6.09 ATEZOLIZUMAB, Solution concentrate for I.V. infusion 840 mg in 14 mL, Tecentriq®, Roche Products Pty Ltd.

1 Purpose of Application

1.1 The minor submission requested extending the November 2019 PBAC recommendation for a new form of atezolizumab (840 mg/14 mL injection) and additional 1680 mg every 4 weeks (Q4W) dosing regimen to include the treatment of previously untreated patients with extensive stage small cell lung cancer (1L ES-SCLC) when atezolizumab monotherapy is used for continuing treatment.

1.2 The minor submission did not request the addition of the 1680 mg Q4W dosing regimen to the 1200 mg every 3 weeks (Q3W) dosing regimen for initial treatment, given atezolizumab is administered every 3 weeks for 4 cycles in combination with carboplatin and etoposide during the initial treatment phase for 1L ES-SCLC.

2 Requested listing

2.1 The minor submission requested the same restriction as the existing PBS listing for continuing treatment of 1L ES-SCLC with the exception of a maximum amount of 1680 mg and number of repeats (3) to reflect the changes in drug administration and duration of treatment for the continuing treatment phase of 1L ES-SCLC.

2.2 The proposed restrictions are provided below with Secretariat suggested additions in italics and deletions in strikethrough.

Name, Restriction, Manner of administration and form	Max. amount	№.of Rpts	Proprietary Name and Manufacturer	
ATEZOLIZUMAB 840 mg/14 mL injection, ~~1 x~~ 14 mL vial [*new MPP*]	1680 mg	3	Tecentriq®	Roche Products Pty Ltd

New 4-weekly continuing treatment Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy - Public hospitals / Private hospitals
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Authority Required – Streamlined
	Severity: Extensive-stage ~~primary~~
	Condition: ~~Small cell carcinoma of lung~~ *small cell lung cancer*
24247	**Indication:** ~~Extensive-stage primary small cell carcinoma of lung~~ *Extensive-stage small cell lung cancer*
	Treatment Phase: Continuing treatment
7910	**Clinical criteria:**
7909	The treatment must be as monotherapy

	AND
11365	**Clinical criteria:**
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
23679	**Clinical criteria:**
23678	Patient must not have developed disease progression while being treated with this drug for this condition
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised
7608	**Administrative Advice:** Special Pricing Arrangements apply

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Background

Registration status

3.1 Atezolizumab 840 mg in 14 mL injection for the 1680 mg Q4W dosing regimen is currently TGA registered for the following indications:

- Second-line treatment as monotherapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.
- First-line treatment of patients with metastatic non-squamous NSCLC in combination with bevacizumab, paclitaxel and carboplatin. Atezolizumab 840 mg injection can be administered as monotherapy when bevacizumab is discontinued during the maintenance phase.
- First-line treatment of patients with ES-SCLC in combination with carboplatin and etoposide, and that atezolizumab 840 mg be administered as monotherapy during the maintenance phase without chemotherapy.
- Treatment as monotherapy for patients with locally advanced or metastatic urothelial carcinoma (mUC) who are considered cisplatin ineligible and whose tumours express PD-L1, as determined by a validated test, or are considered ineligible for any other platinum-containing chemotherapy regardless of the level of tumour PD-L1 expression.
- Treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) in combination with paclitaxel protein-bound, whose tumours express PD-L1 as determined by a validated test and who have not received prior chemotherapy for metastatic disease. Atezolizumab 840 mg injection is administered on days 1 and 15, followed by 100 mg/m^2 nab-paclitaxel (nanoparticle albumin-bound paclitaxel) on days 1, 8 and 15 for each 28-day cycle.

Previous PBAC consideration

3.2 Atezolizumab 1200 mg/20 mL injection is currently listed on the PBS for the treatment of locally advanced or metastatic NSCLC as monotherapy (2L NSCLC) and Stage IV (metastatic) NSCLC in combination treatment with bevacizumab and platinum-doublet chemotherapy (1L NSCLC).

3.3 At its November 2019 meeting, the PBAC recommended the Section 100 (Efficient Funding of Chemotherapy Program), Authority Required (STREAMLINED) listing of atezolizumab for the treatment of previously untreated patients with ES-SCLC when used as combination therapy with carboplatin and etoposide initially, then as monotherapy for continuing treatment. Atezolizumab was PBS listed for 1L ES-SCLC on 1 March 2020.

3.4 At its November 2019 meeting, the PBAC also recommended the Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing of atezolizumab 840 mg/14 mL injection and additional 1680 mg Q4W dosing regimen for the existing PBS indications for 2L NSCLC and 1L NSCLC where atezolizumab is administered as monotherapy.

