7.14 NIVOLUMAB

Injection concentrate for I.V. infusion, 40 mg in 4 mL, Injection concentrate for I.V. infusion, 100 mg in 10 mL,

Opdivo®, Bristol-Myers Squibb Australia Ltd

1 Purpose of Application

1.1 This minor resubmission requested a Section 100 (Efficient Funding of chemotherapy – Public and Private Hospital) listing for treatment of recurrent or metastatic (RM) squamous cell carcinoma of the oral cavity, pharynx or larynx (SSCHN) in patients who have progressed within 6-months after platinum-based chemotherapy.

1.2 This minor resubmission also sought to address the issues regarding the economic model raised by the PBAC at its November 2017 meeting. The minor resubmission proposed a [redacted]% reduction to the effective price offered in November 2017, and a [redacted]% reduction in the number of eligible patients. It also presented revised financial estimates to reflect the price reduction offered in the minor resubmission and other concerns raised by DUSC and PBAC at their September 2017 and November 2017 considerations of the previous major submission, respectively.

2 Requested listing

2.1 This minor resubmission did not propose any changes to the listing requested in the previous major submission. Additions proposed by the Secretariat to the previously requested listing are in italics. The effective price listed below reflects the [redacted]% reduction offered in the minor resubmission.

2.2 In November 2017 the PBAC advised that the 'PBS indication' component of any PBS restriction should exclude the nasopharyngeal subgroup of SCCHN. The PBAC previously advised that all remaining aspects of the proposed restriction were appropriate and consistent with the current listing of nivolumab for unresectable Stage III or Stage IV malignant melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC) (paragraph 7.2, November 2017 PBAC meeting).

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg 360 mg	8 8	$7560.13 (Public, published) $[redacted] *(Public, effective)* $7703.43 (Private, published) $[redacted] *(Private, effective)*	Opdivo	Bristol Myers Squibb Pty Ltd.
Category / Program :	Section 100 - Efficient funding of Chemotherapy				
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives				
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:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined				
Clinical criteria:	Patient must have a WHO performance status of 0 or 1 AND The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must have progressed within 6 months of receiving prior platinum based chemotherapy *AND* *Patient must not have received prior treatment with a PD-1 inhibitor for this condition.*				
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.				
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. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.				

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg 360 mg	11 11	$7560.13 (Public, published) $[redacted] *(Public, effective)* $7703.43 (Private, published) $[redacted] *(Private, effective)*	Opdivo	Bristol Myers Squibb Pty Ltd.
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:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition AND Patient must have stable or responding disease AND The treatment must be the sole PBS-subsidised therapy for this condition
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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

3 Background

3.1 Nivolumab was registered on the Australian Register of Therapeutic Goods (ARTG) on 11 July 2017 for the following indication: as monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum based therapy.

3.2 Nivolumab is PBS listed for unresectable Stage III or Stage IV malignant melanoma, locally advanced or metastatic NSCLC, and stage IV clear cell variant RCC.

3.3 Nivolumab for the treatment of RM SSCHN was considered by the PBAC in November 2017. The PBAC decided not to recommend listing based on "uncertainty in the nature and magnitude of its incremental clinical benefit in Australian clinical practice, and a high and overoptimistic estimated incremental cost effectiveness ratio at the price proposed by the submission."

3.4 A summary of the matters of outstanding concern to the PBAC as noted in the minutes of the November 2017 meeting, and how they have been addressed in the minor resubmission, is provided in the table below.

