

6.14 NIVOLUMAB

Injection concentrate for I.V. infusion, 40 mg in 4 mL, 100 mg in 10 mL Opdivo[®], Bristol-Myers Squibb Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested the addition of two flat dosing regimens to the current 3 mg/kg every two weeks (Q2W) weight based dosing regimen to allow clinicians choice of either:
1. weight-based 3 mg/kg Q2W dosing, or
 2. flat 240 mg Q2W dosing, or
 3. flat 480 mg Q4W dosing
- 1.2 The minor submission requested that all three dosing regimens be made available for all existing nivolumab PBS listed indications for the treatment of unresectable Stage III or Stage IV malignant melanoma (both as monotherapy and in the maintenance phase following treatment with ipilimumab), second line non-small cell lung cancer (2L NSCLC), second line renal cell carcinoma (2L RCC) and recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN).
- 1.3 The minor submission also requested that the three dosing regimens be made available for all future PBS listed indications where nivolumab monotherapy is used, including the indication for the treatment of first line renal cell carcinoma (1L RCC, in the maintenance phase following ipilimumab) to be listed on 1 March 2019.

2 Requested listing

- 2.1 The minor submission requested a change in the maximum amount from 360 mg to 480 mg and an amendment to the criterion specifying that “treatment must not exceed a maximum dose of 3 mg per kg every 2 weeks” in the initial and continuing treatment restrictions for unresectable Stage III or Stage IV malignant melanoma.
- 2.2 Additions proposed by the minor submission to the existing listings are added in italics and suggested deletions are crossed out with strikethrough. Due to the size and number of restrictions that the requested changes apply to, abbreviated versions of the restrictions including only the requested changes are shown below.

Name, Restriction, Manner of administration and form	Max. Qty Amt	No. of Rpts	Proprietary Name and Manufacturer	
NIVOLUMAB			Opdivo [®]	Bristol-Myers Squibb Australia Pty Ltd
40 mg/4 mL injection 1 x 4mL vial	360 mg	8		
100 mg/10 mL injection 1 x 4mL vial	480mg			

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners

Public Summary Document – March 2019 PBAC Meeting

Severity:	Unresectable Stage III or Stage IV
Condition:	malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial treatment 1
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must not exceed a total of 9 doses 18 weeks at a maximum dose of 3 mg per kg every 2 weeks</p> <p><i>The treatment must not exceed a total of 18 weeks at a dose of 3mg/kg or 240mg every two weeks or 480mg every four weeks</i></p>

Item codes 10764M and 10775D

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Unresectable Stage III or Stage IV
Condition:	malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial treatment 2
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must not exceed a total of 9 doses 18 weeks at a maximum dose of 3 mg per kg every 2 weeks</p> <p><i>The treatment must not exceed a total of 18 weeks at a dose of 3mg/kg or 240mg every two weeks or 480mg every four weeks</i></p>

Item codes 10764M and 10775D

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Unresectable Stage III or Stage IV
Condition:	malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must not exceed a total of 9 doses 18 weeks at a maximum dose of 3 mg per kg every 2 weeks</p> <p><i>The treatment must not exceed a total of 18 weeks at a dose of 3mg/kg or 240mg every two weeks or 480mg every four weeks</i></p>

Item codes 10745M and 10748Q

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Unresectable Stage III or Stage IV
Condition:	malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma

Treatment phase:	Maintenance treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must not exceed a total of 9 doses 18 weeks at a maximum dose of 3 mg per kg every 2 weeks</p> <p><i>The treatment must not exceed a total of 18 weeks at a dose of 3mg/kg or 240mg every two weeks or 480mg every four weeks</i></p>

Item codes 10745M and 10748Q

3 Background

3.1 Nivolumab is currently TGA registered for the following indications:

- Adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection;
- Treatment of patients with unresectable or metastatic melanoma as monotherapy or in combination with ipilimumab;
- Treatment of locally advanced or metastatic squamous and non-squamous non-small cell lung cancer with progression on or after prior chemotherapy;
- Treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma in combination with ipilimumab;
- Treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy;
- Treatment of patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin;
- Treatment of recurrent or metastatic squamous cell cancer of the head and neck patients progressing on or after platinum based therapy;
- Treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy; and
- Treatment of patients with hepatocellular carcinoma after prior sorafenib therapy.

