6.13 PEMBROLIZUMAB, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda®, Merck Sharp & Dohme (Australia) Pty Ltd.

1 Purpose of Application

1.1 The minor submission requested the addition of a 400 mg every six weeks (Q6W) flat dosing regimen to the current 200 mg every three weeks (Q3W) flat dosing regimen. This change was requested for the existing PBS indications for the treatment of unresectable Stage III or Stage IV malignant melanoma, and first-line treatment of patients with Stage IV (metastatic) non-small cell lung cancer (NSCLC), who are epidermal growth factor receptor (EGFR) wild type, negative for anaplastic lymphoma kinase (ALK) or c-ROS proto-oncogene (ROS1) gene rearrangement.

1.2 The minor submission also requested the 400 mg Q6W dosing regimen be made available, if implemented, for the adjuvant treatment of patients with completely resected Stage IIIB, IIIC, and IIID malignant melanoma, and first-line treatment of BRAF V600 positive patients with unresectable Stage III or Stage IV malignant melanoma as those indications were recommended by the PBAC at the March 2020 meeting.

2 Requested listing

2.1 The minor submission requested a change in the maximum amount from 200 mg to 400 mg. No other changes to the existing PBS restrictions were proposed.

2.2 An abridged version of the requested listings are provided below.

PBS Code	Name, restriction, manner of administration and form	Max Amount	Number of repeats	Dispensed Price for Max Amount (Published)	Proprietary name and manufacturer
10424P melanoma (continuing)	PEMBROLIZUMAB 100 mg injection, 1 vial	400 mg	7	$17,434.92 (private)	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited
10436G melanoma (continuing)	PEMBROLIZUMAB 100 mg injection, 1 vial	400 mg	7	$17,118.12 (public)	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited
10475H melanoma (initial)	PEMBROLIZUMAB 100 mg injection, 1 vial	400 mg	5	$17,330.09 (private)	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited
10493G melanoma (initial)	PEMBROLIZUMAB 100 mg injection, 1 vial	400 mg	5	$17,053.06 (public)	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited
11492W NSCLC	PEMBROLIZUMAB 100 mg injection, 1 vial	400 mg	6	$17,330.09 (private)	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited

PBS Code	Name, restriction, manner of administration and form	Max Amount	Number of repeats	Dispensed Price for Max Amount (Published)	Proprietary name and manufacturer
11494Y NSCLC	PEMBROLIZUMAB 100 mg injection, 1 vial	400 mg	6	$17,053.06 (public)	KEYTRUDA® Merck Sharp & Dohme (Australia) Pty Limited

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Background

Registration status

3.1 The 200 mg Q3W flat dosing regimen was approved by the TGA on 14 November 2017 and replaced the weight-based dosing regimen of 2 mg per kg.

3.2 The 400 mg Q6W flat dosing regimen for the treatment of melanoma and NSCLC was approved by the TGA on 16 October 2019.

Previous PBAC consideration

3.3 At the March 2015 meeting, the PBAC recommended the listing of pembrolizumab for the treatment of unresectable Stage III or Stage IV malignant melanoma as monotherapy. Pembrolizumab was listed on the PBS for this indication on 1 September 2015.

3.4 At the July 2018 meeting, pembrolizumab was recommended by the PBAC for the first-line treatment of metastatic NSCLC in patients whose tumours express PD-L1 at TPS ≥50%, EGFR wildtype and ALK translocation negative (paragraph 6.1, pembrolizumab (NSCLC) PSD, July 2018).

3.5 At its November 2018 meeting, the PBAC agreed with the request to remove the weight-based dosing regimen for the treatment of unresectable Stage III or Stage IV malignant melanoma to align with the impeding change to the dose regimens in the PI at the time of PBAC consideration (paragraph 7.1, pembrolizumab PSD, November 2018).

3.6 The 400 mg Q6W dosing regimen for pembrolizumab has not been considered by the PBAC.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

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

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The individuals' comments were

not related to the proposed Q6W dosing regimen and instead, described patients' experience with pembrolizumab treatment in general.

4.3 Lung Foundation Australia indicated its support for an additional 400 mg Q6W dosing regimen on the basis that the less frequent dosing option would provide greater flexibility and reduced burden for patient.

