Atezolizumab Monotherapy – 21 Day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.	C34	00544a	ODMS 01/03/2019 (IV) 01/06/2024 (SC)
Treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC) after prior platinum-containing chemotherapy.	C65, C66, C67, C68	00544b	ODMS 01/03/2021 (IV) 01/06/2024 (SC)
Treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥5%.	C65, C66, C67, C68	00544c	ODMS 01/07/2021 (IV) 01/06/2024 (SC)
As monotherapy for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.	C34	00544d	ODMS 01/10/2021 (IV) 01/06/2024 (SC)
Adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with non-small cell lung cancer (NSCLC) with a high risk of recurrence whose tumours have PD-L1 expression on ≥50% of tumour cells and who do not have EGFR mutant or ALK-positive mutations.	C34	00544e	ODMS 05/03/2024 (IV) 01/06/2024 (SC)

* This is for 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.

For locally advanced or metastatic indications atezolizumab is administered once every **21 days** until disease progression or unacceptable toxicity develops.

For **adjuvant NSCLC** atezolizumab is administered once every 21 days for a maximum treatment duration of **12 months** unless disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer treatment (SACT) is administered.

There are two different formulations of atezolizumab available depending on the route of administration, see Table 1 and Table 2 below which refer to intravenous and subcutaneous administration routes respectively.

Table 1: Treatment Schedule for Atezolizumab (IV) Monotherapy – 21 Day

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Atezolizumab	1200mg	IV infusion*	250mL 0.9% NaCl over 60 minutes [a]	Every 21 days [b]
[a] Initial dose must be given over 60 minutes; subsequent doses may be given over 30 minutes if tolerated					
[b] If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.					
*See alternative treatment schedule for Atezolizumab SC below.					

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

ALTERNATIVE TREATMENT SCHEDULE:

Table 2: Treatment Schedule for Atezolizumab (SC) Monotherapy – 21 Day

Day	Drug	Dose	Route	Rate	Cycle
1	Atezolizumab	1875mg	Subcutaneous*	Over 7 minutes [a]	Every 21 days [b]
[a] Use of a subcutaneous infusion set (e.g. winged/butterfly) is recommended. The remaining residual hold-up volume in the tubing should not be administered to the patient. The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard.					
[b] If a planned dose of atezolizumab is missed, it should be administered as soon as possible, it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.					
*See alternative treatment schedule for Atezolizumab IV above.					

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Adequate haematological and organ function
- **Non-Small Cell Lung Cancer (NSCLC): adjuvant (00544e)**
  - Complete resection of stage II to IIIA NSCLC as per the UICC/AJCC staging system 7th Edition
  - Confirmation of PD-L1 expression on ≥50% of tumour cells as demonstrated by a validated test method on the resection specimen of NSCLC of predominantly non-squamous type
  - No EGFR or ALK mutation
  - Must have completed platinum- based adjuvant chemotherapy commenced within 12 weeks of resection of NSCLC without disease progression
  - Adjuvant atezolizumab should start within 12 weeks or less from the last cycle of adjuvant platinum-based chemotherapy

- **NSCLC: First Line metastatic (00544d)**
  - Histologically or cytologically confirmed stage IV non-squamous or squamous NSCLC with no sensitizing EGFR mutations or ALK translocations
  - No prior treatment for Stage IV non-squamous or squamous NSCLC
  - Confirmation of PD-L1 tumour proportion score of ≥ 50% or PD-L1 stained tumour-infiltrating immune cells (IC) tumour area (IC ≥ 10%) by a validated test. Patients who have received prior neo-adjuvant, adjuvant chemotherapy or chemoradiotherapy for non-metastatic disease must have experienced a treatment-free interval of at least 6 months since the last chemotherapy or chemoradiotherapy cycle

- **NSCLC : Second Line metastatic (00544a)**
  - Locally advanced or metastatic (Stage IIIB, Stage IV, or recurrent) NSCLC
  - Prior treatment with ≥1 platinum based combination chemotherapy regimen
  - Patients with EGFR mutations or an ALK fusion oncogene are required to have received previous tyrosine kinase inhibitor therapy

