Ipilimumab Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of advanced (unresectable or metastatic) melanoma in adults	C43	00105a	ODMS

*This applies to post 2012 indications only

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 patients individual clinical circumstances.

Ipilimumab is administered once every 21 days for a total of 4 doses until disease progression or unacceptable toxicity develops, whichever is first. 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 90 minutes 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 blood pressure should be taken every 30 minutes for the duration of the infusion and 1 hour following completion of the infusion.				
The line should be flushed with 0.9% NaCl after the ipilimumab infusion has finished.				

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Adequate haematological, hepatic and renal function

EXCLUSIONS:

- Hypersensitivity to ipilimumab or any of the excipients

CAUTIONS:

- Presence of HIV, Hepatitis B or C
- Uncontrolled brain metastases
- History of autoimmune disease including: inflammatory bowel disease, SLE, Guillain- Barré syndrome
- Concomitant high dose steroids or other immunosuppressive therapy

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, liver and renal profile
- Blood glucose
- TFTs

Regular tests:

- FBC, liver, renal profile and blood 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.

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	1. Omit dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs before the next scheduled dose, resume therapy at next scheduled dose[b]. 3. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule[b] 4. 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 aetiology	
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

Other organ systems[c]: (e.g. nephritis, pneumonitis, pancreatitis, non- infectious myocarditis)	• ≥ Grade 3 immune-related events[d] • ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy. • Grade 4 diabetes

[a]NCI- CTCAE v4.
[b]Until administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.
[c]Any 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.
[d] Patients 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
Ipilumumab	No dose adjustment is needed Haemodialysis: No need for dose adjustment is expected	No need for dose adjustment is expected
Renal and hepatic dose modifications from Giraud et al 2023		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

Ipilimumab : Low (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

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

Patient Information Guide and Alert Card:

https://assets.hpra.ie/products/Human/9440/0781c3d7-ff8d-4cc7-9f0a-80cf9a10e59f.pdf

REFERENCES:

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2. Premedication and management of infusion reactions associated with ipilimumab administration. Bristol Myers Squibb Pharmaceuticals
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Ipilimumab (Yervoy®) Summary of Product Characteristics. Last updated: 22/07/2024. Accessed December 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	28/06/2011		Dr Paul Donnellan
2	29/04/2014	Reformat to new template Previous treatment with ipilimumab added to exclusion list.	Dr Paul Donnellan Dr Maccon Keane
3	25/03/2016	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	Dr Maccon Keane

		management	
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
7	24/02/2025	Regimen reviewed. Updated eligibility and exclusions section. Added cautions section.Updated standard wording in baseline tests section. Updated renal and hepatic dose modifications to align with Giraud et al. Updated regimen to align with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.