Clinical trials

4.4 The minor submission did not present any clinical evidence for pembrolizumab administered at 400 mg Q6W. The minor submission referred to pharmacokinetic (PK) modelling data previously presented to the TGA in support of the requested 400 mg Q6W doing regimen.

Comparative effectiveness

4.5 The minor submission noted the key outcomes of the PK exposure simulations demonstrated that:

- The 400 mg Q6W dosing regimen leads to similar exposures to that of the approved Q3W dosing regimen (see Table 1).
- The mean predicted OS profiles for the 400 mg Q6W, 200 mg Q3W and 2mg/kg Q3W (see Figure 1) largely overlap with each other and are all within the 90% prediction interval for 2mg/kg Q3W in melanoma (Keynote 002) and NSCLC (Keynote 010).

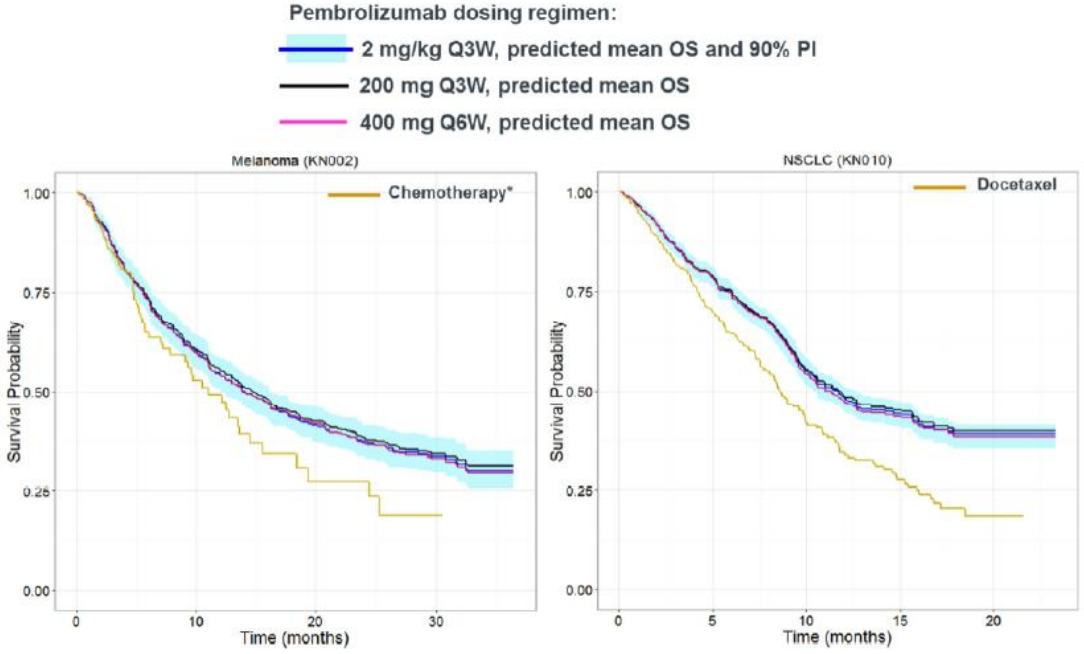
4.6 The following data were presented in the minor submission.

Table 1: PK exposure metrics (C_{max}, AUC, C_{min}) for 200 mg Q3W and 400 Q6W dosing regimens

PK exposure metrics, overall GM* (95% CI)	200 mg Q3W	400 mg Q6W	% difference in overall GM of 400 mg Q6W compared with 200 mg Q3W
Steady State, days 168 to 210			
$C_{max,ss}$ (mcg/mL)	92.8 (91.7, 94.1)	147.5 (146.1, 149.4)	59
$AUC_{,ss}$ (mcg/mL)	50.4 (49.8, 51.0)	50.7 (50.1, 51.3)	0.7
$C_{min,ss}$ (mcg/mL)	30.9 (30.5, 31.4)	20.3 (19.8, 20.9)	-34
Early cycle, week 6			
C_{max} (mcg/mL)	59.1 (58.5, 59.7)	123.0 (121.6, 124.3)	108
AUC (mcg/mL)	27.9 (27.7, 28.1)	32.4 (32.0, 32.7)	16
C_{min} (mcg/mL)	18.1 (17.8, 18.3)	10.6 (10.4, 10.8)	-41

