

Ipilimumab Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of advanced (unresectable or metastatic) melanoma in adults	C43	00105a	ODMS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Ipilimumab is administered once every 21 days for a total of 4 doses until disease progression or unacceptable toxicity develops. 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 should be conducted only after completion of induction therapy.

Facilities to treat anaphylaxis MUST be present when ipilimumab is administered.

Drug	Dose	Route	Diluent & Rate	Cycle
Ipilimumab	3mg/kg	IV infusion Observe post infusion*	0.9% NaCl to a concentration between 1 and 4mg/ml over 90min using a 0.2-1.2 micron low-protein binding in-line filter.	Every 21 days for 4 cycles
Ipilimumab must not be administered as an intravenous push or bolus injection.				
*Vital signs including temperature, pulse and BP should be taken every 30mins for the duration of the infusion and 1 hour following completion of the infusion.				
The line should be flushed with 0.9% sodium chloride after the ipilimumab infusion has finished.				

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Adequate haematological, hepatic and renal function
- Life expectancy > 4 months.
- No systemic treatment for metastatic disease within previous 28 days

EXCLUSIONS:

- Hypersensitivity to ipilimumab or any of the excipients
- Patients who have previously received treatment with PD-1/ PD-L1 inhibitors*
- Uncontrolled brain metastases.
- Co-morbidity or mental incapacity which would, in the opinion of the treating oncologist, preclude treatment.
- History of autoimmune disease including: inflammatory bowel disease, SLE, Guillain- Barré syndrome
- Presence of HIV, Hepatitis B or C.

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- Concomitant high dose steroids or other immunosuppressive therapy.
- Previous treatment with ipilimumab. (Exceptional circumstances suggesting the requirement to retreat a patient should be discussed in advance of treatment with the NCCP).

**Prescribers should contact NCCP directly re patients who are intolerant to PD-1/PD-L1 inhibitors*

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- Blood, liver and renal profile
- Glucose
- TFTs
- Hepatitis B (HBV sAg) and Hepatitis C (HCV RNA)

Regular tests:

- Blood, liver and renal profile and glucose prior to each cycle
- TFTs prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of ipilimumab therapy and institution of systemic high-dose corticosteroid.
- Dose reduction is not recommended.
- Guidelines for withholding of doses or permanent discontinuation are described in tables 1 and 2.

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Table 1: When to withhold dose of ipilimumab

Mild to moderate Adverse Reactions	Action
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs	<ol style="list-style-type: none"> Omit dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). If resolution occurs before the next scheduled dose, resume therapy at next scheduled dose^b. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule.^b Discontinue ipilimumab if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic: Grade 2 elevation in AST, ALT or total bilirubin	
Skin: Moderate to severe (Grade 3) ^a skin rash or widespread/intense pruritus regardless of etiology	
Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy	
Neurological: Moderate (Grade 2) ^a unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	
Other moderate adverse reactions^c	

Table 2: When to permanently discontinue ipilimumab

Severe Adverse Reaction	Grade ^a
Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity	Grade 3 or 4 elevation in AST, ALT or total bilirubin.
Skin: Life threatening skin rash (including Stevens- Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	Grade 4 rash or Grade 3 pruritus
Neurologic: New onset or worsening severe motor or sensory neuropathy	Grade 3 or 4 motor or sensory neuropathy

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Other organ systems^c: (e.g. nephritis, pneumonitis, pancreatitis, non- infectious myocarditis)	\geq Grade 3 immune-related events ^d \geq Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy.
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^aNCI- CTCAE v4.

^bUntil administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.

^cAny other adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. Decision whether to withhold/discontinue ipilimumab should be based on severity.

^dPatients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.

Renal and Hepatic Impairment:

Table 3: Dose modification of ipilimumab in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Ipilimumab	No specific dose adjustment is necessary in patients with mild to moderate renal dysfunction.	Administer with caution in patients with transaminase levels $\geq 5 \times$ ULN or bilirubin levels $>3 \times$ ULN at baseline.

ULN = upper limit of normal

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (Refer to local policy).

PREMEDICATIONS: Not usually required. Pre-medication with paracetamol and an antihistamine may be considered in patients who experience mild or moderate infusion – related reactions.