Table 1: Matters of outstanding concern to the PBAC and how they have been addressed in the minor resubmission

Matters of outstanding concern at November 2017 consideration	Response in minor resubmission
'…a high and overoptimistic estimated incremental cost effectiveness ratio at the price proposed by the submission.' (paragraph 7.1, November 2017 PBAC PSD)	Revised effective price of $[redacted]/100 mg vial reflecting a [redacted]% reduction
'...the PBAC agreed with ESC, and advised that the applicability of the results to the Australian setting remained uncertain. The PBAC remained particularly uncertain about the consequence of replacing cetuximab with capecitabine as a comparator on the incremental effectiveness of nivolumab.'	Comparators unchanged; disparity acknowledged

Matters of outstanding concern at November 2017 consideration	Response in minor resubmission
(paragraph 7.4, November 2017 PBAC PSD)	
'The PBAC was concerned that the results of a subgroup analysis showed that OS HR ([redacted] (95% CI: [redacted])) was more favourable when nivolumab was compared to cetuximab, than to methotrexate or docetaxel, noting that this disparity in comparators contributed to uncertainty in estimating the magnitude of incremental clinical benefit derived with nivolumab in the Australian clinical setting.' (paragraph 7.6, November 2017 PBAC PSD)	Not addressed
'The PBAC was also concerned regarding the likely reduced effectiveness of nivolumab in the older patient population (>75 years.' (paragraph 7.7, November 2017 PBAC PSD)	Not addressed
'…any further evidence that may be available to demonstrate the comparative effectiveness of nivolumab in the proposed PBS population, to compensate for the disparity in comparator choice;' (paragraph 7.19, November 2017 PBAC PSD)	Not addressed
'...an updated economic model based on more realistic post-progression utilities in modelled arms, and either methods of extrapolation and estimates of nivolumab treatment duration which are less favourable to nivolumab, or which are based on more persuasive justifications of the log-logistic method of extrapolating OS and the [redacted]% increase in nivolumab treatment duration for the base case of the updated economic model;' (paragraph 7.19, November 2017 PBAC PSD)	i. "Modified" utility values were applied to the 'Alive Following Progression' health state using treatment specific utilities observed in Study CA209141 for the within trial period, and then equal utility values ([redacted]) applied for the extrapolated period ii. Method of extrapolation unchanged (i.e. log-logistic); the justification provided centred on comparison with proposed trends in long-term OS from other immunotherapies, and mathematical properties of the model ii. [redacted]% increase in nivolumab treatment duration; which was stated to be based on the mean number of additional infusions received by patients treated beyond progression
'...a base case ICER of [redacted]/QALY, which the PBAC considered would be a relevant incremental cost-effectiveness target to account for the current context given the uncertainties from the clinical evidence in estimating the extent to which nivolumab would address the unmet clinical need in Australian patients and also in the economic model;' (paragraph 7.19, November 2017 PBAC PSD)	Revised base case ICER = $[redacted]/QALY; which was stated to be based on the lowest effective price available from the sponsor's global partner
'The PBAC considered that the estimated financial cost to the PBS was high, and that there were significant uncertainties in the financial estimates presented in the submission, noting the concerns raised by DUSC regarding potential (i) overestimation of the eligible patient population; (ii) overestimation of the uptake rate; (iii) underestimation of the treatment duration due to risk of post-progression treatment; and (iv) underestimation of the average Australian body weight.'	[redacted]% reduction in the eligible patient numbers Mean number of infusions revised from [redacted] to [redacted] Uptake rate and average Australian body weight unchanged

Matters of outstanding concern at November 2017 consideration	Response in minor resubmission
(paragraph 7.18, November 2017 PBAC PSD)	
'…a proposal for a risk-share agreement with 100% rebate beyond the agreed subsidisation caps to mitigate the uncertainties raised by DUSC, including the risk of nivolumab use beyond disease progression.' (paragraph 7.19, November 2017 PBAC PSD)	Agreed

Source: November 2017 PBAC minutes; March 2018 minor resubmission.

The redacted table shows ICERs in the range of $45,000/QALY - $75,000/QALY.

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

4 Comparator

4.1 The previous major submission nominated current Australian standard of care (SOC) as the main comparator, specifically one of: paclitaxel, docetaxel, methotrexate or capecitabine. The nominated main comparator was unchanged in the minor resubmission.

