Atezolizumab 1680mg Monotherapy – 28 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	00593a	ODMS 01/03/2019
Treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC) after prior platinum-containing chemotherapy	C67	00593b	ODMS 01/03/2021
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%	C67	00593c	ODMS 01/07/2021
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	00593d	ODMS 01/10/2021
For the maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), where this is a continuation of treatment for patients who have completed the induction chemotherapy component of the treatment	C34	00593e	ODMS 01/03/2022
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	00593f	ODMS 05/03/2024

* 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 28 days until disease progression or unacceptable toxicity develops.

For adjuvant NSCLC atezolizumab is administered once every 28 days for a maximum treatment duration of 12 months unless disease progression or unacceptable toxicity develops.
Facilities to treat anaphylaxis MUST be present when atezolizumab is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Atezolizumab	1680mg	IV infusion	250ml 0.9% NaCl over 60 minutes [a]	Every 28 days
[a]Initial dose must be given over 60 minutes; subsequent doses may be given over 30 minutes if tolerated.					
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 4-week interval between doses.					

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Adequate haematological and organ function
- **Non-Small Cell Lung Cancer (NSCLC): adjuvant (00593f)**
  - 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 (**00593d**)**
  - 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 (00593a)**
  - 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** 00593c)
  - 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** 00593b)
  - Locally advanced or metastatic urothelial carcinoma that shows predominantly transitional-cell features on histologic testing prior treatment with ≥1 platinum based combination chemotherapy regimen

- **Small Cell Lung Cancer: First line (**00593e)
  - ≥18 years
  - No prior systemic treatment for ES-SCLC

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 **(00593c)**
  - PD-L1 testing using the SP142 Antibody on the Ventana platform
- **Adjuvant NSCLC (00593f)**
  - PD-L1 expression 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 (00593d)**
  - 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 1.

Table 1: Guidelines for withholding or discontinuation of atezolizumab

Immune related adverse reaction	Treatment modification
Pneumonitis Grade 2 Grade 3 or 4	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
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 antithyroid medicinal product and thyroid function is improving.

Immune related adverse reaction	Treatment modification
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 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.

Immune related adverse reaction	Treatment modification
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-related adverse reactions Grade 2 or Grade 3 Grade 4 or recurrent Grade 3	Withhold until adverse reactions 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).
Other adverse reactions **Infusion-related Reactions** Grade 1 or 2 Grade 3 or 4	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved Permanently discontinue atezolizumab
Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).	
[1]Regardless of severity	
[2] Conduct a detailed cardiac evaluation to determine the etiology and manage appropriately	

Renal and Hepatic Impairment:

Table 2: Dose modification of atezolizumab 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		
<30	No need for dose for dose adjustment is expected	**Moderate/Severe**	No need for dose for dose adjustment is expected
Haemodialysis	No need for dose for dose adjustment is expected		
Renal and hepatic dose recommendations from Giraud et al.			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: Not usually required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

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

- **Immune-mediated adverse reactions:** Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab. For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered. Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones.
- **Infusion related reactions:** have been observed in clinical trials with atezolizumab. The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

- **Immune-related severe cutaneous adverse reactions (SCARs):** Immune-related severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. In case a SCAR is suspected, atezolizumab should be withheld and patients should be referred to a specialist in SCARs for diagnosis and treatment. If SJS or TEN is confirmed, and for any grade 4 rash/SCAR, treatment with atezolizumab should be permanently discontinued. Caution is recommended when considering the use of atezolizumab in patients with previous history of a severe or life-threatening SCAR with other immune-stimulatory cancer medicines.

DRUG INTERACTIONS:

- No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab.
- Current 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 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	09/04/2020		Prof Maccon Keane
2	19/08/2020	Updated emetogenic potential	Prof Maccon Keane
3	01/03/2021	Updated reimbursement status	Prof Maccon Keane
4	31/03/2021	Updated adverse effects with respect to HPRA safety update and risk of SCARS.	Prof Maccon Keane
5	01/07/2021	Addition of new indication for urothelial carcinoma. Updated company support resources.	Prof Maccon Keane
6	09/09/2021	Reviewed. Updated Table 1 (Rash/SCAR, myositis), amended dose modification in hepatic impairment, amended adverse effects (SCARS nomenclature).	Prof Maccon Keane
7	01/10/2021	Addition of new indication: first line treatment of metastatic NSCLC.	Prof Maccon Keane
8	08/07/2022	Addition of new indication	Prof Maccon Keane
9	16/12/2022	Amended dose modifications table	Prof Maccon Keane
10	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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.