3.5 Atezolizumab 840 mg/14 mL injection and the 1680 mg Q4W dosing regimen for 1L ES-SCLC has not been previously considered by the PBAC.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

4.1 The proposed comparator, atezolizumab 1200 mg Q3W, was previously considered by PBAC to be the appropriate main comparator in its November 2019 consideration of atezolizumab 1680 mg Q4W for 2L and 1L NSCLC indications (paragraph 6.3, atezolizumab Public Summary Document (PSD), November 2019).

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from organisations (1) via the Consumer Comments facility on the PBS website. Lung Foundation Australia indicated its support for the addition of a 1680 mg Q4W flat dosing regimen as the less frequent dosing option would provide greater flexibility and reduce any burden on patients associated with treatment.

Clinical trials

5.3 The minor submission presented pharmacokinetics (PK) modelling of atezolizumab dosing regimens and an exposure-response (E-R) analysis, based on pooled data from 3 clinical studies in patients with mUC and NSCLC. The Secretariat noted that the same PK modelling and E-R analysis were considered for the 1680 mg Q4W dosing regimen for NSCLC by the PBAC in November 2019. No new evidence for 1L ES-SCLC was included in this submission.

5.4 In the November 2019 submission for NSCLC, the results of the PK simulations and E-R analysis showed that no clinically meaningful E-R relationships for efficacy and safety were identified for atezolizumab monotherapy in mUC or NSCLC patients, and the additional 1680 mg Q4W dosing regimen was expected to achieve comparable overall exposure to that of the 1200 mg Q3W regimen.

5.5 The PBAC previously considered that based on the evidence presented, the 1680 mg Q4W dosing regimen was likely comparable to the 1200 mg Q3W dosing regimen when used as monotherapy for NSCLC, in the absence of new clinical data to support the claim of non-inferiority in terms of efficacy and safety (paragraph 6.2, atezolizumab PSD, November 2019).

5.6 As a minor submission, the analyses were not independently evaluated.

Clinical claim

5.7 The minor submission claimed that based on the PK modelling and the E-R analysis, atezolizumab 1680 mg administered Q4W is equally effective and safe as atezolizumab 1200 mg administered Q3W.

5.8 While the PBAC noted that no clinical evidence was provided, the PBAC considered that the 1680 mg Q4W dosing regimen is likely comparable to the 1200 mg Q3W dosing regimen in terms of effectiveness and safety, based on the available data.

Economic analysis

5.9 The minor submission presented a cost-minimisation analysis (CMA) comparing the 1680 mg Q4W dosing regimen to the 1200 mg Q3W dosing regimen, based on the proposed effective ex-manufacturer price (EEMP) of $[redacted] ([redacted]% rebate on the proposed published price of $5,233.41) per 840 mg vial in 1L ES-SCLC. A comparison of the costs per month (30.44 days on average) for the 1680 mg Q4W and 1200 mg Q3W dosing regimens is shown in Table 1 below.

Table 1: Cost-minimisation for 1L ES-SCLC at the proposed effective DPMA

	Atezolizumab 1200mg Q3W	Atezolizumab 1680mg Q4W
EEMP per administration[a]	$[redacted]	$[redacted]
EEMP per month[b]	$[redacted]	$[redacted]
Weighted[c] DPMA[d] per administration	$[redacted]	$[redacted]
Weighted DPMA per month	$[redacted]	$[redacted]
Cost of administration (IV infusion)[e]	$66.10	$66.10
Cost of administration per month	$95.81	$71.85
Total cost per administration	$[redacted]	$[redacted]
Total cost per month (cost-minimised)	**$[redacted]**	**$[redacted]**

Source: Table 5.1, p14 of the submission

Abbreviations: EEMP: effective ex-manufacturer price; DPMA: dispensed price for maximum amount

[a] Based on the proposed effective prices.

[b] Based on 1.45 administrations per month for Q3W dosing and 1.09 for Q4W dosing

[c] The weightings across public (34.3%) and private (65.7%) hospital settings were derived from the 2018 calendar year PBS utilisation data for nivolumab (11284X, 11277M, 11309F, 11297N) and atezolizumab (11153B, 11158G, 11143L,11152Y) in 2L NSCLC as a proxy for 1L

ES-SCLC.
[d] DPMA was calculated using EEMP and applicable fees and mark-ups under the Efficient Funding of Chemotherapy (EFC) initiative in the public and private hospital settings, which included the preparation fee ($85.06) in the public and private settings, and the ready prepared dispensing fee ($7.39), distribution fee ($27.02), diluent fee ($5.35) and mark ups at 1.4% of the drug cost in the private hospital setting only.
[e] Administration/infusion costs based on MBS item 13915

5.10 The CMA was calculated on a cost per month basis using the weighted effective DPMA, however, the Secretariat noted that pricing agreements be made under the *National Health Act 1953* at the ex-manufacturer level. Therefore, the Secretariat has presented the alternative CMA calculated at the ex-manufacturer level in Table 2.

