

## 7.07 NIVOLUMAB, Injection concentrate for I.V. infusion, 40 mg in 4 mL, 100 mg in 10 mL, Opdivo<sup>®</sup>, as monotherapy, or in combination with IPILIMUMAB, Injection concentrate for I.V. infusion, 50 mg in 10 mL, 200 mg in 40 mL, Yervoy<sup>®</sup>, Bristol-Myers Squibb

### 1 Purpose of Application

- 1.1 The submission requested expansion of the existing PBS listing for nivolumab as monotherapy (NIVO), and the listings for nivolumab and ipilimumab as combination therapy (NIVO+IPI), for the treatment of unresectable Stage III or Stage IV malignant melanoma, to allow use as first-line therapy in patients whose condition is positive for a BRAF V600 mutation.
- 1.2 The submission also suggested flow-on changes to the current restrictions for BRAF inhibitors to allow their use as second-line therapy following progression on an immunotherapy, permitting treating doctors to determine the most appropriate treatment sequence.
- 1.3 The submission was based on a cost-analysis in which the first-line costs of treating a patient with NIVO monotherapy, NIVO+IPI and dabrafenib+trametinib (DAB+TRAM) were the same. The key components of the clinical issue addressed by the submission are presented below.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients with unresectable Stage III or IV malignant melanoma with a BRAF V600 mutation, previously untreated with PBS listed medicine for this indication
Intervention	NIVO monotherapy, or NIVO in combination with IPI
Comparator	PBS listed BRAF inhibitor/MEK inhibitor combinations (Main: DAB+TRAM, secondary: VEM+COBI, ENCO+BINI)
Outcomes	OS, PFS, ORR, adverse events, HRQoL
Clinical claim	NIVO and NIVO+IPI are no worse than DAB+TRAM in terms of efficacy outcomes. NIVO is no worse than DAB+TRAM in terms of safety outcomes. NIVO+IPI has an inferior profile compared with DAB+TRAM in terms of safety outcomes.

BINI = binimetinib; COBI = cobimetinib; DAB = dabrafenib; ENCO = encorafenib; HRQoL = health related quality of life; IPI = ipilimumab; NIVO = nivolumab; ORR = overall response rate; OS = overall survival; PFS = progression free survival; TRAM = trametinib; VEM = vemurafenib

Source: Table 1, p14 of the submission.

### 2 Background

#### **Registration status**

- 2.1 Nivolumab is listed on the Australian Register of Therapeutic Goods (ARTG) for the following indications relevant to the current submission:
- As monotherapy, for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma;
  - In combination with ipilimumab for the treatment of patients with unresectable or metastatic melanoma.
- 2.2 Ipilimumab is listed on the ARTG for the following indications:
- As monotherapy, for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma;
  - In combination with nivolumab for the treatment of patients with unresectable or metastatic melanoma.

***Previous PBAC consideration***

- 2.3 Both NIVO monotherapy and NIVO+IPI have previously been considered by PBAC for treatment of Stage III or Stage IV malignant melanoma, irrespective of BRAF mutation status. NIVO monotherapy was recommended for first-line therapy in patients with BRAF mutation negative melanoma, and subsequent to BRAF+MEK inhibitor therapy in patients with BRAF V600 mutation positive melanoma in November 2015. NIVO+IPI was considered three times for the treatment of unresectable Stage III or Stage IV melanoma and recommended for listing at the July 2018 PBAC meeting. The submission presented a cost-analysis in which the total cost of treating a patient with NIVO+IPI (including subsequent therapies) was equal to the cost of treating a patient with NIVO monotherapy (including subsequent therapies). NIVO+IPI was recommended on the basis of cost neutrality to the PBS, with the restriction being aligned with that for NIVO monotherapy.
- 2.4 None of the previous submissions for NIVO monotherapy or NIVO+IPI for unresectable Stage III or Stage IV malignant melanoma, presented a comparison with BRAF+MEK inhibitors as first-line treatment in the subgroup of patients with BRAF mutation positive melanoma.
- 2.5 Both NIVO monotherapy and NIVO+IPI are currently listed on the PBS for:
- First-line immunotherapy in patients with unresectable Stage III or Stage IV malignant melanoma that is negative for a BRAF V600 mutation, and
  - Later-line therapy in patients who have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor), unless contraindicated or not tolerated, in patients with unresectable Stage III or Stage IV malignant melanoma that is positive for a BRAF V600 mutation.

- 2.6 The PBAC noted that BRAF±MEK inhibitors were recommended as first-line treatment for patients with BRAF mutant unresectable or metastatic melanoma in March 2015 as “A comparison across the available trials suggested greater response rates and prolonged median progression-free survival for these cheaper targeted therapies (i.e. BRAF±MEK inhibitors) over the immune therapies” (paragraph 7.3, Pembrolizumab Public Summary Document (PSD), March 2015).
- 2.7 In addition, DAB+TRAM was recommended as adjuvant treatment for patients with Stage IIIB, IIIC or IIID BRAF positive melanoma at the July 2019 PBAC meeting and listed on the PBS for this indication as of 1 November 2019. Nivolumab as adjuvant treatment was deferred at the July 2019 meeting, with a deferral proposal reconsidered at the November 2019 PBAC meeting. Pembrolizumab as adjuvant treatment was rejected in July 2019, with a minor resubmission reconsidered at the November 2019 meeting. The availability of DAB+TRAM and/or programmed cell death-1 (PD-1) inhibitors in the adjuvant setting will impact on the treatments used in unresectable setting.

For more detail on PBAC’s view, see section 7 PBAC outcome.