4.2 At its November 2017 meeting, the PBAC was uncertain of the applicability of the SOC comparators in the key trial to the nominated SOC comparators in Australia, and was particularly uncertain regarding the consequence of replacing cetuximab with capecitabine as a comparator on the incremental effectiveness of nivolumab (paragraph 7.4, November 2017 PBAC PSD).

4.3 The PBAC had also requested that any future resubmission should include further evidence that may be available to demonstrate the comparative effectiveness of nivolumab in the proposed PBS population, to compensate for the disparity in comparator choice (paragraph 7.19, November 2017 PBAC PSD).

4.4 The minor resubmission acknowledged that one of the investigator's choice (IC) options is not used in the Australian setting, but argued that the SOC for treating this condition is varied, and therefore maintained the previous approach of assuming the trial's comparative results applied directly to Australia. The minor resubmission confirmed that no additional trial evidence was likely to be available in the near future to inform the comparative efficacy or safety of nivolumab monotherapy versus the SOC defined for the proposed PBS population.

For more detail on the 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 individuals (2), health care professionals (3) and organisations (1) via the Consumer comments facility on the PBS website. The comments described a range of benefits of treatment with nivolumab for SSCHN including increased survival and avoidance of surgery.

5.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong and ongoing support for nivolumab for treatment of SCCHN, on the basis of high clinical need. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab for SCCHN, which was 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement), based on a comparison with chemotherapy[1]. The PBAC considered that an ESMO-MCBS of 3 better reflected the evidence available, and acknowledged that the score may increase with expected updated data.

Clinical trials

5.4 As a minor submission, no new clinical evidence was presented in the resubmission.

5.5 The minor resubmission re-emphasised previously presented quality of life (QoL) data (EORTC-QLQ-C30, EORTC-QLQ-H&N35 and EQ-5D), claiming that nivolumab stabilised patient-reported symptoms and functioning from baseline to weeks 9 and 15, whereas treatment with the IC led to clinically meaningful deterioration.

5.6 The clinical claim was unchanged in the minor resubmission.

Economic analysis

5.7 In response to several concerns raised by the PBAC at its November 2017 consideration of the major submission, the minor resubmission presented revised assumptions in the cost-utility (cost per QALY gained) model comparing nivolumab to current SOC for the treatment of patients with recurrent or metastatic SCCHN.

5.8 The PBAC had considered that a number of key drivers in the economic model favoured nivolumab, including: the model used to extrapolate overall survival (OS); the application of different utility values across the post-progression health state; the use of progression-free survival (PFS) to estimate treatment duration; and the exclusion of costs associated with subsequent therapies in the economic model (paragraphs 7.11 and 7.19, November 2017 PBAC PSD). The Committee had advised that any future resubmission should address these issues with the economic model.

5.9 Revisions to the key assumptions in the economic model across the November 2017 and March 2018 submissions are presented in the table below.

1 Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

Table 2: Revisions to the economic model across submissions

Matters of outstanding concern	Nov-17 major submission	Nov-17 Pre-PBAC response	Mar-18 minor resubmission
KEY ASSUMPTIONS			
Time & convergence	[redacted] years; converge from [redacted] years	Unchanged	Unchanged
Parametric function	Log-logistic PFS & OS	Unchanged	Unchanged
KM estimates	Median time to follow-up	Unchanged	Unchanged
Utilities	Treatment specific based on CA209141	Unchanged	Treatment-specific utilities within trial; same values post-trial
Patient weight	[redacted] kg	Unchanged	Unchanged
Maximum duration of treatment	Modelled PFS	Modelled nivolumab PFS + [redacted]%	Unchanged
Price per 100 mg vial	[redacted]	[redacted]	[redacted]
ICER			
Cost/LY	[redacted]	[redacted]	[redacted]
Cost/QALY	[redacted]	[redacted]	[redacted]

Source: Table 11, p.12 of the minor resubmission.
Abbreviations: ICER = incremental cost effectiveness ratio; LY = life year; QALY = quality adjusted life year; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival.

The redacted table shows ICERs in the range of $45,000 – $105,000.