- **Urothelial Carcinoma: First Line metastatic (00544c)**
  - Locally advanced or metastatic urothelial carcinoma that shows predominantly transitional-cell features on histologic testing
  - PD-L1 expression ≥5% as demonstrated by a validated test method

- **Urothelial Carcinoma: Second Line metastatic (00544b)**
  - Locally advanced or metastatic urothelial carcinoma that shows predominantly transitional-cell features on histologic testing
  - Prior treatment with ≥1 platinum based combination chemotherapy regimen

CAUTION:

Use with caution in:

- Patients with clinically significant autoimmune disease

EXCLUSIONS:

- Hypersensitivity to atezolizumab or any of the excipients
- Symptomatic central nervous system (CNS) metastases
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids)
- Symptomatic interstitial lung disease
- Any active clinically significant infection requiring therapy
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is available here

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- TFTs
- Virology Screen: Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- First line **metastatic** Urothelial Cancer **(00544c)**:
  - PD-L1 testing using the SP142 Antibody on the Ventana platform
- Adjuvant NSCLC (**00544e)**:
  - PD-L1 testing using SP263 Antibody on the Ventana platform on resection specimen. PD-L1 testing will only be carried out on the request of a Consultant Medical Oncologist or following a tumour conference recommendation.
  - EGFR and ALK testing using a validated test method and may be carried out in parallel or sequential to PD-L1 testing
- First Line metastatic NSCLC **(00544d)**
  - PD-L1 testing using the SP142 antibody on the Ventana platform on the request of a Consult Medical Oncologist on patients who do not have EGFR mutant or ALK-positive NSCLC where there is an intention to treat with atezolizumab in line with this licensed indication
  - EGFR and ALK testing using a validated test method.

Regular tests:

- FBC, renal, liver profile and glucose prior to each cycle
- TFTs every 3 to 6 weeks

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
- Dose reduction of atezolizumab is not recommended
- Guidelines for withholding of doses or permanent discontinuation are described below in Table 3

Table 3: Guidelines for withholding or discontinuation of atezolizumab

Immune-mediated adverse reaction	Treatment modification
Pneumonitis Grade 2	Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day
Grade 3 or 4	Permanently discontinue atezolizumab

Immune-mediated adverse reaction	Treatment modification
Hepatitis Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] or blood bilirubin > 1.5 to 3 x ULN) Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day Permanently discontinue atezolizumab
Colitis Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone equivalent per day Permanently discontinue atezolizumab
Hypothyroidism or hyperthyroidism Symptomatic	Withhold atezolizumab. **Hypothyroidism**: Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing **Hyperthyroidism:** Treatment may be resumed when symptoms are controlled by anti-thyroid medicinal product and thyroid function is improving
Adrenal insufficiency Symptomatic	Withhold atezolizumab. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day and patient is stable on replacement therapy
Hypophysitis Grade 2 or 3 Grade 4	Withhold atezolizumab. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day and patient is stable on replacement therapy. Permanently discontinue atezolizumab
Type 1 diabetes mellitus Grade 3 or 4 hyperglycaemia (fasting glucose >250 mg/dL or 13.9 mmol/L)	Withhold atezolizumab. Treatment may be resumed when metabolic control is achieved on insulin replacement therapy.
Rash/Severe cutaneous adverse reaction Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1] Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Withhold atezolizumab. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day Permanently discontinue atezolizumab
Myasthenic syndrome/ myasthenia gravis, Guillain-Barré syndrome, Meningoencephalitis and Facial paresis	

