

11.02 NIVOLUMAB,

Injection concentrate for I.V. infusion 40 mg in 4 mL,

Injection concentrate for I.V. infusion 100 mg in

10 mL

Opdivo®

IPILIMUMAB

Injection concentrate for I.V. infusion 50 mg in 10 mL

Yervoy®

BRISTOL-MYERS SQUIBB AUSTRALIA PTY LTD

1 Purpose of Submission

- 1.1 This Category 3 submission requested the PBAC to revise the previously estimated utilisation for nivolumab (Opdivo®) and ipilimumab (Yervoy®) (herein referred to as NIVO+IPI) for the treatment of unresectable malignant mesothelioma to reflect the higher than estimated utilisation of NIVO+IPI for first-line mesothelioma treatment since listing on 1 July 2021.
- 1.2 The sponsor proposed that the existing risk sharing arrangement (RSA) caps be increased to reflect these revised estimates. The sponsor also proposed that the percentage rebate could be lowered in the case that the changes to the RSA caps were not acceptable.

2 Background

- 2.1 Nivolumab and ipilimumab are currently listed on the PBS as a Section 100 (s100) Efficient Funding of Chemotherapy (EFC) (Public/Private Hospital) Authority Required (STREAMLINED) listing for use together to treat unresectable malignant mesothelioma.

Registration status

- 2.2 Nivolumab and ipilimumab are TGA registered for the following indication:
'(Nivolumab), in combination with ipilimumab, is indicated for the first-line treatment of patients with unresectable malignant pleural mesothelioma.
(ipilimumab), in combination with nivolumab, is indicated for the first-line treatment of patients with unresectable malignant pleural mesothelioma.'

Previous PBAC consideration

2.3 NIVO+IPI for the treatment of unresectable malignant pleural mesothelioma was recommended by the PBAC at its March 2021 meeting. NIVO+IPI has been listed on the PBS since July 2021.

Current utilisation, RSA and expenditure

2.4 At its February 2024 meeting, the Drug Utilisation Sub-Committee (DUSC) considered an analysis of the predicted versus actual utilisation of NIVO+IPI over the first 24 months of listing for unresectable malignant mesothelioma. The report found that while numbers of patients and scripts were similar to the estimated numbers, the overall expenditure was higher than estimated. Consequently, the RSA caps were being exceeded (Table 1). A potential counting error has been identified with the number of predicted patients included in Table 1. The DUSC will reconsider the figures and liaise with the sponsor at a subsequent DUSC meeting.

Table 1: Estimated and actual utilisation and expenditure of NIVO+IPI

		Year 1 1 July 2021 to 30 June 2022	Year 2 1 July 2022 to 30 June 2023	Year 3 1 July 2023 to 30 June 2024*
Patients	Predicted# ⁺	1 (1)	1 (1)	1 (1)
	Actual	748	742	502
	Difference#	- % (-%)	- % (-%)	NA
Prescriptions	Predicted#	2 (3)	3 (3)	3
	Actual	7,997	7,724	3,387
	Difference#	- % (-%)	- % (-%)	NA
Net Cost PBS/RPBS	Predicted#	4 (5)	6 (6)	6
	Actual	\$58,009,360	\$59,793,100	\$27,911,298
	Difference#	- % (-%)	- % (-%)	NA
Total Commonwealth Payment	Actual	7	7	7
RSA Cap Threshold	Actual	7	7	7
Total % of Cap Reached	Actual			NA

Source: Table 2 and Table 3, Item 7.2 DUSC Report, DUSC Meeting February 2024; total Commonwealth payments have been updated with the latest available data to May 2024.

* Year 3 contains data up to May 2024 and is not representative of a full listing year.

Note: Total Commonwealth payment is based on Special Pricing Arrangements resulting in less cost to PBS/RPBS than the published DPMQ.

Figures in italics were derived by the Secretariat, adjusted from calendar year to a 1 July start. For example, first listing year 500 to < 5,000 patients = 7/12 x 500 to < 5,000 + 5/12 x 500 to < 5,000

+ A potential counting error has been identified in the number of predicted patients and will be reconsidered at a subsequent DUSC meeting.