5.10 The minor resubmission noted that [redacted]% of patients were treated beyond a 'response evaluation criteria in solid tumours' (RECIST)-defined progression, therefore the 'Alive Following Progression' health state includes patients still on therapy. As such, the resubmission claimed that it was reasonable to apply treatment specific utilities in this health state that are higher than those in the IC arm. However, in light of PBAC's concerns regarding the appropriateness of assuming an ongoing difference in utility values in the 'Alive Following Progression' health state beyond the trial period (paragraphs 7.17 and 7.19, November 2017 PBAC PSD), the minor resubmission applied 'modified' utility values in this health state. These modified utility values comprised an ongoing difference for the trial period ([redacted] for the nivolumab arm versus [redacted] for the IC arm), and the same utility value ([redacted]) in both arms for the extrapolated period, in the 'Alive Following Progression' health state.

5.11 In the November 2017 submission, a log-logistic function was used to extrapolate OS in the nivolumab arm of Study CA209141. At its October 2017 meeting, the ESC considered that fitting a log-logistic model to the OS data was the least conservative choice, and advised that exponential curves would have been the most appropriate method for extrapolation. Additionally, the PBAC had sought for '…more persuasive justifications of the log-logistic method of extrapolating OS…' in a future resubmission (paragraph 7.19, November 2017 PBAC PSD).

5.12 The minor resubmission maintained that log-logistic, and not exponential, was the most appropriate method to extrapolate OS, in terms of goodness of fit statistics, consistency with the trial data and clinical plausibility, as summarised in the table below. This information has not been independently verified.

Table 3: Comparison of log-logistic and exponential models to extrapolate OS

	Log-logistic	Exponential
Goodness of fit statistics	AIC: [redacted] BIC: [redacted]	AIC: [redacted] BIC: [redacted]
Visual inspection	Best fit with KM data 1 years: [redacted]% v [redacted]% 2 years: [redacted]% v [redacted]%	Not a good fit 1 years: [redacted]% v [redacted]% 2 years: [redacted]% v [redacted]%
Clinical plausibility: long term extrapolation of OS for nivolumab	Gradually declining OS 3 years: [redacted]% 4 years: [redacted]% 5 years: [redacted]%	Sharp decrease in OS 3 years: [redacted]% 4 years: [redacted]% 5 years: [redacted]%

Source: Table 5, p.6 of the minor resubmission.
Abbreviations: AIC = Akaike information criteria; BIC = Bayesian information criteria; KM = Kaplan-Meier; OS = overall survival.

5.13 Additionally, the minor resubmission claimed that the mathematical properties of the log-logistic distribution matched the underlying scientific assumptions of immunotherapy agents as it allows a clinically plausible "plateau" in survival, noting that it is an accelerated failure time model that allows non-zero initial hazards as well as non-monotonic decreasing hazards. The PBAC had previously noted this argument, and advised that '...the choice of the method of extrapolation of OS [and of different post-progression utilities] depended on the nature of the clinical evidence, and therefore what was deemed appropriate in one cancer setting was not necessarily predictive of other cancer settings' (paragraph 7.16, November 2017 PBAC meeting).

5.14 The updated economic model in the minor resubmission also included an [redacted]% increase in nivolumab treatment duration for the base case. An [redacted]% increase (i.e. PFS duration of treatment (DOT) + [redacted]%) in nivolumab treatment duration was previously used as the rationale for a reduction in requested price during the November 2017 pre-PBAC response, which stated that the estimate of [redacted]% was based on the mean number of additional infusions received per patient treated beyond progression (constituting [redacted]% of patients from the trial) (paragraph 7.14, November 2017 PBAC PSD). The underlying assumption of this estimate was that the mean DOT observed in CA209141 ([redacted] infusions) applied to patients treated no further than RECIST-defined PFS, and that the mean DOT for patients treated beyond progression was [redacted] infusions ([redacted]); as such, an overall mean DOT for the patients in the nivolumab arm should be [redacted] infusions ([redacted]). The minor resubmission's statement that patients treated beyond progression in Study CA209141 received [redacted] infusions on average was not independently verifiable, and may itself be an underestimate due to truncated follow-up (i.e., not all of these patients may have recorded their final dose at the time their results were used to calculate the average estimate).