### 3 Requested listing

#### Essential elements of the requested listing for nivolumab monotherapy (including maintenance therapy after combination with ipilimumab)

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
NIVOLUMAB			Published price	Opdivo®
100 mg/10 mL injection, 1 x 10 mL vial	480 mg	Initial: 8	\$7,561.36 (public)	Bristol-Myers
40 mg/4 mL injection, 1 x 4 mL vial		Continuing: 11	\$7,705.78 (private)	Squibb Australia
			Effective price	
			To be determined <sup>a</sup>	

<sup>a</sup> The submission proposed listing on a cost-minimisation basis against the effective price of DAB+TRAM

#### Essential elements of the requested listing – NIVO+IPI induction treatment

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
NIVOLUMAB			Published price	Opdivo®
100 mg/10 mL injection, 1 x 10 mL vial	120 mg	3	\$2,577.16 (public)	Bristol-Myers
40 mg/4 mL injection, 1 x 4 mL vial			\$2,651.81 (private)	Squibb Australia
			Effective price	
			To be determined <sup>a</sup>	
IPILIMUMAB			Published price	Yervoy®
200 mg/40 mL injection, 1 x 40 mL vial	360 mg	3	\$45,092.42 (public)	Bristol-Myers
50 mg/10 mL injection, 1 x 10 mL vial			\$45,762.26 (private)	Squibb Australia
			Effective price	
			To be determined <sup>a</sup>	

<sup>a</sup> The submission proposed listing on a cost-minimisation basis against the effective price of DAB+TRAM

Public Summary Document – November 2019 PBAC Meeting

**Requested restriction – nivolumab monotherapy**

<b>Initial treatment (Authority code 6070)</b>	
<b>Category/Program</b>	Section 100 – Efficient Funding of Chemotherapy
<b>Prescriber type</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks.
<b>Prescriber Instructions:</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated. 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.
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

**Requested restriction – nivolumab in combination with ipilimumab**

<b>Induction therapy (Authority code 8182)</b>	
<b>Category/Program</b>	Section 100 – Efficient Funding of Chemotherapy
<b>Prescriber type</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Induction treatment
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition, AND Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND The condition must not be ocular or uveal melanoma, AND The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition.  Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.  Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks
<b>Prescriber Instructions:</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
<b>Caution</b>	Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.

Public Summary Document – November 2019 PBAC Meeting

<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
<b>Induction therapy - grandfather patients (Authority code 8146)</b>	
<b>Category/Program</b>	Section 100 – Efficient Funding of Chemotherapy
<b>Prescriber type</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Induction treatment – Grandfather patients
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have received combined therapy with ipilimumab and nivolumab as induction for this condition prior to 1 December 2018; OR Patient must have received monotherapy with nivolumab as maintenance for this condition prior to 1 December 2018, AND Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor prior to initiating combined therapy with ipilimumab and nivolumab as induction for this condition, AND Patient must not have developed disease progression while being treated with combined therapy with ipilimumab and nivolumab as induction for this condition; OR Patient must not have developed disease progression while being treated with monotherapy with nivolumab as maintenance for this condition, AND Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, AND The condition must not be ocular or uveal melanoma, AND The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition; OR The treatment must be as monotherapy as maintenance for this condition.</p> <p>Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.</p> <p>Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.</p> <p>Maintenance treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks.</p> <p>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.</p>
<b>Prescriber Instructions:</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
<b>Caution</b>	Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Public Summary Document – November 2019 PBAC Meeting

**Requested restriction – ipilimumab in combination with nivolumab**

<b>Induction treatment (Authority code 8206)</b>	
<b>Category/Program</b>	Section 100 – Efficient Funding of Chemotherapy
<b>Prescriber type</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Induction treatment
<b>Restriction:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition,  AND  Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1,  AND  The condition must not be ocular or uveal melanoma,  AND  The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction for this condition.</p> <p>Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.</p> <p>Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks</p>
<b>Prescriber Instructions:</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

- 3.1 The restrictions for continuing treatment with NIVO monotherapy (Authority code 9298), and for the maintenance treatment phase (single agent phase) of combination NIVO+IPI (Authority code 9214) were unchanged from the current restrictions.
- 3.2 The submission proposed a Special Pricing Arrangement (SPA), with the final effective price of NIVO monotherapy and NIVO+IPI to be determined based on the effective approved ex-manufacturer prices (AEMP) of dabrafenib and trametinib.
- 3.3 The current PBS listings for initial treatment with NIVO monotherapy, and for induction treatment with NIVO+IPI, are stratified by BRAF mutation status. The submission proposed deleting the initial/induction treatment listings relevant to BRAF V600 mutation positive melanoma, and modifying the current initial treatment listings for BRAF V600 mutation negative melanoma by removing the clinical criterion 'The condition must be negative for a BRAF V600 mutation'. The requested amendments to the current listings for NIVO and NIVO+IPI are consistent with their respective TGA indications for unresectable Stage III or Stage IV melanoma, which do not restrict use by line of therapy or BRAF mutation status.
- 3.4 The restrictions for continuing treatment with NIVO monotherapy (including when used as maintenance therapy following induction with NIVO+IPI) remain unchanged.