*Median (2.5th and 97.5th percentile) values (GM C_{max}, GM C_{AUC}, GM C_{min}) from 100 replicate simulations
Source: Table 1, Table 2, p12 of Pharmacometric Evaluation Report (attachment 1)
Abbreviations: GM: geometric mean, C_{max}: maximum of simulated concentrations, AUC: area under the serum concentration-time curve C_{min}: minimum of simulated concentrations, SS: steady-state

Figure 1: Mean predicted OS for 400mg Q6W vs 200mg Q3W and 2mg/kg Q3W dosing regimens for different tumour types from a C_{min}-based Exposure-OS model



Predicted mean OS for pembrolizumab dosing regimens (solid lines) based on 100 simulations from a model driven by Cmin,wk6 as the exposure predictor, relative to the observed survival for the control arm in the trial are shown.
2 mg/kg Q3W was one of the doses tested in these trials; the 90% prediction interval (shaded area) is shown for the 2 mg/kg Q3W regimen for all pembrolizumab treated subjects in the trial.
* Chemotherapy of investigator's choice (carboplatin+paclitaxel or paclitaxel alone or dacarbazine or temozolomide) was the control arm in KN002; Docetaxel was the control arm in KN010.

Source: Figure 4, p17 of Pharmacometric Evaluation Report (attachment 1)
Abbreviations: OS: overall survival, C_{min}: minimum of simulated concentrations

Clinical claim

4.7 The minor submission claimed that, based on PK modelling data, the 400 mg Q6W dosing regimen of pembrolizumab is likely to deliver the same effectiveness and safety compared with the 200 mg Q3W dosing regimen for melanoma and NSCLC.

Economic analysis

4.8 The minor submission did not present an economic analysis.

4.9 The minor submission stated that no additional costs offsets or vial price increases were being requested for the 400 mg Q6W dosing regimen. The proposed dispensed price for maximum amount (DPMA) for the requested PBS listings based on the current ex-manufacturer price per 100 mg vial are presented in the table below.

Table 2: Proposed dispensed price at the maximum amount of 400 mg

PBS Code	10424P[b] melanoma (continuing)	10436G[c] melanoma (continuing)	10475H[b] melanoma (initial)	10493G[c] melanoma (initial)	11492W[b] NSCLC	11494Y[c] NSCLC
Proposed DPMA at the maximum amount of 400 mg[a]	$17,310.10	$17,033.06	$17,310.10	$17,033.06	$17,310.10	$17,033.06

Source: Table 1, pp5-6 of the submission; Ex-manufacture prices (Efficient Funding of Chemotherapy) – January 2020
Abbreviations: EEMP: effective ex-manufacturer price; DPMA: dispensed price for maximum amount
[a] Secretariat corrected DPMA based on the approved AEMP for KEYTRUDA of $4,237.00 per 100mg vial
[b] Private hospital; [c]: Public hospital

Estimated PBS usage & financial implications

4.10 The minor submission presented the estimated utilisation and financial impact of the addition of the 400 mg Q6W dosing regimen (see Table 3).

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

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of melanoma patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of NSCLC patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for pembrolizumab 200 mg Q3W dosing						
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments (published price[b])	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments (effective price[c])	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications accounting for 400 mg Q6W dosing						
Number of scripts dispensed[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments (published price[b])	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments (effective price[c])	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications of the addition of 400 mg Q6W dosing (i.e. cost of 400 mg Q6W – cost of 200 mg Q3W)						
Net cost to MBS[e]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to Government (published/ effective price)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

[a] Assuming an average of 16.5 scripts per patient for NSCLC and 13.3 scripts per patient for melanoma when administered at 200 mg Q3W
[b] The weighted published DPMAs of $17,231.79 for 400 mg Q6W and $8,681.25 for 200 mg Q3W, based on a 35.49% and 64.51% split between Public and Private respectively, derived from the number of PBS services in the 2019 calendar year. The published AEMP is $4,237.00 per 100 mg vial.
[c] The weighted effective DPMAs of $[redacted], $[redacted] (400 mg Q6W) and $[redacted], $[redacted] (200 mg Q3W) for melanoma and NSCLC indications respectively, based on a 35.49% and 64.51% split between Public and Private respectively, derived from the number of PBS services in the 2019 calendar year. The effective AEMP is $[redacted] per 100 mg vial for melanoma, $[redacted] per 100 mg vial for NSCLC.
[d] Assuming an average of 6.0 and 7.0 scripts per patient for melanoma and NSCLC respectively for Q3W dosing. Assuming an average of 3.65 and 4.75 scripts per patient for melanoma and NSCLC respectively for Q6W dosing.
[e] Administration/infusion costs of $66.10 based on MBS item 13915

The redacted table shows that at Year 6, the estimated total number of patients was less than 10,000.