5.15 The PBAC had previously considered that this estimate was not independently verified, and could be an underestimate of the treatment duration due to truncated follow-up (paragraph 7.15, November 2017 PBAC PSD). It remained unclear in the minor resubmission whether patients whose treatment was continuing when they

were last followed-up were either censored from the calculation of the average, or if their duration of use contributing to the calculation of the average was truncated. The PBAC may also wish to note that the implied assumptions about average duration of use might not align with the selection of a log-logistic extrapolation function for health outcomes.

5.16 With the reduced effective price proposed in the minor resubmission, equal post-progression utility values for the extrapolated period and application of an [redacted]% increase in nivolumab treatment duration, the revised base case ICER was $45,000/QALY – 75,000/QALY gained, compared to $75,000/QALY – $105,000/QALY gained in the November 2017 major submission and the PBAC's target of $45,000/QALY – 75,000/QALY defined to be relevant in the current context (paragraph 7.19, November 2017 PBAC PSD).

5.17 A summary of key sensitivity analyses on the issues of outstanding concern have been presented in the table below.

Table 4: Results of sensitivity analyses

	Incremental cost	Incremental QALYs	ICER/QALY
Base case (log-logistic OS, 'modified' post-progression utilities, DOT – PFS+[redacted]%)	[redacted]	[redacted]	[redacted]
Univariate sensitivity analysis			
OS – exponential extrapolation in both arms	[redacted]	[redacted]	[redacted]
Same post-progression utilities in both arms	[redacted]	[redacted]	[redacted]
Duration of treatment (PFS+[redacted]%)^	[redacted]	[redacted]	[redacted]
Multivariate sensitivity analysis			
Exponential extrapolation of OS + same post-progression utilities ([redacted]) in both arms	[redacted]	[redacted]	[redacted]
Exponential extrapolation of OS + same post-progression utilities ([redacted]) in both arms + duration of treatment (PFS+[redacted]%)	[redacted]	[redacted]	[redacted]

Analyses in italics were carried out for the minor overview.
Abbreviations: DOT=duration of treatment; ICER = incremental cost effectiveness ratio; OS = overall survival; QALY = quality adjusted life year.
^as advised by ESC at its October 2017 meeting (paragraphs 6.33 and 6.40, November 2017 PBAC PSD)
Source: Economic model spreadsheet App_1_nivo SCCHN economic evaluation_minor resubmission.xlsx provided with the resubmission.

Drug cost/patient/course

5.18 The November 2017 major submission presented an average cost for nivolumab of $[redacted], assuming a cost of $[redacted] per infusion and patients receiving [redacted] infusions of nivolumab, based on the mean number of doses received by patients in the nivolumab arm of Trial CA209141.

5.19 Noting that an additional [redacted]% treatment duration (beyond PFS) was incorporated in the economic model to account for the [redacted]% of nivolumab patients on Study CA209141 who were treated beyond progression, the minor resubmission proposed that the mean number of infusions be updated from [redacted] to [redacted].

5.20 If recommended for listing, the drug cost/patient/course would need to be re-estimated to reflect the [redacted]% price reduction offered in the minor resubmission. The PBAC's advice on whether the mean number of infusions be updated from [redacted] to [redacted] (as proposed by the minor resubmission) would also need to be accounted for in the estimation of drug cost/patient/course.

Estimated PBS usage & financial implications

5.21 The PBAC previously requested that "any future resubmission include amended utilisation estimates addressing the concerns raised by DUSC regarding potential: overestimation of the eligible patient population; overestimation of the uptake rate; … and underestimation of the average Australian body weight" (paragraph 7.18, November 2017 PBAC PSD).