- 3.5 The submission did not present any proposed changes to the restrictions for ipilimumab grandfathered patients (Authority codes 8178 and 8180). The submission indicated that there were 25 patients receiving NIVO in the NIVO+IPI patient access program, who may be 'grandfathered' to PBS-subsidised NIVO maintenance therapy.
- 3.6 The requested restriction was consistent with the eligibility criteria for the key trial for NIVO monotherapy and NIVO+IPI (CA209-067), which included patients who had not previously received systemic therapy for unresectable or metastatic melanoma. Patients with active brain metastases and ocular melanoma were excluded from the trial.
- 3.7 While the main body of the submission noted that the sponsor is not in a position to directly apply for a change in the PBS listing of BRAF-targeted therapy, the Pre-Sub-Committee Response (PSCR) requested flow on changes to the existing PBS restrictions for dabrafenib and vemurafenib to allow their use as second-line treatment. In CA209-067, of patients with BRAF mutation positive melanoma who received any subsequent systemic therapy, 39/43 (91%) in the NIVO+IPI arm and 54/60 (90%) in the NIVO monotherapy arm received a BRAF inhibitor ( $\pm$ MEK inhibitor), although the line of therapy at which this was received was not reported. The Economics Sub-Committee (ESC) agreed that amended PBS restrictions to allow second-line use of BRAF-targeted therapy would be required if first-line NIVO and NIVO+IPI were listed for BRAF positive melanoma. The PBAC considered that this was appropriate.
- 3.8 The ESC noted that current Australian and international guidelines\* state that first-line systemic therapy be individualised, with BRAF-targeted therapy preferred for symptomatic or rapidly progressing disease given the potential for more rapid and reliable responses, immunotherapy preferred for asymptomatic disease given the potential for more durable responses, and consideration of susceptibility to particular toxicities such as autoimmune disease. The pre-PBAC response noted that:
- The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for cutaneous melanoma were updated on 30 September, 2019 and state that "No direct randomised comparison exists between the two approaches [i.e. targeted therapy (BRAF inhibitors) and immunotherapy], but meta-analyses suggest that,

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\* Long G, Atkinson V, et al. Summary of recommendations and practice points: Clinical practice guidelines for the diagnosis and management of melanoma. Cancer Council of Australia. Available from: [www.wiki.cancer.org.au/australiawiki/index.php?oldid=199932](http://www.wiki.cancer.org.au/australiawiki/index.php?oldid=199932).

Sosman J. Overview of the management of advanced cutaneous melanoma. Available from: [www.uptodate.com/contents/overview-of-the-management-of-advanced-cutaneous-melanoma](http://www.uptodate.com/contents/overview-of-the-management-of-advanced-cutaneous-melanoma)  
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 2.2019. Available from: [www.nccn.org/](http://www.nccn.org/)

despite better outcomes within the first 12 months for targeted therapies, immunotherapy patients may have a better survival after one year”; and

- The National Comprehensive Cancer Network (NCCN) cutaneous melanoma guidelines were updated on 22 October 2019 to list NIVO+IPI combination therapy as a “preferred regimen”, upgraded from “useful in circumstances”. PD-1 inhibitor monotherapy and BRAF+MEK remain as “preferred regimens”.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Australia and New Zealand have the highest rates of melanoma in the world. The target population was patients with BRAF mutation positive unresectable Stage III or Stage IV melanoma.
- 4.2 BRAF±MEK inhibitors are currently PBS listed for first-line therapy in the target population. The submission proposed nivolumab monotherapy and NIVO+IPI combination therapies as alternative first-line therapies for these patients, as recommended in current Australian and international guidelines.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The submission nominated DAB+TRAM as the main comparator. The ESC considered that this was the appropriate comparator for first-line treatment. However, the proposed listing of NIVO monotherapy and NIVO+IPI as first-line therapy would have an impact on subsequent lines of therapy, which will affect both treatment outcomes and the costs.
- 5.2 Currently, the most commonly used treatment sequence in the target population is first-line BRAF+MEK inhibitors, followed by second-line immunotherapy (pembrolizumab, NIVO monotherapy or NIVO+IPI). There are two possible treatment sequences resulting from the proposed first-line listing of NIVO monotherapy and NIVO+IPI combination therapy, depending on whether or not BRAF+MEK inhibitors are available post-progression following first-line immunotherapy. The possible treatment sequences, and the comparisons relevant to the submission, are summarised below. The PBAC recommended that BRAF+MEK inhibitors be available post-progression following first-line immunotherapy (i.e. Scenario 2).

**Table 2: Comparisons relevant to the submission**

Line of therapy	Intervention		Comparator
	Scenario 1 BRAFi restricted to 1L (current PBS listing)	Scenario 2 BRAFi available 2L	Current PBS listings
First-line	NIVO or NIVO+IPI	NIVO or NIVO+IPI	BRAF±MEK inhibitors
Second-line	IPI <sup>a</sup> /chemotherapy/BSC	BRAF±MEK inhibitors	Immunotherapy <sup>b</sup>
Third-line+	BSC	IPI <sup>a</sup> /chemotherapy/BSC	IPI <sup>c</sup> /chemotherapy/BSC

1L = first-line; 2L = second line; BSC = best supportive care; BRAFi = BRAF inhibitor; IPI = ipilimumab; NIVO = nivolumab

<sup>a</sup> In patients who received first-line nivolumab monotherapy

<sup>b</sup> Pembrolizumab monotherapy, nivolumab monotherapy, or NIVO+IPI

<sup>c</sup> In patients who received second-line PD-1 inhibitor monotherapy

Source: Table compiled during the evaluation based on current and proposed PBS restrictions, and Australian and international treatment guidelines.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 6 Consideration of the evidence

### **Sponsor hearing**

6.1 The sponsor requested a hearing for this item. The clinician presented the practical considerations that clinicians consider when determining the treatment sequence for patients with BRAF mutant unresectable or metastatic melanoma, discussed when NIVO monotherapy or NIVO+IPI would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative.

### **Consumer comments**

6.2 The PBAC noted and welcomed the input from individuals (21), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with first-line NIVO monotherapy and NIVO+IPI including improved response rates, fewer side effects and the peace of mind that comes with being able to choose the sequence of therapy.