4.12 The minor submission estimated a cost saving of less than $10 million per year and a total net saving of $10 – $20 million to the Government over the first 6 years of listing. The estimated cost savings to Government are due to a reduction in administration and dispensing fees, associated with fewer scripts dispensed for the 400 mg Q6W dosing regimen. Although a cost saving is likely given that fewer scripts are required for Q6W dosing, the magnitude of savings is uncertain.

4.13 The number of NSCLC patients was based on the patient numbers previously agreed with the Department for the listing of pembrolizumab for the first-line treatment of patients with Stage IV (metastatic) NSCLC. The number of melanoma patients was estimated from the number of PBS items processed between January 2016 to September 2019 for item codes 10424P, 10436G, 10475H and 10493G, assuming an average of 13.3 scripts per patient and a growth rate of 2% per year. The pre-PBAC response indicated that the 13.3 scripts per patient was derived based on the mean number of days on pembrolizumab as a first line regimen of 276 reported in the May 2018 DUSC report on medicines for the treatment of melanoma. The pre-PBAC response acknowledged that 276 days equates to 13.14 rather than 13.3 however considered that this adjustment should have no impact on the nil cost to Government. The pre-PBAC response also indicated that the 2% growth rate was applied to the number of scripts to reflect population growth in Australia.

4.14 The minor submission considered that most patients are likely to be initiated on a Q3W dosing regimen and then move to the Q6W dosing regimen for continuing treatment if there is a treatment response. Therefore, the minor submission assumed that all patients would be prescribed the Q3W dosing regimen for the initial treatment phase and the Q6W dosing regimen for the continuing treatment phase. The minor submission indicated that this assumption was for simplicity. However, the minor submission noted that in the PBAC's consideration of nivolumab 240 mg Q2W and 480 mg Q4W flat dosing regimens at the March 2019 meeting, the PBAC considered it was reasonable to assume that the majority of patients would be prescribed the 480 mg Q4W dosing regimen if available (paragraph 5.4, Nivolumab PSD, March 2019).

4.15 The minor submission considered that the addition of the Q6W dosing regimen is unlikely to result in an increase in the use of pembrolizumab given most patients are likely to be initiated on a Q3W regimen.

4.16 The PBAC considered that should this new dosing regimen become available, most patients will subsequently be moved to this dosing regimen. However, the PBAC noted that no basis was provided for use of the Q3W dosing regimen for initial treatment and the Q6W dosing regimen for continuing treatment. Therefore, the financial estimates should be updated to show the move of patients from the Q3W dosing regimen to the Q6W dosing regimen across all treatment phases.

Risk Sharing Arrangements

4.17 There are currently Risk Sharing Arrangements (RSAs) in place for pembrolizumab for the treatment of unresectable Stage III or Stage IV malignant melanoma and locally advanced or metastatic NSCLC.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the addition of the 400 mg Q6W flat dosing regimen to the existing 200 mg Q3W flat dosing regimen for all existing and recommended pembrolizumab PBS listings for melanoma and non-small cell lung cancer (NSCLC) indications where pembrolizumab monotherapy is used.

5.2 The PBAC noted that no clinical data comparing the 400 mg Q6W dosing regimen to the 200 mg Q3W dosing regimen was provided. However, based on the pharmacokinetic (PK) modelling data evaluated by the TGA, the PBAC considered that the effectiveness and safety of the two flat dosing regimens would likely be comparable. The PBAC noted that it would welcome further data to demonstrate equi-effectiveness of different dosing regimens of pembrolizumab.

5.3 The PBAC considered that although the estimated utilisation of the 400 mg Q6W dosing regimen was uncertain, it was likely that the majority of patients would be prescribed this dosing regimen if available. Therefore, the PBAC considered there would be some cost savings to the Government associated with the addition of the 400 mg Q6W dosing regimen due to reduced administration and dispensing fees from fewer scripts dispensed for the 400 mg Q6W dosing regimen compared to that for the 200 mg Q3W dosing regimen.