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- Immune-mediated adverse reactions:**

- Ipilimumab can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.
- The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.
- Ipilimumab should be permanently discontinued and systemic high dose corticosteroid therapy initiated for severe immune-mediated reactions. Patients should be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy and clinical chemistries evaluated including liver function tests and thyroid function tests at baseline and before each dose.
- Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and ipilimumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening

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complications.

- Cases of cytomegalovirus (CMV) infection/reactivation have been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up should be performed upon presentation of diarrhoea or colitis to exclude infectious or other alternate etiologies.
- Management of immune-related adverse reactions may require high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy. Specific guidelines for management of Immune Mediated Adverse Events are available.
- **Infusion-related reactions:** Isolated cases of severe reaction have been reported. In case of a severe reaction, ipilimumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab with close monitoring. Premedications with paracetamol and anti-histamine may be considered. Specific guidelines are available for the management of infusion-related reactions (2) and are detailed below

For mild symptoms:

- For localized cutaneous reactions such as mild pruritus, flushing, and rash, decrease the rate of infusion until recovery from symptoms, remain at bedside, and monitor patient; complete ipilimumab or placebo infusion at the initial planned rate.
- Diphenhydramine 50 mg may be administered at the discretion of the treating physician.
- Patients may receive additional doses with close monitoring; premedication may be given at the discretion of the investigator.

For moderate symptoms:

- For any symptoms not considered mild or severe, eg, generalized pruritus, flushing, rash, dyspnea, and hypotension with systolic blood pressure greater than 80 mm Hg, interrupt ipilimumab infusion, administer diphenhydramine 50 mg intravenously, remain at bedside, and monitor patient until resolution of symptoms.
- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician. Resume ipilimumab infusion after recovery from symptoms.
- At the discretion of the treating physician, ipilimumab infusion may be resumed at one-half the initial infusion rate and then increased gradually to the initial infusion rate. If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
- The next dose of ipilimumab may be given with premedication (diphenhydramine and paracetamol and careful monitoring, following the same treatment guidelines outlined above.
- At the discretion of the treating physician, additional oral or IV antihistamine may be administered.

For severe symptoms:

- For any reaction such as bronchospasm, generalized urticaria, systolic blood pressure < 80 mm Hg, or angioedema, the infusion of ipilimumab must be immediately discontinued.
- Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV, as needed.
- Patients should be monitored until the investigator is comfortable that the symptoms will not recur. No further ipilimumab should be administered.
- In case of late-occurring hypersensitivity symptoms (e.g., appearance within 1 week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

- **Patients with auto-immune disease:** Ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening. In

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other patients with a history of autoimmune disease, ipilimumab should be used with caution after careful consideration of the potential risk-benefit on an individual basis.

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DRUG INTERACTIONS:

- The use of systemic corticosteroids or immunosuppressants before starting ipilimumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of nivolumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions
- Concomitant use of ipilimumab with anti-coagulants may increase risk of GI haemorrhage so close monitoring is required.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Ipilimumab L01XC11

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

HCP Guide:

<https://www.hpra.ie/img/uploaded/swedocuments/1cf868fa-4933-4240-874e-2c648af1e139.pdf>

Patient Information and Alert Card:

<https://www.hpra.ie/img/uploaded/swedocuments/2a69a6f6-b3cb-4341-8214-660e0b84e621.pdf>

<https://www.hpra.ie/img/uploaded/swedocuments/e3951065-f4d0-487b-bc90-b015b1ed6604.pdf>

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3. Ipilimumab (Yervoy®) Summary of Product Characteristics. Last updated: 20/12/2019 Accessed Jan 2020. Available at https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf

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Version	Date	Amendment	Approved By
1	28/6/2011		Dr Paul Donnellan
2	29/4/2014	Reformat to new template Previous treatment with ipilimumab added to exclusion list.	Dr Paul Donnellan Dr Maccon Keane
3	25/3/2016	Inserted standard wording re treatment. Updated adverse reactions/regimen specific complications	Dr Maccon Keane
4	08/06/2016	Previous treatment with PD-1/ PDL-1inhibitors added to exclusion list Updated infusion related reaction management	Dr Maccon Keane
5	17/01/2018	Updated with new NCCP regimen template, updated dosing for hepatic adverse reactions as per SmpC	Prof Maccon Keane
6	14/01/2020	Reviewed. Standardisation of treatment table. Update of adverse events	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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