6.3 The PBAC noted the correspondence received from (i) Melanoma Patients Australia and (ii) Australian Melanoma Consumer Alliance and the Melanoma Research Victoria Consumer Reference Group. These organisations expressed their support for the PBS listing of NIVO monotherapy and NIVO+IPI as a first-line treatment option in patients with BRAF positive unresectable melanoma, citing the lack of clinical data supporting the current PBS restriction.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for first-line NIVO monotherapy or NIVO+IPI in the treatment of BRAF positive patients with unresectable Stage III or IV melanoma, categorising it as one of the therapies of 'highest priority for PBS listing' on the basis of the Checkmate 067 trial. The PBAC

noted that NIVO monotherapy and NIVO+IPI were unable to be scored on the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) as there are no direct comparisons of NIVO monotherapy or NIVO+IPI versus BRAF±MEK inhibitors as first-line treatments in the BRAF positive population.

### **Clinical trials**

6.5 The submission presented a naïve side-by-side comparison, based on subgroup analyses of patients with BRAF mutation positive melanoma in the relevant treatment arms from a three-arm randomised controlled trial (RCT) comparing NIVO monotherapy and NIVO+IPI with IPI monotherapy (CA209-067), and the results for the intention to treat (ITT) population in the relevant treatment arms from an RCT comparing DAB+TRAM with vemurafenib monotherapy (COMBI-V) and an RCT comparing DAB+TRAM with DAB monotherapy (COMBI-D), both of which only included patients with BRAF mutation positive melanoma. These were the key trials considered by the PBAC when they recommended listing of NIVO monotherapy, NIVO+IPI and DAB+TRAM for the treatment of unresectable Stage III or Stage IV melanoma.

- CA209-067 was a randomised, double-blind, three-arm trial comparing NIVO monotherapy (N=313) and NIVO+IPI (N=313) with IPI monotherapy (N=311) in previously untreated, unresectable Stage III or Stage IV melanoma. Randomisation was stratified by tumour BRAF status (V600 mutation negative vs mutation positive).
- COMBI-D was a double-blind randomised trial comparing DAB+TRAM (N=211) with dabrafenib monotherapy (N=212) in patients with previously untreated, unresectable Stage IIIC or Stage IV melanoma with a BRAF V600E or V600K mutation.
- COMBI-V was an open-label, randomised trial comparing DAB+TRAM (N=352) with vemurafenib monotherapy (N=352) as first-line therapy in patients with unresectable Stage IIIC or Stage IV melanoma with a BRAF V600E or V600K mutation.

6.6 Details of the trials presented in the submission are provided in the table below.

Public Summary Document – November 2019 PBAC Meeting

**Table 3: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
CA209-067	<p>A phase 3, randomised, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma.</p> <p>Interim Clinical Study Report: database lock February 2015.</p> <p>Final Clinical Study Report: database lock September 2016.</p> <p>Ad hoc report_3 year: database lock May 2017</p> <p>Binder3_AE by BRAF status: database lock May 2017</p> <p>Addendum 02 Clinical Study Report: database lock May 2018</p> <p>Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma.</p> <p>Hodi FS, Chiarion-Sileni V, Gonzalez R et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial.</p> <p>Schadendorf D, Larkin J, Wolchok J et al. Health-related quality of life results from the phase III CheckMate 067 study.</p>	<p>June 2015</p> <p>December 2016</p> <p>-</p> <p>June 2019</p> <p>August 2018</p> <p><i>NEJM</i> 2015; 373 (1): 23-34.</p> <p><i>Lancet Oncology</i> 2018; 19: 1480-92.</p> <p><i>Eur J Cancer</i> 2017; 82: 80-91.</p>
COMBI-D	<p>Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma.</p> <p>Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial.</p> <p>Schadendorf D, Amonkar MM, Stroyakovskiy D, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma.</p> <p>Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study</p>	<p><i>NEJM</i> 2014; 371(20): 1877-1888</p> <p><i>Lancet</i> 2015; 386 (9992): 444-451</p> <p><i>Eur J Cancer</i> 2015; 51 (7): 833-840</p> <p><i>Ann Oncol</i> 2017; 28(7): 1631-1639</p>
COMBI-V	<p>Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib.</p> <p>Grob JJ, Amonkar MM, Karaszewska B, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial</p>	<p><i>NEJM</i> 2015; 372(1): 30-39</p> <p><i>Lancet Oncol</i> 2015; 16(13): 1389-1398</p>
COMBI-D and COMBI-V pooled analyses	<p>Schadendorf D, Long GV, Stroyakovskiy D et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials.</p> <p>Robert C, Grob JJ, Stroyakovskiy D et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma.</p> <p>Long GV, Grob JJ, Nathan P, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials.</p>	<p><i>Eur J Cancer</i> 2017; 82: 45-55</p> <p><i>NEJM</i> 2019; 381: 626-36</p> <p><i>Lancet Oncol</i> 2016; 17(12): 1743-1754</p>

Source: Table 18, pp48-49 of the submission

- 6.7 The ESC identified a recent network meta-analysis by An and Lui, 2019 which compared the efficacy and safety of combination therapies for advanced melanoma.<sup>†</sup> The pre-PBAC response identified an additional network meta-analysis (Zoratti 2019) which compared therapies for previously untreated BRAF mutant melanoma.<sup>‡</sup>
- 6.8 The submission also identified two RCTs that are currently being conducted to determine the optimal sequence of immunotherapy and BRAF+MEK targeted therapy in patients with Stage III or Stage IV BRAF mutation positive melanoma (NCT02631447 and NCT02224781). The SECOMBIT trial (NCT02631447) is a three armed RCT evaluating the best sequential approach to combination therapy with NIVO+IPI and encorafenib+binimetinib in patients with unresectable Stage III or Stage IV BRAF mutation positive melanoma<sup>§</sup>; the estimated study completion date is December 2021. NCT02224781 is a RCT comparing NIVO+IPI followed by DAB+TRAM versus DAB+TRAM followed by NIVO+IPI in patients with Stage III-IV BRAF mutation positive melanoma; the estimated primary completion date is October 2022. The ESC considered that these ongoing trials reflected clinical equipoise regarding optimal first-line therapy, and considered that the results of these trials may provide critical information for future PBAC decision making.
- 6.9 The key features of the randomised trials are summarised in the table below.