Immune-mediated adverse reaction	Treatment modification
Facial paresis Grade 1 or 2 All grades or Facial paresis Grade 3 or 4	Withhold atezolizumab. Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding atezolizumab, permanently discontinue atezolizumab. Permanently discontinue atezolizumab
Myelitis Grade 2,3 or 4	Permanently discontinue atezolizumab
Pancreatitis Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis Grade 4 or any grade of recurrent pancreatitis	Withhold atezolizumab. Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day. Permanently discontinue atezolizumab
Myocarditis Grade 2 or above	Permanently discontinue atezolizumab
Nephritis Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN) Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Withhold atezolizumab.Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day Permanently discontinue atezolizumab
Myositis Grade 2 or 3 Grade 4 or recurrent Grade 3	Withhold atezolizumab Permanently discontinue atezolizumab
Pericardial disorders Grade 1 Grade 2 or above	Withhold atezolizumab[2] Permanently discontinue atezolizumab
Haemophagocytic lymphohistiocytosis Suspected haemophagocytic lymphohistiocytosis[1]	Permanently discontinue atezolizumab
Other immune-mediated adverse reactions Grade 2 or Grade 3 Grade 4 or recurrent Grade 3	Withhold until adverse reaction recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10mg prednisolone or equivalent per day. Permanently discontinue atezolizumab (except endocrinopathies controlled with replacement hormones)

Immune-mediated adverse reaction	Treatment modification
Other adverse reactions **Infusion-related or Subcutaneous-related Reactions**	
Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved
Grade 3 or 4	Permanently discontinue atezolizumab
Note: Toxicity should be graded with the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).	
[1] Regardless of severity [2] Conduct a detailed cardiac evaluation to determine the etiology and manage appropriately	

Renal and Hepatic Impairment:

Table 4: Dose modification of atezolizumab[a] in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
CrCl (mL/min)	**Dose**	**Mild**	No dose adjustment is needed
≥30	No dose adjustment is needed	**Moderate/Severe**	No need for dose adjustment is expected
<30	No need for dose for dose adjustment is expected		
Haemodialysis	No need for dose for dose adjustment is expected		
[a] Atezolizumab: Renal and hepatic dose recommendations from Giraud et al. (2023)			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here:

Atezolizumab: Minimal (**Refer to local policy).**

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

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS:

- None usually required unless patient has experienced a previous hypersensitivity reaction.
- Patients with Grade 1 or 2 infusion-related or subcutaneous-related reaction may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered as clinically indicated.

OTHER SUPPORTIVE CARE:

- Women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab.

ADVERSE EFFECTS

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

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

DRUG INTERACTIONS:

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

COMPANY SUPPORT RESOURCES/Useful Links:

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

Patient Alert Card
https://www.hpra.ie/img/uploaded/swedocuments/b5b77d64-e247-4fd0-bdcb-f5aea32e03a1.pdf

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Version	Date	Amendment	Approved By
1	01/03/2019		Dr Richard Bambury
2	11/03/2019	Updated immune related adverse reactions regarding nephritis	Dr Richard Bambury
3	24/07/2019	Addition of new indication for urothelial carcinoma Inclusion of caution for use in patients with history of serious auto-immune disease Updated immune related adverse reactions regarding myositis	Prof Maccon Keane
4	24/09/2019	Clarification of eligibility criteria and baseline testing	Prof Maccon Keane
5	19/08/2020	Updated emetogenic potential	Prof Maccon Keane
6	01/03/2021	Updated reimbursement status	Prof Maccon Keane
7	30/03/2021	Updated adverse effects with respect to HPRA safety update and risk of SCARS.	Prof Maccon Keane
8	01/07/2021	Addition of new indication for urothelial carcinoma. Updated company support resources.	Prof Maccon Keane
9	09/09/2021	Reviewed. Updated Table 1 (Rash/SCAR, myositis), amended dose modification in hepatic impairment.	Prof Maccon Keane
10	01/10/2021	Addition of new indication: first line treatment of metastatic NSCLC.	Prof Maccon Keane
11	16/12/2022	Amended dose modifications table	Prof Maccon Keane
12	19/02/2024	Addition of new indication: adjuvant treatment of NSCLC. Updated Table 1 in line with SmPC update. Updated dosing recommendation for renal and hepatic impairment in line with Giraud et al.	Prof Maccon Keane
13	14/06/2024	- Amended regimen title - Added subcutaneous formulation option (Table 2) - Updated Table 3 to align with revised SmPC - Updated Supportive Care section to align with revised SmPC - Updated Adverse Effects and Drug Interactions section to align with NCCP Standardisation - NCCP Standardisation	Prof Maccon Keane
13a	08/05/2025	- Update to ICD-10 codes	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.