3.2 Nivolumab has previously been recommended by the PBAC for the indications shown in Table 1.

Table 1: Summary of PBAC recommendations for listing nivolumab

PBS Indication	PBAC meeting recommended	Date listed
Unresectable Stage III or Stage IV malignant melanoma (monotherapy)	November 2015	1 May 2016
Locally advanced or metastatic non-small cell lung cancer	March 2017	1 August 2017
Stage IV clear cell variant renal cell carcinoma (following TKI treatment)	March 2017	1 August 2017
Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx	March 2018	1 August 2018
Unresectable Stage III or Stage IV malignant melanoma (in combination with ipilimumab)	July 2018	1 December 2018
Stage IV clear cell variant renal cell carcinoma (first line, in combination with ipilimumab)	November 2018	1 March 2019

- 3.3 A resubmission requesting listing for the adjuvant treatment of patients who have had completely surgically resected Stage III or Stage IV malignant melanoma will be considered by the PBAC at the March 2019 meeting (item 7.09 refers).
- 3.4 Risk sharing arrangements (RSAs) in the form of expenditure caps are currently in place for all PBS subsidised indications. The RSA in place for the treatment of unresectable Stage III or Stage IV malignant melanoma is shared with the sponsor for pembrolizumab while the RSA in place for the treatment of non-small cell lung cancer is shared with the sponsor for pembrolizumab and the sponsor for atezolizumab. The RSAs for the treatment of recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx and the treatment of Stage IV clear cell variant renal cell carcinoma (following TKI treatment) are currently not shared with any other sponsor.

Committee-in-Confidence information

3.5 At its March 2018 meeting, the PBAC recommended an amendment to the existing PBS restrictions for pembrolizumab, for the treatment of unresectable Stage III or Stage IV malignant melanoma, to allow either a weight-based dose of 2 mg/kg or a flat dose of 200 mg, every three weeks. The PBAC noted [REDACTED]

[REDACTED] The PBAC noted that the change in dosing has the effect of wasting on average 25% of the drug because the flat dosing results in a higher administered dose without any additional patient benefit. For this reason, the PBAC concluded that a change from the weight-based to flat dose regimen would not be cost-effective on a per-patient basis, as currently the mean dose of pembrolizumab is significantly less than 200 mg. However, the PBAC noted that there is currently a relevant risk sharing arrangement in place, [REDACTED]

[REDACTED]. These caps have been exceeded in previous years. If the caps continue to be exceeded, the overall net cost to Government with the restriction amendment would remain the same as it would be contained by the risk sharing arrangement. The PBAC therefore advised that subsequent annual expenditure caps for this melanoma-based Deed of Agreement should be negotiated with the sponsor for pembrolizumab based on the weight-based dosing regimen, to ensure that the PBS listing remains acceptably cost-effective (March 2018 pembrolizumab minutes, paragraph 5.3).

End Committee-in-Confidence information

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 that there was no consumer comment for this submission.

Clinical trials

4.3 The minor submission did not present any new clinical evidence, however, it included a description of the pharmacokinetic/pharmacodynamic/efficacy/safety analysis used to support the TGA approvals of 240 mg Q2W and 480 mg Q4W flat dosing regimens. The minor submission claimed, "These analyses indicate that any differences in nivolumab exposures resulting from dosing at 240 mg Q2W or 480 mg Q4W would not alter the safety and efficacy profile established with the approved 3mg/kg Q2W". The minor submission also provided a list of active clinical trials investigating nivolumab monotherapy or combination with ipilimumab using the 480 mg Q4W dosing regimen anticipated to report within the next two years.

Clinical claim

4.4 The minor submission claimed that the nivolumab flat dosing regimens of 240 mg Q2W and 480 mg Q4W are non-inferior to the weight based dosing regimen of 3 mg/kg Q2W in terms of safety and efficacy. The PBAC noted that these claims were largely based on pharmacokinetic and pharmacodynamic data rather than clinical trial data.

Economic analysis

4.5 A comparison of the costs per 4 week treatment course with each nivolumab dosing regimen is presented below in Table 2.

Table 2: Cost comparison of the 480 mg Q4W, 240 mg Q2W and 3 mg/kg Q2W nivolumab dosing regimens

Cost per 4 weeks of therapy	3 mg/kg Q2W	240 mg Q2W flat dose	480 mg Q4W flat dose
AEMP drug cost /mg ^a	\$20.77	\$20.77	\$20.77
AEMP drug cost ^b	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Mark-up costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Administration/infusion costs ^c	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total cost difference	[REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Total cost (@DPMA) per 4 weeks	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
% reduction from DPMA	[REDACTED]	% [REDACTED]	% [REDACTED]

Source: Table 11, p34 of the minor submission

Abbreviations: AEMP: approved ex-manufacturer price; DPMA: dispensed price for maximum amount

^a Based on published prices.