**Table 4: Key features of the included evidence – indirect comparison**

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
<b>NIVO±IPI vs IPI</b>					
CA 209-067	NIVO: 98 <sup>a</sup> NIVO+IPI: 103 <sup>a</sup>	R, DB minimum 48 months <sup>c</sup>	Low	Unresectable Stage III or Stage IV melanoma who have not been previously treated	PFS, OS
<b>DAB+TRAM vs BRAF inhibitor monotherapy</b>					
COMBI-D	211	R, DB minimum 5 years <sup>c</sup>	Low	BRAF mutant unresectable Stage III or Stage IV melanoma who have not been previously treated.	PFS, OS
COMBI-V	352	R, OL minimum 5 years <sup>c</sup>	Low <sup>b</sup>	As above	PFS, OS

DB = double blind; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised; NIVO = nivolumab; IPI = ipilimumab; DAB = dabrafenib; TRAM = trametinib.

<sup>a</sup> BRAF mutation positive subgroups of the relevant treatment arms.

<sup>b</sup> Due to the open label design of the study, there was a high risk of bias for subjective outcomes, such as patient-reported outcomes and adverse events.

<sup>c</sup> Minimum follow-up in all patients alive at the time of analysis

Note: Comparison of the majority of the efficacy outcomes were not confounded by differences in duration of follow-up (e.g. median survival and landmark survival analyses); safety data for both the BRAF mutation positive subgroup in CA209-067 and in COMBI-D were compared at a minimum follow-up of 36 months.

<sup>†</sup> An Q and Liu Z. Comparative efficacy and safety of combination therapies for advanced melanoma: a network meta-analysis. BMC Cancer. 2019; 19(43): doi.org/10.1186/s12885-018-5259-8

<sup>‡</sup> Zoratti MJ, Davji T, Levine O, et al. Network meta-analysis of therapies for previously untreated advanced BRAF-mutated melanoma. Cancer Treatment Reviews. 2019; 74: 43-48.

<sup>§</sup> SECOMBIT includes the following treatment arms: ENCO+BINI followed by NIVO+IPI; NIVO+IPI followed by ENCO+BINI; ENCO+BINI for 8 weeks, then NIVO+IPI until progression, followed by ENCO+BINI post-progression.

*Public Summary Document – November 2019 PBAC Meeting*

Source: Compiled during the evaluation based on information presented in Sections 2.3 and 2.4 of the submission.

- 6.10 The ESC considered that although the risk of bias in each individual trial was low, the risk of bias in the naïve indirect comparison presented in the submission was high.
- 6.11 All patients in the COMBI trials were BRAF positive, whereas the CA209-067 trial recruited patients who were BRAF positive and negative. Therefore, the indirect analysis compared the total population of the COMBI trials with the BRAF mutation positive subgroups from CA209-067 (N=98 in the NIVO monotherapy arm and N=103 in the NIVO+IPI arm).
- 6.12 Although the three key trials required eligible patients to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, at baseline, a greater proportion of patients in the COMBI trials had an ECOG PS of 1 compared with CA209-067. This suggested that patients in the COMBI trials may have had more advanced disease.
- 6.13 In CA209-067, at a minimum follow-up of 36 months, of those patients with BRAF mutation positive melanoma who received any subsequent systemic therapy, 39/43 (91%) in the NIVO+IPI arm and 54/60 (90%) in the NIVO monotherapy arm received a BRAF inhibitor, although the proportion receiving a MEK inhibitor was considerably lower (51-55%). This use of BRAF inhibitors as subsequent therapy following progression on first-line immunotherapy was consistent with current Australian and international clinical guidelines and the proposed treatment algorithm in the submission.
- 6.14 In COMBI-D, at a minimum follow-up of 36 months, 57/101 (56%) of patients who received any subsequent anti-cancer therapy received immunotherapy, with the remainder, 41/101 (41%), receiving ipilimumab. Only 20/101 (20%) received NIVO or pembrolizumab. Similarly, in COMBI-V, at a minimum follow-up of five years, while 129/186 (69%) of patients who received any subsequent anti-cancer therapy received immunotherapy at some later-line of treatment, only 70/186 (38%) received a PD-1 inhibitor. The submission noted that, in the current treatment environment, a greater proportion of patients would receive PD-1 inhibitors based treatment following progression on a BRAF inhibitor, and that the low proportion of patients receiving PD-1 inhibitor treatments for subsequent therapy in the COMBI trials may have resulted in poorer survival outcomes than would be expected in current clinical practice. The lower use of subsequent PD-1 inhibitors in the COMBI trials and the high use of subsequent BRAF inhibitors in the CA209-067 trials may have biased the result of indirect comparison in favour of NIVO±IPI.
- 6.15 Despite claiming that NIVO monotherapy and NIVO+IPI are no worse than DAB+TRAM in terms of efficacy outcomes, the submission did not present a formal assessment of non-inferiority using a well-reasoned non-inferiority margin.