5.11 The pre-PBAC response indicated that the alternative cost-minimised price of a 840 mg vial calculated by the Secretariat, using the EEMP of a 1200 mg vial and the MBS administration fee at 85% of the item cost, was not consistent with the PBAC recommended methodology for economic evaluations set out in the Manual of resource items and their associated unit costs (version 5.0). The pre-PBAC response argued that the PBAC's preferred approach, in accordance with this Manual, is to *'use the relevant MBS Schedule Fee for administering the medicine or preparation'* without explicit reference to rebate amount, and *'the price applied to the proposed medicine is the equivalent of the DPMA for the amount suitable for the average patient receiving the therapy*' when a Section 100 EFC (Efficient Funding of Chemotherapy) listing is being sought. The Secretariat noted that the guidance in the Manual of resource items and their associated unit costs is in the context of costs applied to economic models, which differs from the basis upon which prices for PBS listings are agreed under the *National Health Act 1953*.

Table 2: A comparison of the costs per month using the effective ex-manufacturer price of atezolizumab

	1200 mg Q3W	1680 mg Q4W
EEMP per administration	$[redacted][a]	$[redacted][b]
EEMP per 4 weeks	$[redacted]	$[redacted]
Cost of administration – 85% benefit (IV infusion)[c]	$56.20	
Cost of administration per 4 weeks	$74.93	$56.20
Total cost per 4 weeks (cost-minimised)	**$[redacted]**	**$[redacted]**

Source: alternative calculations performed by the Secretariat
Abbreviations: EEMP: effective ex-manufacturer price
[a] The proposed effective ex-manufacturer price (AEMP) of $[redacted] per 1,200 mg vial in November 2019 (paragraph 5.14, atezolizumab (ES-SCLC) PSD, November, 2019)
[b] Estimated effective ex-manufacturer price for atezolizumab 840 mg x 2 vials
[c] Administration/infusion costs of $66.10 based on MBS item 13915.

Estimated PBS usage & financial implications

5.12 The minor submission presented the financial estimates based on the predicted utilisation of atezolizumab 1200 mg Q3W for 1L ES-SCLC, which the PBAC considered were sufficiently reliable to form the basis for the RSA in November 2019 (paragraph 6.10, atezolizumab (ES-SCLC) PSD, November, 2019). The estimated use and financial implications for the addition of atezolizumab 1680 mg Q4W dosing regimen as monotherapy for continuing treatment in 1L ES-SCLC is presented below in Table 3.

Table 3: Estimated use and financial implications for 1L ES-SCLC as monotherapy for continuing treatment

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients[a] for continuing treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of atezolizumab 1680 mg Q4W – Continuing treatment						
Number of scripts dispensed[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for atezolizumab 1200 mg Q3W – Continuing treatment						
Number of scripts dispensed[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments[e]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS[f]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to Government	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Sensitivity analysis: uptake rate 100% → 50%[g]						
Net cost to Government	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

[a] Number of patients were estimated using an epidemiologic approach based on data reported by Australian Institute of Health and Welfare and Australian hospital registries in the previous submission for 1L ES-SCLC (atezolizumab PSD, July 2019).
[b] Number of treatment cycles (3.68 cycles) for continuing treatment at a dose of 1680 mg Q4W = the extrapolated mean treatment duration of 6.17 months (8.91 cycles) – number of treatment cycles (4 cycles) for initial treatment at a dose of 1200 mg Q3W
[c] The financial estimates incorporated the effective DPMA of $[redacted] per 840 mg vial weighted at public (34.3%) and private (65.7%) hospital settings.
[d] Number of treatment cycles (4.91 cycles) for continuing treatment at a dose of 1200 mg Q3W = the extrapolated mean treatment duration of 6.17 months (8.91 cycles) – number of treatment cycles (4 cycles) for initial treatment at a dose of 1200 mg Q3W
[e] The financial estimates incorporated the effective DPMA of $[redacted] per 1200 mg vial weighted at public (34.3%) and private (65.7%) hospital settings.
[f] Administration/infusion costs based on MBS item 13915
[g] Calculated by the Secretariat assuming an uptake rate of 50% for the 1680 mg Q4W dosing regimen in the continuing treatment phase
Abbreviations: PBS: Pharmaceutical Benefits Scheme; RPBS: Repatriation Pharmaceutical Benefits Scheme; MBS: the Medicare Benefits Schedule
Source: Section 4 workbook 1L ES-SCLC supplied with the submission

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than $10 million per year.

5.13 The minor submission estimated that the addition of atezolizumab 840 mg injection for the 1680 mg Q4W flat dosing regimen in 1L ES-SCLC to be cost neutral to the Government.