The redacted values correspond to the following ranges:

1 500 to < 5,0000

2 10,000 to < 20,000

3 5,000 to < 10,000

4 \$60 million to < \$70 million

5 \$50 million to < \$60 million

6 \$40 million to < \$50 million

7 \$10 million to < \$20 million

8 \$20 million to < \$30 million

- 2.5 DUSC considered that the discrepancy in estimated and actual expenditure was due to:
- An increase in patients undergoing initial treatment as the incidence of mesothelioma increases (as predicted by DUSC and PBAC during the March 2021 submission), resulting in a higher-than-expected number of prevalent patients.
 - Clinicians preferring to use two- or three-weekly flat dosing of 240 mg or 360 mg (approximately 62% of scripts) rather than the by-weight dose of 3 mg/kg presented in the March 2021 submission, resulting in a higher expenditure.
 - For patients receiving weight-based dosing, as identified by PBAC and DUSC when considering the March 2021 submission, using the average patient weight from the Checkmate 743 trial of 72.75 kg would underestimate expenditure, as the larger male patients who were more likely to be diagnosed with mesothelioma in Australia would need higher doses; and
 - DUSC identified some patients were receiving NIVO+IPI treatment beyond the 24 months limited in the restriction.
- 2.6 As part of their response to the DUSC Report, the sponsor requested that the PBAC recommend increasing the RSA caps or reducing the rebate to account for the uptake and dosage utilisation identified by DUSC and consequent exceeding of expenditure and RSA caps.
- 2.7 At its March 2024 meeting, the PBAC considered the DUSC report and agreed with DUSC on the main drivers of utilisation beyond the March 2021 estimates. The PBAC noted the sponsor's request and said that the current cap was working as intended, to account for uncertainty related to the incidence rates and the higher proportion of flat-dosing. The PBAC considered that an application to change the RSA caps on the basis of a higher proportion of flat-dosing would not be appropriate.
- 2.8 The DUSC report and the submission both state that the RSA cap for the year 2023/2024 is likely to be exceeded.

3 Requested listing

- 3.1 The submission proposed no changes to the existing listing.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from organisations (1) via the Consumer Comments facility on the PBS website. The comments from the Lung Foundation of Australia supported continued PBS-listing of NIVO+IPI for unresectable malignant

mesothelioma. The Lung Foundation described a range of benefits of continuing the listing, including access to a variety of treatments for unresectable malignant mesothelioma patients, the clinical benefit compared to other treatments for the disease and that NIVO+IPI is an effective treatment which improves patient outcomes.

Rationale for changes to the key inputs for financial estimates

- 4.3 The submission requested consideration of new financial estimates where the following changes were made:
- An increased uptake rate for first-line (1L) mesothelioma patients.
 - Applying a new public/private hospital split, based upon current usage.
 - Lower prices as both NIVO and IPI have undergone statutory price reductions.
- 4.4 The submission concurred with the PBAC's finding that the patient numbers in the March 2021 submission were underestimated. However, the submission argued that the number of initiating patients was higher than estimated due to a higher-than-expected uptake rate in first-line malignant pleural mesothelioma (MPM), as well as use in non-pleural mesothelioma and 2L MPM, rather than a higher incidence of mesothelioma. The submission argued that the age-adjusted incidence rate has remained consistent for the previous three years (2020 through 2023) at 2.8 cases per 100,000 population. The submission thus did not present a change in incidence for mesothelioma.
- 4.5 The submission proposed that a challenge in estimating the uptake rates was that NIVO+IPI was one of the few new medicines for mesothelioma in 10 years and that there was not a comparable situation from which to estimate uptake rates.
- 4.6 A possible driver for higher uptake identified by the submission was the clinical management environment. The submission raised that Australian clinical management guidelines from the Asbestos Diseases Research Institute were last updated in 2013, and that many oncologists would be referring to more recent guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO). The NCCN guidelines released in 2024 "recommend NIVO+IPI as a preferred treatment option for both first-line and second-line for patients with epithelioid and non-epithelioid malignant unresectable pleural and non-pleural mesothelioma" and the ESMO guidelines published in 2021 recommend "NIVO+IPI as the preferred first line option for unresectable MPM". As such, the submission argued that more patients with unresectable MPM and non-pleural mesothelioma could be assumed to be accessing NIVO+IPI as first-line treatment. No evidence was provided to support this assertion.
- 4.7 Additionally, the submission presented that the improvement NIVO+IPI provided over existing treatments at the time of listing may have encouraged more patients to seek treatment rather than best supportive care (BSC), combined with NIVO+IPI being available on the PBS resulted in more patients than estimated. The improved

outcomes also means that clinicians will be more likely to prescribe, with the sponsor's survey of 12 Australian mesothelioma clinicians (February 2024) finding that 1L NIVO+IPI was the preferred treatment in 100% of cases for patients with unresectable malignant mesothelioma with a WHO rating of 0 or 1. It would be reasonable to assume that the uptake rates presented in March 2021 accounted for the superiority of NIVO+IPI over BSC and subsidised access of NIVO+IPI.