### ***Comparative effectiveness***

- 6.16 The overall survival (OS) and progression free survival (PFS) results for the BRAF mutation positive subgroups in the NIVO monotherapy and NIVO+IPI arms of CA209-067, and for the DAB+TRAM treatment arms in COMBI-D and COMBI-V, are summarised below.
- 6.17 The ESC noted that the PSCR provided updated data from the CA209-067 trial that was presented at the ESMO Congress, Barcelona, in September 2019. This indicated that the five-year survival rate for BRAF positive patients treated with NIVO+IPI or NIVO monotherapy were 60% and 46% respectively. The PSCR also referenced recently published data from the COMBI-D and COMBI-V trials which reported that the five-year survival rate for patients treated with DAB+TRAM was approximately 34%.<sup>\*\*</sup>

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<sup>\*\*</sup> Robert C, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *New Engl J Med.* 2019; 381(7): 626-636.

**Table 5: Overall survival and progression free survival across the relevant treatment arms in the randomised trials**

	CA209-067 BRAF positive subgroup		COMBI-D	COMBI-V
	NIVO+IPI <sup>a</sup> N=103*	NIVO mono <sup>a</sup> N=98	DAB+TRAM N=211	DAB+TRAM N=352
<b>Overall survival</b>				
Events, n (%)	40 (38.8%) <sup>a</sup>	48 (49.0%) <sup>a</sup>	114 (54.0%) <sup>b</sup>	190 (54.0%) <sup>b</sup>
Median OS, months (95% CI)	NR <sup>a</sup>	45.5 (26.4, NR) <sup>a</sup>	26.7 (19.0, 38.2) <sup>b</sup>	26.1 (22.6, 35.1) <sup>b</sup>
Landmark OS, KM% (95% CI)				
12 months	81% (72, 87)	80% (70, 87)	74% (67, 79) <sup>c</sup>	72% (67, 77) <sup>f</sup>
24 months	71% (61, 79)	62% (51, 71)	52% (45, 59) <sup>b</sup>	53% (48, 58) <sup>b</sup>
36 months	68% (58, 76)	56% (46, 66)	44% (37, 51) <sup>b</sup>	45% (39, 50) <sup>b</sup>
48 months	62% (52, 71)	50% (39, 59)	35% <sup>d</sup>	39% <sup>d</sup>
60 months <sup>#</sup>	60%	46%	32%	36%
<b>Progression free survival</b>				
Events, n (%)	59 (57.3%) <sup>a</sup>	67 (68.4%) <sup>a</sup>	151 (71.6%) <sup>b</sup>	249 (70.7%) <sup>b</sup>
Median PFS, months (95% CI)	16.5 (8.3, 32.0) <sup>a</sup>	5.6 (2.8, 9.5) <sup>a</sup>	11.0 (8.0, 13.9) <sup>c</sup>	12.6 (10.7, 15.5) <sup>g</sup>
Landmark PFS, KM% (95% CI)				
12 months	52% (41, 61)	38% (28, 48)	-	-
24 months	43% (33, 53)	30% (20, 39)	30% (24-37) <sup>e</sup>	31% <sup>d</sup>
36 months	39% (29, 49)	23% (15, 33)	22% (16-28) <sup>e</sup>	25% <sup>d</sup>
48 months	39% (29, 49)	23% (15, 33)	17% <sup>d</sup>	23% <sup>d</sup>

CI = confidence interval; DAB = dabrafenib; IPI = ipilimumab; KM = Kaplan-Meier; mono = monotherapy; NIVO = nivolumab; NR = not reached; OS = overall survival; PFS = progression free survival; TRAM = trametinib

<sup>a</sup> Minimum follow-up 48 months (p1485, Hodi et al, 2018)

<sup>b</sup> Source: Schadendorf et al (2017) and Table A2, supplementary data, minimum follow-up 36 months (COMBI-D February 2016 data cutoff; COMBI-V July 2016 data cutoff)

<sup>c</sup> Source: Long et al (2015), median follow-up 20 months, January 2015 data cutoff

<sup>d</sup> Source: Robert et al (2019), minimum 5 years follow-up (COMBI-D December 2018 data cutoff; COMBI-V October 2018 data cutoff).

<sup>e</sup> Source: Long et al (2017), minimum follow-up 36 months, February 2016 data cutoff

<sup>f</sup> Source: Robert et al (2015), median follow-up 11 months, April 2014 data cutoff

<sup>g</sup> Source: <https://slideplayer.com/slide/8371753/>, March 2015 data cutoff and Table 1 of the PSCR

\* Addendum 2 to the CSR reported 103 BRAF mutation positive patients, while all other CSR documents reported 102 BRAF mutation positive patients in the NIVO+IPI arm.

<sup>#</sup> Updated in the PSCR

Note: The submission stated that the post-hoc subgroup analyses by BRAF mutation status were based on the 3 year follow-up data. However, the results were reported in CA067 Addendum 2 to CSR (August 2018), which was based on the May 2018 database lock at 4 years of follow-up (p16, CA067 Addendum 2 to CSR).

Source Table 31, p84 and Table 32, p86 of the submission; Schadendorf et al (2017); Long et al (2015); Robert et al (2019); Long et al (2017) and Robert et al (2015).

6.18 Due to the considerable potential for confounding, the ESC considered that the results of the naïve comparison should be interpreted with caution. In particular, due to the limited use of PD-1 inhibitors for later-line therapy in COMBI-D and COMBI-V, the OS results may be biased in favour of NIVO monotherapy and NIVO+IPI over DAB+TRAM.

6.19 The submission stated that it was not possible to compare the results of patient-reported outcomes for DAB+TRAM in COMBI-D and COMBI-V with those for NIVO monotherapy and NIVO+IPI in CA209-067. Any comparison across the trials would be subject to considerable potential for bias and confounding, especially considering the subjective nature of patient reported outcomes and the potential transitivity issues discussed above.