5.22 In response to the PBAC's previous concerns about the estimated financial implications, the minor resubmission:

- reduced the number of eligible patients by [redacted]%;
- reduced the % of patients rechallenged with platinum therapy from [redacted]% to [redacted]%; and
- maintained that the mean duration of therapy was [redacted] infusions.

5.23 The tables below summarise the revised PBS usage estimates presented in the minor resubmission.

Table 5: Summary of utilisation assumptions presented across PBAC submissions

Variable	November 2017 submission	November 2017 pre-PBAC response	March 2018 minor resubmission
Eligible population	-	No adjustment	[redacted]% reduction in eligible patients
% patients rechallenged with platinum therapy	[redacted]%	No change	Reduced to [redacted]%
Uptake of nivolumab	[redacted]%	No change	No change
Average weight	[redacted] kg	No change	No change
Average number of vials per patient per course	[redacted]	[redacted]	[redacted]
Price per 100 mg vial	$[redacted]	$[redacted]	$[redacted]

Source: Table 12, p.17 of the minor resubmission.

Table 6: Summary of patient number estimates presented across PBAC submissions

Patients treated on PBS/RPBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated – original major submission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated – pre-PBAC response major submission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated – minor resubmission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 13, p.17 of the minor resubmission.

Table 7: Summary of net cost to combined government health budgets presented across PBAC submissions

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net cost – original major submission	$	$	$	$	$	$
Net cost - pre-PBAC response major submission	$	$	$	$	$	$
Net cost – minor resubmission	$	$	$	$	$	$

Source: Table 14, p.17 of the minor resubmission

The redacted tables show that at year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be $20 – 30 million.

5.24 The minor resubmission estimated the revised net cost to the PBS/RPBS of $20 – 30 million in the first year of listing, increasing to $20 – 30 million in the sixth year of listing (compared to the November 2017 major submission's net cost estimates of $30 – 60 million in the first year, increasing to $30 – 60 million in the sixth year of listing). These estimates were not independently verified.

5.25 The Secretariat noted that the number of eligible patients in the minor resubmission was higher than anticipated, based on the incidence and prevalence of head and neck cancers in Australia[2]. The Secretariat noted that this disparity was due to the inclusion of patients with lip neoplasms in the estimated PBS population.

Financial Management – Risk Sharing Arrangements

5.26 The PBAC had previously requested 'a proposal for a risk-share agreement with 100% rebate beyond the agreed subsidisation caps to mitigate the uncertainties raised by DUSC, including the risk of nivolumab use beyond disease progression' (paragraph 7.19, November 2017 PBAC PSD).

5.27 The minor resubmission emphasised the sponsor's willingness to enter a risk sharing arrangement (RSA), agreeing to a 100% rebate beyond the agreed subsidisation caps to mitigate the uncertainties raised by DUSC and PBAC at their respective September 2017 and November 2017 considerations of the previous major submission.

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

6 PBAC outcome

6.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy - Public and Private Hospital) Authority Required (STREAMLINED) listing of nivolumab for the treatment of SCCHN. In making this recommendation, the PBAC considered the high unmet clinical need in an aggressive and debilitating malignancy and advised that

[2] https://www.aihw.gov.au/getmedia/bdccebf2-dbe6-44e2-9104-8461d7e7c165/16933.pdf.aspx?inline=true https://head-neck-cancer.canceraustralia.gov.au/statistics

nivolumab treatment resulted in modest yet meaningful clinical benefit for some patients.

6.2 The PBAC noted that, following the exclusion of the nasopharyngeal subgroup of SCCHN, the proposed restriction and clinical place in therapy were appropriately not further modified in the minor resubmission.