- 4.8 The final contributor to increased uptake of NIVO+IPI identified by the submission was that clinical trials for other immunotherapies have now either stopped recruiting or have not been launched in Australia, directing more patients to NIVO+IPI. It is unclear whether clinical trial recruitment was a factor in estimating the uptake in March 2021.
- 4.9 The submission agreed with the PBAC and DUSC that the preference for flat-dosing had impacted the utilisation and cost to the PBS. The submission noted the PBAC's opinion that amending the estimated costs and thus financial caps based upon the impact of flat-dosing versus weight-based dosing would be inappropriate. As such the submission did not provide re-calculated estimates based upon the flat-dosing observations by DUSC.
- 4.10 The submission agreed with the PBAC and DUSC that there appeared to be some use of NIVO+IPI beyond the 24 months stopping criteria. The submission argued that this was minimal, with "approximately 8-30 (0.6%-2.2%) patients" continuing past the 2-year stopping point. While acknowledging that this would contribute to higher-than-expected utilisation, the submission stated that it was not a major contributor.

Estimated PBS usage and financial implications

- 4.11 The requested AEMP for nivolumab and ipilimumab is unchanged from the current listing for this indication.
- 4.12 Table 2 outlines the changes between the July 2021 listing and the new inputs used for this submission.

Table 2: Summary of key inputs and assumptions to the financial estimates for the PBS listing and current submission

Model input		Base case variable	PBS Listing	March 2024 Submission	Note
Eligible 1L mesothelioma population		ABS population statistics - incidence rate for mesothelioma cancer	3.0 per 100,000 ABS population statistics; PBAC & DUSC recommendation	3.0 per 100,000 ABS population statistics; PBAC & DUSC recommendation	Unchanged
		Proportion of mesothelioma that is unresectable	93.52% (Linton, et al. 2014)	93.52% (Linton, et al. 2014)	Unchanged
		Proportion of all mesothelioma patients who are ECOG 0-1	79.39% (Lau, Boyer, Lee, & Kao 2020)	79.39% (Lau, Boyer, Lee, & Kao 2020)	Unchanged
		Uptake rate First-line (if NIVO+IPI available)	58.99% PBAC recommendation	% February 2024 Clinician Survey (87%) & Sponsor reduction to account for expertise of survey respondents (%)	Changed to reflect increased initiation with NIVO+IPI
PBS/ RPBS split	NIVO + IPI	PBS Listing - Based on existing PBS Item Statistics for last 12 months (January 2023 – December 2023) for NIVO+IPI for the treatment of unresectable malignant mesothelioma and CHEMO	97.00% PBS; 3.00% RPBS	96.42% PBS; 3.58% RPBS	Changed to reflect current split.
	CHEMO		98.14% PBS; 1.86% RPBS	98.53% PBS; 1.47% RPBS	Changed to reflect current split.
Public/ Private split	NIVO + IPI		34.35% public; 65.65% private	25.85% public; 74.45% private	Changed to reflect current split.
	CHEMO		39.04% public; 60.96% private	40.82% public; 59.18% private	Changed to reflect current split.
NIVO+IPI Price	NIVO	In April 2022, NIVO incurred a 5% 5 Year Statutory Price Reduction	Published/Effective AEMP NIVO 40 mg: \$830.70/\$ NIVO 100 mg: \$2,076.75/\$	Published/Effective AEMP NIVO 40 mg: \$789.17/\$ NIVO 100 mg: \$1,972.91/\$	Changed to reflect current prices.
	IPI	In April 2024, IPI will incur a 5% 10 Year Statutory Price Reduction	Published/Effective AEMP IPI 50 mg: \$5,625.92/\$	Published/Effective AEMP IPI 50 mg: \$5,344.62/\$	Changed to reflect current prices.