## Comparative harms

6.20 A comparison of key adverse events (AEs) occurring in the BRAF mutation positive subgroups in the NIVO+IPI and NIVO monotherapy treatment arms of CA209-067 and the DAB+TRAM arms of COMBI-D and COMBI-V is presented below.

**Table 6: Comparison of key adverse events across the relevant treatment arms from the trials (BRAF mutation positive patients)**

	CA209-067 (BRAF positive subgroups) <sup>a</sup>		COMBI-D	COMBI-V
	NIVO+IPI	NIVO monotherapy	DAB+TRAM	DAB+TRAM
N	N=101 n (%)	N=98 n (%)	N=209 n (%)	N=350 n (%)
Follow-up	Min 36 months	Min 36 months	Min 36 months <sup>c</sup>	Median 11 months <sup>d</sup>
Any cause AEs				
One or more AE	NR <sup>b</sup> (NR%)	NR <sup>b</sup> (NR%)	203 (97%)	343 (98%)
Serious AE	NR <sup>b</sup> (NR%)	NR <sup>b</sup> (NR%)	95 (45%)	131 (37%) <sup>e</sup>
Grade 3-4 AE	NR <sup>b</sup> (NR%)	NR <sup>b</sup> (NR%)	100 (48%)	(52%)
AE leading to discontinuation	NR <sup>b</sup> (NR%)	NR <sup>b</sup> (NR%)	29 (14%)	(13%)
Death due to drug-related AE	NR <sup>b</sup>	NR <sup>b</sup>	0	0

AE = adverse event; IPI = ipilimumab; min = minimum; NIVO = nivolumab; NR = not reported

<sup>a</sup> Source: pp89, 159 and 201 CA067\_Binder3\_AE by BRAF status

<sup>b</sup> Deaths due to drug-related AEs were not reported by BRAF status. In the full safety analysis set, there were 2 deaths due to drug-related AEs in the NIVO+IPI arm and 1 in the NIVO monotherapy arm.

<sup>c</sup> Source: Long et al (2017), p1635, Table S3 and Table S4.

<sup>d</sup> Source: Long et al (2014)

<sup>e</sup> This could not be confirmed as it could not be located in Long et al (2014).

<sup>g</sup> Source: Table S9, Robert et al (2019)

Source: Table 35, p95, Table 36, p97 of the submission; pp89, 159 and 201 CA067\_Binder3\_AE by BRAF status; Long et al (2017); Long et al (2014).

6.21 The submission stated that the frequencies of experiencing a serious AE, a severe AE (≥ Grade 3 toxicity) or an AE leading to discontinuation, regardless of causality, were higher with NIVO+IPI than with DAB+TRAM. These results suggested that NIVO+IPI was inferior in terms of safety compared with DAB+TRAM. While any naïve comparison of safety data across treatment arms from separate trials should be interpreted with caution, at a minimum 36 months of follow-up, the proportion of patients experiencing at least one serious AE, a Grade 3-4 AE or an AE leading to discontinuation was reasonably similar for patients with BRAF mutation positive melanoma in the NIVO monotherapy arm of CA209-067 and the DAB+TRAM arm of COMBI-D.

### **Clinical claim**

- 6.22 The submission described NIVO monotherapy as non-inferior in terms of effectiveness and non-inferior in terms of safety compared with DAB+TRAM, and described NIVO+IPI as non-inferior in terms of effectiveness and inferior in terms of safety compared with DAB+TRAM.
- 6.23 The evaluators considered that the therapeutic conclusion, in regard to the comparative effectiveness of NIVO monotherapy, NIVO+IPI and DAB+TRAM, was not adequately supported by the evidence presented in the submission as the indirect comparison was potentially biased in favour of NIVO monotherapy and NIVO+IPI over DAB+TRAM, given:
- patients in COMBI-D and COMBI-V may, on average, have had more advanced disease than those in the BRAF positive subgroups in CA209-067; and
  - the subsequent therapies received by patients with progressive disease in the COMBI trials did not reflect current clinical practice, with only a limited proportion of patients receiving a PD-1 inhibitor following progression on DAB+TRAM.
- 6.24 The ESC considered that the evidence presented in the submission was of low quality, given that it was a naïve indirect comparison and subject to a high risk of bias and considerable potential for confounding. However, the ESC also considered that the evidence did not provide a compelling signal of difference in the efficacy of NIVO or NIVO+IPI compared to DAB+TRAM in terms of overall survival.
- 6.25 The ESC noted that a recently published network meta-analysis by An and Lui, 2019 did not find a significant difference in overall survival for the combination of BRAF+MEK inhibitors compared to PD-1 inhibitors (HR = 0.85, 95% CI: 0.59, 1.21). The ESC considered that the conclusions should be considered with caution given heterogeneity and indirect comparisons.
- 6.26 The ESC noted that there was genuine clinical equipoise amongst clinicians as to the optimal sequence of systemic therapies in BRAF mutant metastatic melanoma, with two international randomised clinical trials comparing the effects on overall survival of BRAF-targeted therapy and immunotherapy (DREAMseq and SECOMBIT) in progress. The ESC considered it important that the PBAC reviews results of these trials when made available, as they will provide critical information on the efficacy, safety and cost-effectiveness of first-line therapies.
- 6.27 Although the comparative safety of NIVO monotherapy and DAB+TRAM was difficult to interpret due to the naïve, indirect nature of the comparison and the different safety profiles of the two therapies the ESC accepted the submission's claim that NIVO was no worse than DAB+TRAM in terms of safety outcomes. The ESC accepted the

submission’s claim that NIVO+IPI had an inferior safety profile when compared with DAB+TRAM.