5.14 The minor submission assumed that 95% of patients initiating atezolizumab at a dose of 1200 mg Q3W in combination with carboplatin and etoposide during the initial treatment phase would continue to use atezolizumab monotherapy and 100% of those patients would switch from the 1200 mg Q3W to 1680 mg Q4W dosing regimen for continuing treatment. The Secretariat considered that the assumption of 100% uptake for the 1680 mg Q4W dosing regimen was uncertain but noted that the financial implications were not sensitive to this assumption (see the sensitivity analysis in Table 3).

5.15 As a minor submission, the financial estimates have not been independently evaluated.

Financial Management – Risk Sharing Arrangement

5.16 The PBAC recommended atezolizumab in November 2019 for 1L ES-SCLC based on, among other matters, its assessment that the cost-effectiveness of atezolizumab would be acceptable at the price applied in the economic model. The PBAC was satisfied that the proposal to achieve cost-effectiveness through RSA rebates, in addition to a proposed reduction in the effective price, was reasonable in this case as the Committee had a high degree of confidence in the financial estimates (paragraph 6.1, atezolizumab (ES-SCLC) PSD, November, 2019).

5.17 The Secretariat noted that, if implemented, the new form of atezolizumab, 840 mg/14 mL injection, would be included under the RSA for ES-SCLC.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended extending its November 2019 recommendation for the 840 mg in 14 mL injection of atezolizumab and the addition of the 1680 mg Q4W flat dosing regimen to include the treatment of previously untreated patients with extensive stage small cell lung cancer (1L ES-SCLC) where atezolizumab monotherapy is used for continuing treatment.

6.2 The PBAC noted that no new clinical evidence was provided to compare the two flat dosing regimens in terms of efficacy and safety. However, the PBAC recalled it previously considered that the 1680 mg Q4W dosing regimen was likely comparable to the 1200 mg Q3W dosing regimen based on the same evidence in its November 2019 consideration of the addition of the 1680 mg Q4W dosing regimen for NSCLC indications. In this regard, the PBAC considered that the effectiveness and safety of the 1680 mg Q4W dosing regimen is likely comparable to that of the 1200 mg Q3W dosing regimen for 1L ES-SCLC.

6.3 The PBAC noted that the sponsor had previously agreed to pricing for the 1680 mg Q4W dosing regimen in 1L and 2L NSCLC based on cost-minimisation at the ex-manufacturer level compared to the 1200 mg Q3W dosing regimen, and considered it would be appropriate to apply consistent methodology for the 1L ES-SCLC indication. Further, the PBAC considered that the cost of treatment with the 1680 mg Q4W dosing regimen should not exceed that of the 1200 mg Q3W dosing regimen.

6.4 The PBAC noted the uncertainty around the estimated 100% uptake of the 1680 mg Q4W dosing regimen for continuing treatment. However, the PBAC considered it was likely that most patients would be prescribed this new dosing regimen once it became available. The PBAC considered that overall the addition of the 1680 mg Q4W dosing regimen for 1L ES-SCLC, would likely have a negligible financial impact for the Government.

6.5 The PBAC considered that 3 repeats for continuing treatment, which would provide 16 weeks of therapy under a Q4W dosing regimen, would be appropriate.

6.6 The PBAC considered that additional grandfathering provisions for the 1680 mg Q4W dosing regimen would not be required as any 1L ES-SCLC grandfathered patients could be prescribed the 1680 mg Q4W dosing regimen under the continuing treatment restriction following PBS subsidised treatment under the existing grandfather restriction for 1L ES-SCLC.

6.7 The PBAC considered that improved convenience from less frequent dosing would be beneficial for patients, particularly those in rural or remote areas.

6.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

7 Recommended listing

7.1 Add new vial presentation (840 mg/14 mL injection, 14 mL vial) and 4-weekly dosing regimen listing in the continuing treatment phase only as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
ATEZOLIZUMAB Injection	NEW (Public) NEW (Private)	1680 mg	3	Roche Products Pty Ltd
Available brands				
Tecentriq® (atezolizumab 840 mg/14 mL injection, 14 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy - Public hospitals / Private hospitals
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒Authority Required – Streamlined
Indication: Extensive-stage small cell lung cancer **Treatment Phase:** Continuing treatment – 4 weekly treatment regimen **Clinical criteria:** ▪ The treatment must be as monotherapy **AND** ▪ Patient must have previously received PBS-subsidised treatment with this drug for this condition **AND** ▪ Patient must not have developed disease progression while being treated with this drug for this condition
Administrative Advice: No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised Special Pricing Arrangements apply

Flow-on changes – for ease in differentiating between listings, amend the current treatment phase description of 'Continuing treatment' to 'Continuing treatment – 3 weekly treatment regimen' in the current extensive-stage small cell lung cancer listing (Streamlined Authority code 10203, PBS item codes 11928T (Private) & 11929W (Public)).

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.