Source: Table 3 of the submission, with “Notes” column added by the secretariat.

Abbreviations: 1L = first line; NIVO = nivolumab; IPI = ipilimumab; CHEMO = chemotherapy; ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; ECOG = Eastern Cooperative Oncology Group; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

- 4.13 The submission presented a revised uptake rate for patients with 1L mesothelioma of % for the re-calculated estimated financial impact which correspond to the remaining 3 years of the RSA deed. This was developed by considering the uptake rate recommended by the PBAC in March 2021 (58.99%) and the results of the Clinician Survey (February 2024) of 12 clinicians (%). The applicant chose to reduce the uptake rate as measured in the survey, as it considered that the 12 clinicians may not be representative of all Australian clinicians. It is noted that the revised uptake rate of % is arbitrary, having been estimated without evidentiary basis.
- 4.14 The submission also included an estimate for first-line patients who have relapsed post-extrapleural pneumonectomy (EPP). The submission assumed an uptake rate of 33% for this patient group. This population was recommended to be added to the model by the PBAC in the March 2021 submission and was included by the sponsor when negotiating the initial RSA.

- 4.15 For the estimated second line use of NIVO+IPI, <500 patients compared to <500 in March 2021 were identified as eligible for treatment. This resulted in <500 rather than <500 patients in the second line treatment arm.
- 4.16 The estimated extent of use, cost of NIVO+IPI to the PBS/RPBS and the net financial implications to the PBS/RPBS are presented in Table 3. The financial impact to Services Australia will be determined by that agency as part of the post PBAC process.
- 4.17 With the proposed revisions to the estimates, the submission estimated that 500 to < 5,000 patients would be supplied NIVO+IPI over the first six years of listing (500 to < 5,000 in Year 1 to < 500 in Year 6). This is compared to a total of 500 to < 5,000 patients estimated to be treated with NIVO+IPI in the March 2021 submission ranging from < 500 patients in the first year excluding grandfathered patients to < 500 in Year 6.
- 4.18 The submission stated that the estimated net financial impact to the PBS/RPBS for the listing of NIVO+IPI is \$100 million to < \$200 million over six years (Year 1 \$20 million to < \$30 million to Year 6 \$10 million to < \$20 million). This is compared to the estimated costs in March 2021 submission of \$80 million to < \$90 million over six years (Year 1 \$10 million to < \$20 million to Year 6 \$10 million to < \$20 million).

Table 3: Estimated use and financial implications

	Year 1 2021	Year 2 2022	Year 3 2023	Year 4 2024	Year 5 2025	Year 6 2026
Estimated extent of use						
1L MPM without EPP (A)	1	1	1	1	1	1
1L MPM with EPP (B)	1	1	1	1	1	1
1L MPM Total (C)	1	1	1	1	1	1
2L MPM (D)	1	-	-	-	-	-
Total patients 1L+2L (C+D)	2	1	1	1	1	1
Total patients 1L+2L March 2021	1	1	1	1	1	1
Number of scripts dispensed	3	3	3	3	3	3
Estimated financial implications of NIVO+IPI						
Cost to PBS/RPBS less co-payment	4	5	5	5	4	4
Estimated financial implications of comparators						
Cost to PBS/RPBS less co-payment	6	6	6	6	6	6
Net financial implications						
Net cost to PBS/RPBS	4	5	5	5	5	5
March 2021 Net cost to PBS/RPBS	4	5	5	5	5	5

Abbreviations: 1L, first-line treatment; 2L, second-line treatment; EPP = post-extrapleural pneumonectomy; IPI, ipilimumab; MBS = Medical Benefits Scheme; MPM = malignant pleural mesothelioma; NIVO, nivolumab; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: PBS Nivolumab + Ipilimumab MPM vB 20210607 Financial workbook; Nivolumab plus Ipilimumab unresectable malignant mesothelioma Utilisation and Cost Model_March2024

The redacted values correspond to the following ranges:

1 < 500

2 500 to < 5,0000

3 10,000 to < 20,000

4 \$20 million to < \$30 million

5 \$10 million to < \$20 million

6 net cost saving

Risk-sharing arrangements

- 4.19 The submission requested a change to the existing RSA caps based upon these new estimates. The requested changes are in Table 4. The new caps would result in extra cost to the PBS/RPBS of \$10 million to < \$20 million dollars over the remaining 3 years of the RSA.
- 4.20 The Year 3 expenditure as presented by the sponsor was updated during the evaluation to include data up to May 2024. The Secretariat noted that this entire Year 3 period would have elapsed and accrued upon consideration by the PBAC and that the current cap reflects the contractual arrangements under the current Deed of Agreement between the Commonwealth and the sponsor. The PBAC noted that the sponsor calculated the proposed RSA caps based on calendar years which may be different when converted to financial years.
- 4.21 The pre-PBAC response requested that the agreed reimbursement for expenditure above the caps be reduced to account for the increase in utilisation if the proposal to

increase the caps is not the preferred way to amend the deed. The proposed new rebate from the pre-PBAC response is |% compared to the current rebate of |%.

Table 4: Current versus proposed RSA expenditure caps for NIVO+IPI in unresectable malignant mesothelioma

	Year 1 1st July 2021 to 30th June 2022	Year2 1st July 2022 to 30th June 2023	Year 3 1st July 2023 to 30th June 2024*	Year 4 1st July 2024 to 30th June 2025	Year 5 1st July 2025 to 30th June 2026
Current RSA Cap Threshold					
Proposed RSA Cap Threshold	N/A	N/A	¹	¹	¹
Variance between current and proposed RSA	N/A	N/A			
Total Commonwealth Expenditure (Actual)	¹	¹	^{1*}		
Total % of Cap Reached					

Source: Table 6 of the submission; DUSC Report, February 2024 & Worksheet 5. Impact - net; Nivolumab plus Ipilimumab unresectable malignant mesothelioma Utilisation and Cost Model_March2024.

* Year 3 contains data up to May 2024 (11 months through the deed year) and is not representative of a full listing year.

The redacted values correspond to the following ranges:

1 \$10 million to < \$20 million

5 PBAC Outcome

- 5.1 The PBAC did not advise making amendments to the current Risk Sharing Arrangement (RSA) for nivolumab (Opdivo®) and ipilimumab (Yervoy®) for unresectable malignant mesothelioma. The PBAC advised that the evidence provided by the submission did not sufficiently justify the requested changes to the subsidisation caps or rebate for expenditure above the caps. The PBAC considered that the current RSA is working as intended to manage the uncertainty around the original financial estimates.
- 5.2 The submission presented potential causes of an increase in uptake rates and thus expenditure. These included increased initiation with NIVO+IPI as a result of changes to international treatment guidelines and an absence of competitor clinical trials. The PBAC considered that no evidence was provided to support that changes to guidelines had increased uptake of NIVO+IPI. The submission did not provide an explanation of how the original uptake rate accounted for clinical trials of competing treatments at the time of the March 2021 submission. The PBAC concluded that it was unclear how the absence of competitor clinical trials and a change in guidelines would impact the current uptake rate of NIVO+IPI.
- 5.3 The PBAC noted that the uptake rate for the March 2021 submission would presumably have accounted for the superior efficacy of treatment with NIVO+IPI. It also noted that the proposed uptake rate in this submission was not literature-based whereas the March 2021 uptake rate was, and that there was no way to confirm that the clinician survey was representative. Thus, the PBAC considered there was insufficient evidence to change the uptake rate to |% in each year of listing.

- 5.4 The PBAC advised, in agreement with the DUSC, that the use of flat-dosing and an increase in incidence of unresectable malignant mesothelioma were the biggest drivers of expenditure.
- 5.5 The PBAC recalled that in its March 2021 recommendation for listing, the Committee advised that a risk sharing arrangement would be required to address a number of uncertainties informing the financial costs, including the number of second line patients who would access treatment, and the associated cost-effectiveness, as well as the impact of flat dosing (paragraph 7.12, NIVO+IPI minutes, March 2021 PBAC meeting). The PBAC maintained that the RSA in its current form was addressing these uncertainties, particularly as the DUSC analysis indicated that flat dosing had a large impact to expenditure.
- 5.6 The PBAC noted that it is uncertain if the caps will continue to be exceeded for the remainder of the deed.
- 5.7 The PBAC noted that this submission was not eligible for an Independent Review. Independent Review is only available to submissions seeking a change to the listing criteria (such as a request for a new indication, an objectively different subtype of disease or a new treatment population).

Outcome:

Not recommended

6 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.

7 Sponsor's Comment

The sponsor had no comment.