^b AEMP drug costs derived from DPMA weighted across private/public hospital use from PBS expenditure from July 2017 to June 2018.

^c Administration/infusion costs based on MBS item 13915.

4.6 The minor submission calculated the mean drug cost per infusion for the 3 mg/kg dosing regimen based on a mean [REDACTED] mg/infusion informed by Australian population weight data (ABS Weight Data). This approach implicitly assumes that the ABS Australian population data is representative of the distribution of population weight of patients accessing nivolumab on the PBS. The sponsor considered that the ABS population data was the most representative sample of the Australian population. The submission indicated that as nivolumab may be reimbursed in a number of different tumour types in the future, applying the ABS reported population weight distribution provides the most reasonable estimate of average patient weight for nivolumab on the PBS.

4.7 The minor submission estimated a cost of \$ [REDACTED] (difference of \$ [REDACTED] compared to the estimated 4-week treatment cost for the 3 mg/kg dosing regimen of \$ [REDACTED]) for a 4-week treatment course of nivolumab weighted across the estimated utilisation of each dosing regimen (see paragraph 4.3 below). The minor submission claimed that allowing for flat dosing would reduce the cost of nivolumab per 4 weeks of therapy, and the saving was primarily driven by savings in EFC mark-ups and infusion administration fees associated with high utilisation of the nivolumab 480 mg Q4W dosing regimen. In the absence of any evidence demonstrating an additional benefit of the weight based dosing regimen it may be reasonable for the price paid for patients on the weight based dosing regimen to be no higher than the than the cost if flat dosing was used.

- 4.8 The minor submission estimated utilisation of dosing regimens to be ■%, ■% and ■% for the 480 mg Q4W, 240 mg Q2W and 3 mg/kg dosing regimens respectively. The estimated uptake was based on results from an online voluntary survey which was opened to 43 clinicians who participated in 5 BMS advisory boards (malignant melanoma, second line non-small cell lung cancer, second line renal cell carcinoma, relapse/remitting squamous cell carcinoma of the head and neck, and hepatocellular carcinoma). Only 18 out of 43 clinicians provided responses to the survey. The extent to which the voluntary survey data is representative of Australian clinical practice is uncertain.
- 4.9 The minor submission presented a range of univariate sensitivity analyses investigating the impact of using alternative data sources including PBS utilisation data for nivolumab in second line NSCLC, malignant melanoma and second line RCC to inform the mean dose per infusion as well as sensitivity analyses varying the assumed split of nivolumab dosing regimens. The minor submission noted that using an average dose per infusion estimated from the PBS utilisation data available at the time in 2L NSCLC, malignant melanoma and 2L RCC resulted in a cost increase of ■% to the Government for a 4-week treatment period when compared with the current weight based dosing regimen. However, the minor submission argued that this data source was an inappropriate proxy to estimate the mean dose per infusion for all PBS listed nivolumab indications given less than 12 months of data was available for second line NSCLC and second line RCC indications at the time of submission. Departmental analysis of the mean dose per infusion per patient for the currently listed nivolumab indications based on PBS utilisation data indicate that the mean dose per infusion for most indications is below 240 mg indicating there may be a higher cost per patient with the addition of flat dosing regimens (see Table 4 and paragraph 4.8). The pre-PBAC response argued that this analysis is based on historical nivolumab prescribing data that, due to the dynamic PD(L)-1 reimbursement environment, does not reflect future utilisation of nivolumab on the PBS. The pre-PBAC response presented a cost-comparison of dosing regimens across the indications for which nivolumab is currently listed, based on the mean doses per infusion that informed the financial estimates of the listings (Table 3).