6.3 The PBAC noted that the minor resubmission acknowledged that the comparators differed between those included in the investigator's choice of therapy arm of Trial CA209141 (docetaxel, methotrexate, or cetuximab) and standard of care in Australia (paclitaxel, docetaxel, methotrexate, or capecitabine). The PBAC recalled that, at its November 2017 consideration of this submission, it had advised that the applicability of the results to the Australian setting was uncertain (paragraph 7.4, November 2017 PBAC PSD). The PBAC recalled that it was particularly concerned that the results of a subgroup analysis showed that OS HR ([redacted] (95% CI: [redacted])) was more favourable when nivolumab was compared to cetuximab, than to methotrexate or docetaxel, noting that this disparity in comparators contributed to the uncertainty in estimating the magnitude of incremental clinical benefit derived with nivolumab in the Australian clinical setting (paragraph 7.6, November 2017 PBAC PSD).

6.4 The PBAC noted that, although it had requested the provision of any further evidence that may be available to demonstrate the comparative effectiveness of nivolumab in the proposed PBS population, to compensate for the disparity in comparator choice (paragraph 7.19, November 2017 PBAC PSD), no such evidence was provided in the minor resubmission. The PBAC also noted that no evidence or justification to address PBAC's concerns regarding the efficacy of nivolumab in the older patient population (>75 years) was provided in the minor resubmission.

6.5 As such, the PBAC's advice regarding the clinical evidence presented in the minor resubmission remained unchanged. The PBAC maintained that, while nivolumab treatment resulted in modest clinical benefit in some patients, the estimation of the magnitude of incremental benefit in Australian clinical practice from Trial CA209141 was confounded.

6.6 The PBAC recalled that the November 2017 submission presented a partitioned survival model with a [redacted]-year time horizon to estimate the cost-effectiveness of nivolumab. The PBAC recalled that it had considered that a number of key drivers in the economic model favoured nivolumab. These included (i) use of a log-logistic model to extrapolate OS; (ii) application of different utility values across the model's arms for the post-progression health state; (iii) the use of PFS to estimate treatment duration (noting that [redacted]% of nivolumab patients were treated beyond disease progression); and (iv) the exclusion of costs associated with subsequent therapies in the economic model (paragraph 7.11, November 2017 PBAC PSD)

6.7 The PBAC recalled that it had therefore advised that a future resubmission should present an updated economic model based on more realistic post-progression

utilities in modelled arms, and either methods of extrapolation and estimates of nivolumab treatment duration which are less favourable to nivolumab, or which are based on more persuasive justifications of the log-logistic method of extrapolating OS and the [redacted]% increase in nivolumab treatment duration for the base case of the updated economic model (paragraph 7.19, November 2017 PBAC PSD).

6.8 The PBAC noted that the minor resubmission presented an updated economic model, with the following key amendments:

- "modified" utility values were applied to the 'Alive Following Progression' health state using treatment specific utilities observed in Study CA209141 for the trial period, and equal utility values ([redacted]) for the extrapolated period;
- an [redacted]% increase in nivolumab treatment duration, based on the mean number of additional infusions received by patients treated beyond progression.

The PBAC further noted that, while the updated economic model method of extrapolation of OS remained unchanged (i.e. log-logistic) in the minor resubmission, the justification provided centred on comparison with proposed trends in long-term OS from other immunotherapies, and mathematical properties of the model.

6.9 The PBAC noted that the revised base case ICER presented in the minor resubmission was $45,000 – $75,000/QALY. The PBAC also noted that the method of extrapolation remained the key driver of the updated economic model.

6.10 The PBAC recalled that it had advised that a base case ICER of $45,000 - $75,000/QALY would be a relevant incremental cost-effectiveness target to account for the uncertainties from the clinical evidence in estimating the extent to which nivolumab would address the unmet clinical need in Australian patients and also in the economic model (paragraph 7.19, November 2017 PBAC PSD). The PBAC advised that there was no persuasive justification provided in the minor resubmission that warranted any change to its previous advice on the relevant incremental cost-effectiveness target for nivolumab, and noted that, with all other assumptions remaining unchanged from the minor resubmission, a further reduction to the vial price of at least [redacted]% would be required to decrease the current base case ICER to below the previously defined $45,000 - $75,000/QALY threshold. Without this further reduction, the PBAC advised that nivolumab was not acceptably cost-effective in this context.