5.4 The PBAC advised that initial treatment for melanoma with the 400 mg Q6W dosing regimen should be restricted to a maximum of 3 doses to restrict treatment to a maximum of 18 weeks, consistent with the existing listing for unresectable Stage III or Stage IV malignant melanoma. The PBAC also considered it would be appropriate to restrict initial treatment for NSCLC with the 400 mg Q6W dosing regimen to a maximum of 4 doses to restrict treatment to a maximum of 24 weeks, noting the existing listing for Stage IV (metastatic) NSCLC allows for a maximum of 21 weeks treatment under the initial treatment restriction.

5.5 The PBAC advised that continuing treatment for Stage IV (metastatic) NSCLC and grandfathering treatment for Stage IV (metastatic) NSCLC with the 400 mg Q6W dosing regimen should be restricted to a total of 18 cycles or up to 24 months.

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

Outcome:
Recommended

6 Recommended listing

6.1 Add new item:

Add new 6-weekly dosing listings for adjuvant treatment of completely resected Stage IIIB, IIIC, and IIID malignant melanoma, unresectable Stage III or Stage IV malignant melanoma and Stage IV (metastatic) NSCLC:

Adjuvant treatment of resected Stage IIIB, IIIC, and IIID malignant melanoma

Refer to the meeting Public Summary Document (PSD) for agenda item 7.13 of this meeting for the proposed new listings.

Unresectable Stage III or Stage IV malignant melanoma

Refer to the meeting PSD for agenda item 6.03 of this meeting for the proposed new listings.

Stage IV (metastatic) non-small cell lung cancer

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	400 mg	3	Merck Sharp & Dohme (Australia) Pty Ltd
Available brands				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				

Category/Program: Section 100 Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction level: ☒Authority required - Streamlined (NEW CODE)
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. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC) **Treatment Phase:** Initial treatment – 6 weekly treatment regimen **Clinical criteria:** ▪ Patient must not have previously been treated for this condition in the metastatic setting **AND** ▪ Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for non-small cell lung cancer **AND** ▪ Patient must have a WHO performance status of 0 or 1 **AND** ▪ The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene arrangement in tumour material **AND** ▪ The treatment must not exceed a total of 4 doses under this restriction
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

Category/Program: Section 100 Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction level: ☒Authority required - Streamlined (NEW CODE)
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. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC) **Treatment Phase:** Continuing treatment – 6 weekly treatment regimen **Clinical criteria:** ▪ 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 **AND** ▪ The treatment must not exceed a total of 18 cycles or up to 24 months of treatment under this restriction

Category/Program: Section 100 Efficient Funding of Chemotherapy
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction level: ☒Authority required - Streamlined (NEW CODE)
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. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
Indication: Stage IV (metastatic) non-small cell lung cancer (NSCLC) **Treatment Phase:** Grandfathering treatment – 6 weekly treatment regimen **Clinical criteria:** ▪ Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to 1 December 2019 **AND** ▪ Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for non-small cell lung cancer **AND** ▪ Patient must not have had been treated for this condition in the metastatic setting prior to initiating non-PBS subsidised treatment with this drug for this condition **AND** ▪ Patient must have stable or responding disease **AND** ▪ Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS subsidised treatment with this drug for this condition **AND** ▪ The condition must not have evidence of an activating epidermal growth factor receptor (EGFR) gene or an anaplastic lymphoma kinase (ALK) gene rearrangement or a c-ROS proto-oncogene 1 (ROS1) gene arrangement in tumour material **AND** ▪ The treatment must not exceed a total of 18 cycles or up to 24 months of treatment under this restriction
Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later A patient may only qualify for PBS-subsidised treatment under this restriction once

Following completion of the initial PBS subsidised course, further applications for treatment will be assessed under the continuing treatment restriction This Grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

Flow-on changes to existing Stage IV (metastatic) NSCLC pembrolizumab listings:

Amend the treatment phase descriptions in the initial, continuing and grandfather existing listings to differentiate the listings from the 6-weekly treatment regimens more easily.

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

7 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.

8 Sponsor's Comment

The sponsor had no comment.