Table 3: Cost comparison of weight based and proposed flat dosing regimens across nivolumab listed indications

Indication	Unresectable Stage III or Stage IV malignant melanoma	Locally advanced or metastatic non-small cell lung cancer	Stage IV clear cell variant renal cell carcinoma (following TKI treatment)	Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx
Cost-effective mean dose/infusion (mg)	█	█	█	█
Drug cost/infusion ^a	\$ █	\$ █	\$ █	\$ █
Administration/infusion costs ^b	\$ █	\$ █	\$ █	\$ █
Total drug and administration costs	\$ █	\$ █	\$ █	\$ █
Difference to 240 mg Q2W drug and administration costs	█%	█%	█%	█%
Difference to 480 mg Q4W drug and administration costs	█%	█%	█%	█%

Source: Table 2, p2 of the pre-PBAC Response

^a Cost over 4 weeks; ^b Administration/infusion costs based on MBS item 13915.

4.10 The pre-PBAC Response noted that the mean dose per infusion that informed the agreed financial estimates for the listing for R/M SCCHN was below 240 mg and therefore, there may be a higher cost for patients on flat dosing regimens. The pre-PBAC Response stated that the Sponsor is willing to work with the PBAC and Department to adjust the effective from for the R/M SCCHN indication via the current Deed of Agreement.

4.11 The submission provided sensitivity analyses for increased 3 mg/kg Q2W weight based dosing utilisation, and for increased 480 mg Q4W flat dosing, but not for increased 240 mg Q2W flat dosing.

Estimated PBS usage & financial implications

4.12 The estimated financial implications to the PBS/RPBS of the addition of the 240 mg Q2W and 480 mg Q4W nivolumab dosing regimens are presented in Table 4 below.

4.13 As this was a minor submission, these estimates have not been independently evaluated.

Table 4: Estimated net financial implications to the RPBS/PBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated number of patients treated with nivolumab ^a	████	████	████	████	████	████
Total number of nivolumab 3 mg/kg Q2W flat dose infusions on PBS/RPBS	████	████	████	████	████	████
Total number of nivolumab 240 mg Q2W flat dose infusions on PBS/RPBS	████	████	████	████	████	████
Total number of nivolumab 480 mg Q4W flat dose infusions on PBS/RPBS	████	████	████	████	████	████
Total number of nivolumab infusions (flat dose and weight based) ^b	████	████	████	████	████	████
Total cost to PBS/RPBS (minus copayment)	\$████	\$████	\$████	\$████	\$████	\$████
Total cost offset to PBS/RPBS (minus copayment)	\$████	\$████	\$████	\$████	\$████	\$████
Overall Net Cost to PBS/RPBS ^c	-\$████	-\$████	-\$████	-\$████	-\$████	-\$████
Revised Overall Net Cost to PBS/RPBS ^d	-\$████	-\$████	-\$████	-\$████	-\$████	-\$████

Source: Table 19 p44, Table 24 p48 and Table 25 p49 of the submission; Table 5 p4 of the pre-PBAC Response

^a Based on the number of patients treated with nivolumab in the financial estimates agreed for each indication.

^b Calculated by applying the estimated utilisation split across the three dosing regimens to the number of patients and then multiplying by the mean number of infusions per patient per treatment course for the dosing regimen in each indication.

^c Assuming █████% utilisation is in the PBS and █████% utilisation is in the RPBS.

^d Revised financial estimates account for changes described in paragraph 4.15.

4.14 The minor submission estimated that the addition of flat nivolumab dosing regimens would result in cost savings to the PBS/RPBS of approximately less than \$10 million per year. The Secretariat notes that the estimated cost savings to the PBS/RPBS are dependent on the estimated split of nivolumab dosing regimen use and whether the submission's estimated mean dose per infusion (████ mg) for the current weight based dosing regimen is reflective of clinical practice. The financial estimates do not account for the 1 March 2019 listing of nivolumab for the treatment of first line RCC.

4.15 The pre-PBAC Response noted that since the time of submission, several changes have occurred which impact the estimated utilisation of nivolumab. The pre-PBAC response presented revised financial estimates (Table 4) with the following changes:

- Increased patient estimates to account for 1 December 2018 listing of nivolumab + ipilimumab for the treatment of unresectable Stage III or Stage IV malignant melanoma and to account for nivolumab penetration of the pembrolizumab market associated with 480 mg Q4W dosing.
- Decreased patient estimates for NSCLC to account for recent PBS listings of atezolizumab for second line treatment, pembrolizumab for first line treatment and anticipated future listings of other NSCLC agents.
- Decreased patient estimates for second line RCC to account for 1 March listing of nivolumab for first line RCC.
- Included patient estimates to account for a future nivolumab listing for the adjuvant treatment of patients who have resected Stage III or Stage IV malignant melanoma that is to be considered at the March PBAC meeting.