6.11 The PBAC noted that, in response to its previous concerns regarding the uncertainties in assumptions in the financial estimates (paragraph 7.18, November 2017 PBAC PSD), the minor resubmission proposed a [redacted]% reduction in the eligible patient numbers and revised the mean number of nivolumab infusions per patient from [redacted] to [redacted]. The PBAC noted that assumptions regarding the uptake rates and average Australian body weight remained unchanged in the minor resubmission.

6.12 The PBAC considered that, while all other assumptions were potentially reasonable, the number of eligible patients was unacceptably high. The PBAC considered that the higher than anticipated number of eligible patients in the minor resubmission was

potentially due to an overestimate in percentage of patients from the overall HNSCC population proceeding to first and second-line therapy. The PBAC therefore advised that a reduction of [redacted]% or more in usage would be considered appropriate.

6.13 Following its previous advice (paragraph 7.19, November 2017 PBAC PSD), the PBAC maintained that a risk-share agreement should be established based on the revised eligible number of patients, with 100% rebate beyond the agreed subsidisation caps to mitigate the uncertainties raised, including the risk of nivolumab use beyond disease progression.

6.14 The PBAC foreshadowed that further updated data may delineate subgroups of patients who do not derive the same magnitude of benefit from nivolumab treatment, and therefore a review of the eligible PBS population, cost effectiveness and risk share arrangement may be warranted in the future.

6.15 The PBAC advised that the Early Supply Rule should not apply to the listing of nivolumab.

6.16 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* that nivolumab should not be treated as interchangeable on an individual patient basis with any other drugs.

6.17 The PBAC advised that nivolumab is not suitable for prescribing by nurse practitioners.

6.18 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Subsequent to the meeting, the PBAC considered the grandfathering arrangements out of session in May 2018.

6.19 The PBAC noted advice from the sponsor that approximately 30 additional patients are receiving nivolumab for SCCHN via a co-pay program. The PBAC recommended a grandfather arrangement be added to the listing of nivolumab for SCCHN. The PBAC noted that a grandfather arrangement would provide equity of access for a small number of patients who would have met the initial PBS criteria at the time of commencing treatment, but are receiving non-PBS subsidised treatment with nivolumab via another source (such as self-funding). The PBAC noted that the sponsor did not propose to change the patient number caps, and as the rebate above the patient number caps was 100%, this would not represent any additional financial cost to government.

Outcome:
Recommended

7 Recommended listing

7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg 360 mg	8 8	Opdivo	Bristol Myers Squibb Pty Ltd.
Category / Program :	Section 100 - Efficient funding of Chemotherapy			
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives			
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:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined			
Clinical criteria:	Patient must have a WHO performance status of 0 or 1 AND The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must have progressed within 6 months of receiving prior platinum based chemotherapy. AND Patient must not have received prior treatment with a PD-1 inhibitor for this condition.			
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.			
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. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.			

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg 360 mg	8 8	Opdivo	Bristol Myers Squibb Pty Ltd.
Category / Program	Section 100 – Efficient funding of Chemotherapy			
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives			
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 – Grandfather patients
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to <listing date> AND Patient must have had a WHO performance status of 0 or 1 prior to commencing treatment with this drug for this condition AND The condition must have progressed within 6 months of receiving prior platinum based chemotherapy prior to commencing treatment with this drug for this condition AND Patient must not have developed disease progression while receiving treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition
Prescriber Instructions	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
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. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial	360 mg	11	Opdivo	Bristol Myers Squibb Pty Ltd.
nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	11		
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:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition AND Patient must have stable or responding disease AND The treatment must be the sole PBS-subsidised therapy for this condition
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

8 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.

9 Sponsor's Comment

The Sponsor thanks the PBAC for its consideration of this item and looks forward to eligible Australian patients being able to access nivolumab for the treatment of recurrent or metastatic SCCHN via the PBS in the near future.