of the YERVOY prescribing information.

## **ANY FOLLOWING VISIT**

- Conduct 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 an adverse reaction, even if mild, as some can worsen rapidly if not treated.
- Remind the patient that early diagnosis and appropriate management are essential to minimise life-threatening complications.



**PBS Information: Section 100 Authority Required.  
Refer to PBS Schedule for full authority information.**

**NZ ONLY: YERVOY is an unfunded medicine. Charges for treatment with YERVOY including medicine costs and clinic/doctor charges will apply.**

Before prescribing YERVOY, please refer to the Product Information (AU) or YERVOY Data Sheet (NZ) which is available upon request from the BMS Medical Information department by calling 1800 067 567 (AU) / 0800 167 567 (NZ) or at [www.tga.gov.au](http://www.tga.gov.au) (AU) / [www.medsafe.govt.nz](http://www.medsafe.govt.nz) (NZ).

**WARNING: IMMUNE-MEDIATED ADVERSE EVENTS**

**YERVOY therapy should be administered and monitored under the supervision of physicians experienced in the treatment of cancer. YERVOY can cause severe and life-threatening immune-related adverse reactions (irARs), including enterocolitis, intestinal perforation, hepatitis, dermatitis (including toxic epidermal necrolysis), endocrinopathy (which may not be reversible), neuropathy, as well as irARs in other organ systems [see PRECAUTIONS and DOSAGE AND ADMINISTRATION]. Early diagnosis and appropriate management are essential to minimise life-threatening complications.**

**NAME OF THE MEDICINE:** YERVOY® (ipilimumab) 5mg/mL concentrate solution for infusion. NZ only: **CLASSIFICATION:** Prescription medicine. **INDICATIONS:** As monotherapy for the treatment of patients with unresectable or metastatic melanoma. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **PRECAUTIONS:** YERVOY is associated with immune-related adverse reactions (irARs) resulting from increased or excessive immune activity. Early diagnosis and appropriate management are essential to minimise life-threatening complications. Signs and symptoms suggestive of irARs relating to the gastrointestinal tract (diarrhoea, increased stool frequency, bloody stool), liver (liver function test [LFT] elevations), skin (rash) and endocrine system must be considered immune-related and YERVOY-associated unless an alternative aetiology is identified. While most irARs occurred during the induction period, some irARs occurred weeks to months after the last dose of YERVOY. Caution is recommended in patients with active autoimmune disease, those receiving immunosuppressive therapy or in patients with  $\geq 5 \times$  ULN transaminases or  $> 3 \times$  ULN bilirubin. Use in children or adolescents below 18 years of age is not recommended. Concurrent use of YERVOY and vemurafenib is not recommended. Pregnancy Category C. Refer to the Product Information (PI)/Data Sheet (DS) for a complete list of precautions. **INTERACTIONS WITH OTHER MEDICINES:** YERVOY is a human monoclonal antibody that is not metabolised by cytochrome P450 enzymes (CYPs) or other drug metabolising enzymes. YERVOY did not have a significant effect on the pharmacokinetics of substrates of CYP1A2, CYP2E1, CYP2C8 and CYP3A4 when coadministered with substrates of these CYP isozymes (dacarbazine or paclitaxel/carboplatin). **ADVERSE EFFECTS:** YERVOY is most commonly associated with adverse reactions resulting from increased or excessive immune activity. The most frequently reported adverse events ( $\geq 10\%$  of patients) were fatigue, diarrhoea, pruritus, rash, decreased appetite, nausea, vomiting, abdominal pain, cough, headache, pyrexia, infusion reaction and insomnia. Fatalities due to irARs have been reported in clinical trials. Serious irARs including cases of fatal hepatic failure, gastric perforations and toxic epidermal necrolysis have been reported in clinical trials with YERVOY. Other serious irARs such as Guillain-Barré syndrome, myasthenia gravis-like symptoms, severe sensory and motor neuropathies and severe endocrinopathies have also been reported in clinical trials with YERVOY. Please refer to the PI/DS for descriptions of these events. Other adverse effects include colitis, GI haemorrhage, hypotension and abnormal hepatic function. Please refer to the PI/DS for a full list of adverse events. **DOSAGE AND ADMINISTRATION:** Clinical chemistries (e.g., electrolytes, liver and thyroid functions) must be assessed before initiation of YERVOY at baseline and before each dose of YERVOY. Additionally, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, should be assessed during treatment with YERVOY. YERVOY must not be administered as an IV push or bolus injection. Patients should be monitored for the signs and symptoms of irARs during and after cessation of therapy. The recommended induction regimen of YERVOY is 3 mg/kg administered intravenously (IV) over a 90-minute period every 3 weeks for a total of four doses. Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response to YERVOY should be conducted only after completion of induction therapy. Additional treatment with YERVOY (re-induction with 4 doses) may be considered for patients who develop progressive disease after prior CR, PR or SD for  $\geq 3$  months. The recommended re-induction regimen of YERVOY is 3 mg/kg administered IV over a 90-minute period every 3 weeks for a total of four doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Management of immune-related toxicity may require withholding of a dose and initiation of corticosteroid or other immunosuppressive therapy or permanent discontinuation of YERVOY therapy. Please refer to the YERVOY PI/DS for a full description of guidelines. Please refer to full PI/DS for preparation and administration instructions. Each vial of YERVOY is for single use in one patient only. Store in a refrigerator (2°C to 8°C), do not freeze, protect from light. **PRESENTATION:** YERVOY (ipilimumab) concentrate solution for infusion (5 mg/mL) is available in 10 mL vials containing 50 mg of ipilimumab or 40 mL vials containing 200 mg of ipilimumab. Prepared from the Product Information/Data Sheet.

**REFERENCES:** 1. YERVOY (ipilimumab) Product Information, (<http://www.medicines.org.au/files/bqpyervo.pdf>). 2. YERVOY (ipilimumab) Data Sheet, June 2017 (NZ). 3. Ascierto PA and Marincola FM. *J Transl Med* 2014;12:141. 4. Wolchok JD and Saenger Y. *The Oncologist* 2008;13(Suppl 4):2–9. 5. Jochems C and Schlom J. *Exp Biol Med* (Maywood) 2011;236:567–79. 6. Robert L et al. *Clin Cancer Res* 2014;20:2424–32. 7. Kannan R et al. *Clin J Oncol Nurs* 2014;18:311–7.

© 2017 Bristol-Myers Squibb. YERVOY® is a registered trademark of Bristol-Myers Squibb Company. **BMS Medical Information:** 1800 067 567 (AU) / 0800 167 567 (NZ). Bristol-Myers Squibb Australia Pty Ltd, ABN 33 004 333 322, 4 Nexus Court, Mulgrave, VIC 3170. Bristol-Myers Squibb New Zealand Ltd, 88 Shortland St, Auckland, 1010. Mercury approval: 731AU1703488. TAPS approval: MR5323. Date of preparation: October 2017. BMSA0440.



**Bristol-Myers Squibb**



**Immuno-Oncology**

**YERVOY®**  
(ipilimumab)