4.16 Departmental analysis of the mean dose per infusion per patient for the currently listed nivolumab indications based on PBS utilisation data from May 2016 to December 2018 are shown below in Table 5.

Table 5: Mean, median and mode of the nivolumab dose per infusion for currently listed indications

Indication	Mean	Median	Mode
Unresectable Stage III or Stage IV malignant melanoma ^a	mg	mg	mg
Locally advanced or metastatic non-small cell lung cancer	mg	mg	mg
Stage IV clear cell variant renal cell carcinoma (following TKI treatment)	mg	mg	mg
Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx	mg	mg	mg

Source: Data generated by the SAS System ('SASApp', Linux)

^a Includes utilisation data for nivolumab administered as monotherapy only (excluding nivolumab administered in combination with ipilimumab).

4.17 The above analysis indicates that patients on average, across most indications except 2L RCC require a dose less than 240 mg. As such, the addition of flat nivolumab dosing regimens of 240 mg Q2W and 480 mg Q4W may result in a higher average cost per patient to Government for these indications.

Risk Sharing Arrangements

4.18 Departmental data on annual expenditure compared with the corresponding annual expenditure caps under the current risk sharing arrangements for the treatment of unresectable Stage III or Stage IV malignant melanoma, locally advanced or metastatic NSCLC and Stage IV clear cell variant RCC are shown in the tables below. Data on annual expenditure for the treatment of recurrent or metastatic SCCHN is currently not available as nivolumab was only listed for this indication on 1 December 2018.

Committee-in-Confidence information

Table 6: Annual expenditure caps under the risk sharing arrangement for the treatment of unresectable Stage III or Stage IV malignant melanoma

Year	1	2	3
Financial caps	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Annual expenditure	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
% reached	[REDACTED]%	[REDACTED]%	[REDACTED]%

Note: Financial caps are shared with the sponsor of pembrolizumab

Table 7: Annual expenditure caps under the risk sharing arrangement for the treatment of Stage IV clear cell variant renal cell carcinoma

Year	1	2 ^a
Financial caps	\$ [REDACTED]	\$ [REDACTED]
Annual expenditure	\$ [REDACTED]	\$ [REDACTED]
% reached	[REDACTED]%	[REDACTED]%

Note: Data is for 1st quarter of Year 2 only

Table 8: Annual expenditure caps under the risk sharing arrangement for the treatment locally advanced or metastatic non-small cell lung cancer

Year	1	2 ^a
Financial caps ^b	\$ [REDACTED]	\$ [REDACTED]
Annual expenditure	\$ [REDACTED]	\$ [REDACTED]
% reached	[REDACTED]%	[REDACTED]%

^a Data is for 1st quarter of Year 2 only; ^b Financial caps are shared with the sponsors of pembrolizumab and atezolizumab.

End Committee-in-Confidence information

4.19 The annual expenditure for 2L RCC and 2L NSCLC were considerably below the corresponding financial caps and the Year 2 caps for these indications are also currently not projected to be met. Given the mean dose of nivolumab per infusion for 2L NSCLC was less than 240 mg (see Table 4), the addition of flat dosing regimens may result in a dose increase and as such, a higher cost per patient and cost to Government in the event that the RSA cap is not exceeded. Accordingly, if the annual expenditure cap for SCCHN is also not exceeded, there may be an increased cost to Government for this indication.

If the financial caps for malignant melanoma continue to be exceeded, the overall net cost to Government would remain the same irrespective of changes in the average dose per infusion, as it would be contained by the RSA.

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

5 PBAC Outcome

- 5.1 The PBAC recommended the addition of two flat dosing regimens (240 mg Q2W and 480 mg Q4W) to the existing 3 mg/kg Q2W weight based dosing regimen for all existing and future PBS indications where nivolumab monotherapy is used. The PBAC recommended that the maximum amount be adjusted to 480 mg.
- 5.2 The PBAC noted there was limited clinical data to support the claim that the flat dosing regimens are non-inferior in efficacy and safety compared to the 3 mg/kg Q2W weight based dosing regimen. However, based on the overall evidence, the PBAC considered that the efficacy and safety of the flat and weight based dosing regimens would likely be comparable.
- 5.3 The PBAC noted the Departmental analysis of PBS utilisation indicated that mean doses for some indications were below the proposed 240 mg flat dose. However, the PBAC considered the differences to be small and therefore considered that addition of flat dosing regimens were unlikely to be associated with significant wastage or have a significant impact on cost-effectiveness of nivolumab across the different indications. Further, the PBAC noted that if the annual expenditure caps for the treatment of unresectable Stage III or Stage IV malignant melanoma continue to be exceeded as per previous years, the overall net cost to the Government for this indication would remain the same as it would be contained by the risk sharing arrangement.
- 5.4 The PBAC considered that while the estimated utilisation split between flat and weight based dosing regimens was uncertain, it was reasonable to assume that the majority of patients would be prescribed the 480 mg Q4W dosing regimen if available. As such, the PBAC considered there would be some cost-savings to Government associated with the addition of nivolumab flat dosing regimens due to reduced infusion administrations.
- 5.5 The PBAC noted that so long as both the flat dosing and weight-based dosing regimen options were available, there was unlikely to be an increase in overall expenditure for nivolumab. Any changes to the availability of the weight-based dosing regimen would need to be assessed to ensure no increase to the cost per patient.
- 5.6 The PBAC considered that existing and future nivolumab restrictions should include prescriber instructions specifying that patients must only receive a maximum of 240 mg Q2W or 480 mg Q4W under a weight based or flat dosing regimen.
- 5.7 The PBAC noted that this submission is not eligible for an Independent Review as it has received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Amend existing listings as follows:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
NIVOLUMAB 40 mg/4 mL injection 1 x 4mL vial 100 mg/10 mL injection 1 x 4mL vial	360 mg 480mg	8	Opdivo®	Bristol-Myers Squibb Australia Pty Ltd

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Unresectable Stage III or Stage IV
Condition:	malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial treatment 1
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks. Patient must not receive more than 18 weeks of treatment under this restriction at a dose of 3 mg/kg every two weeks, 240mg every two weeks or 480mg every four weeks.
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 10764M and 10775D

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Unresectable Stage III or Stage IV
Condition:	malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial treatment 2
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks. Patient must not receive more than 18 weeks of treatment under this restriction at a dose of 3 mg/kg every two weeks, 240mg every two weeks or 480mg every four weeks.
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 10764M and 10775D

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Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	clear cell variant renal cell carcinoma
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11150W and 11159H

Public Summary Document – March 2019 PBAC Meeting

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Locally advanced or metastatic
non-small cell lung cancer	non-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11143L and 11158G

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
NIVOLUMAB 40 mg/4 mL injection 1 x 4mL vial 100 mg/10 mL injection 1 x 4mL vial	360 mg 480mg	11	Opdivo®	Bristol-Myers Squibb Australia Pty Ltd

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Unresectable Stage III or Stage IV
Condition:	malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<i>The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks. Patient must not receive more than 18 weeks of treatment under this restriction at a dose of 3 mg/kg every two weeks, 240mg every two weeks or 480mg every four weeks.</i>
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 10745M and 10748Q

Public Summary Document – March 2019 PBAC Meeting

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Unresectable Stage III or Stage IV
Condition:	malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Maintenance treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks. Patient must not receive more than 18 weeks of treatment under this restriction at a dose of 3 mg/kg every two weeks, 240mg every two weeks or 480mg every four weeks.
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 10745M and 10748Q

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	clear cell variant renal cell carcinoma
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11157F and 11160J

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	clear cell variant renal cell carcinoma
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Maintenance treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Maintenance treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks.
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11626X and 11642R

Category / Program	Section 100 - Efficient funding of Chemotherapy
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Public Summary Document – March 2019 PBAC Meeting

Prescriber type	Medical Practitioners
Severity:	Recurrent or metastatic
Condition:	squamous cell carcinoma of the oral cavity, pharynx or larynx
PBS Indication:	Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11435W and 11434T

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Recurrent or metastatic
Condition:	squamous cell carcinoma of the oral cavity, pharynx or larynx
PBS Indication:	Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11411N and 11425H

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Recurrent or metastatic
Condition:	squamous cell carcinoma of the oral cavity, pharynx or larynx
PBS Indication:	Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx
Treatment phase:	Grandfather treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11411N and 11425H

Public Summary Document – March 2019 PBAC Meeting

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Locally advanced or metastatic
Condition:	non-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment phase:	Continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11152Y and 11153B

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Locally advanced or metastatic
Condition:	non-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment phase:	Grandfather treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Prescriber Instruction	<i>Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.</i>

Item codes 11152Y and 11153B

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

The sponsor had no comment.