- 6.28 The PBAC considered that the claim of non-inferior comparative effectiveness between NIVO monotherapy, NIVO+IPI and DAB+TRAM was likely to be reasonable.
- 6.29 The PBAC considered that the claim of inferior comparative safety between NIVO+IPI and DAB+TRAM was reasonable. The PBAC considered that the claim of non-inferior comparative safety between NIVO monotherapy and DAB+TRAM was likely to be reasonable.

### Economic analysis

- 6.30 The submission presented a cost-minimisation analysis (CMA) of both NIVO monotherapy and NIVO+IPI versus DAB+TRAM. The PSCR stated that the sponsor proposed a cost-neutral approach to listing NIVO monotherapy and NIVO+IPI compared with the cost of DAB+TRAM. The ESC noted that the approach for NIVO+IPI was inconsistent with the clinical claim made in the submission, which acknowledged that NIVO+IPI is inferior to DAB+TRAM in terms of safety. The PBAC noted that the approach was consistent with that presented in July 2018 for NIVO+IPI in the treatment of unresectable or metastatic melanoma.
- 6.31 The estimated equi-effective doses are summarised in Table 7.
- 6.32 The ESC noted that the mean durations of therapy for NIVO monotherapy and NIVO+IPI differed to those used in the NIVO+IPI cost analysis presented in July 2018. In that analysis, it was assumed that 30.5 infusions of NIVO monotherapy (every two weeks) was equivalent to 20.7 infusions of NIVO (3.2 infusions in the induction phase and 17.5 in the maintenance phase) plus 3.2 infusions of IPI (in the induction phase).

**Table 7: Estimated equi-effective doses of NIVO monotherapy, NIVO+IPI and DAB+TRAM**

Treatment	Dose	Duration	
		Days	Infusions
NIVO monotherapy	NIVO 3 mg/kg <sup>a</sup> Q2W, or 240 mg Q2W, or 480 mg Q4W (IV)	■ days	■ Q2W, or ■ Q4W
NIVO+IPI	Induction: NIVO 1 mg/kg <sup>a</sup> + IPI 3 mg/kg <sup>a</sup> Q3W (IV)	■ <sup>b</sup>	3.2
	Continuing: NIVO 3 mg/kg <sup>a</sup> Q2W, or 240 mg Q2W, or 480 mg Q4W (IV)		■ Q2W, or ■ Q4W
DAB+TRAM	DAB 150 mg BID + TRAM 2 mg SID (oral)	279 days	NA

BID = twice daily; DAB = dabrafenib; IPI = ipilimumab; IV = intravenous; NA = not applicable; NIVO = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SID = once daily; TRAM = trametinib

<sup>a</sup> An average patients body-weight of ■ kg was assumed for all weight-based dosing. The submission stated that this was based on an analysis conducted by the Department of Health, which indicated that the average dose of NIVO monotherapy (at 3 mg/kg) was ■ mg.

<sup>b</sup> The Excel workbook for Seciton 3 assumed that patients receive ■ infusions (every 3 weeks) of NIVO during induction, and either ■ infusions administered every 2 weeks or ■ infusions administered every 4 weeks during the continuing phase of treatment (i.e. ■ x ■ + ■ x ■ = ■ days).

Source: Table 49, p123 of the submission; Excel workbook ‘Elec doc\_Section 3\_CMA model’

- 6.33 As listing of NIVO monotherapy and NIVO+IPI as a first-line treatment option for patients with BRAF mutation positive melanoma would result in changes in the utilisation of second-line therapies. The PSCR provided a supplementary analysis that incorporated the costs associated with second-line therapies (see paragraph 6.41).
- 6.34 Where available, the submission based the duration of therapy for each first-line treatment on the mean duration of therapy reported in the May 2018 DUSC review of medicines for the treatment of melanoma. In the DUSC review, the time on therapy was estimated using a Kaplan-Meier analysis in a cohort of patients who first initiated on PBS therapy between January to June, 2016 (n=919). A patient was assumed to be continuing treatment if the time from their last supply was less than three times the median time between supplies (<63 days) from the data cut-off date; these patients were censored. The Kaplan-Meier curve for time to treatment discontinuation indicated that there was approximately 25% probability of not having discontinued treatment at 2 years, with extensive censoring of patients after the minimum 18 months of follow-up<sup>††</sup>. Therefore, the mean duration of therapy over the duration of follow-up in this analysis will underestimate the true mean duration of treatment.
- 6.35 The table below presents a comparison of the assumed duration of therapy for each treatment in the CMA presented in the submission, the duration of treatment reported in each trial, and the estimates in the May 2018 DUSC review of medicines for the treatment of melanoma.

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<sup>††</sup> 158/607 (26%) of patients treated with an anti-PD-1 (nivolumab or pembrolizumab) and 62/286 (21.7%) treated with BRAF targeted therapy as their first drug regimen were censored.

**Table 8: Comparison of duration of therapy used in the CMA with that reported in the clinical trials and by the DUSC**

	NIVO monotherapy	NIVO+IPI	DAB+TRAM
Trial data	BRAF positive subgroup <sup>b</sup>  Mean: █ infusions (Q2W); approx. █ days Median: █ infusions (Q2W); approx. █ days	BRAF positive subgroup <sup>b</sup>  Mean: IPI: █ infusions; NIVO: █ infusions (Q2W); approx. █ days <sup>d</sup> Median: IPI: 4 infusions; NIVO: █ infusions (Q2W); approx. █ days	Mean: NR Median: 11.8 months; approx. 354 days
DUSC data <sup>a</sup>	NIVO: mean 239 days PEMBRO: mean: 276 days	Data for NIVO+IPI combination was not available from the DUSC review.	BRAFi±MEKi: mean 279 days
CMA base case	█ days  █ infusions Q2W or █ infusions Q4W  Weighted average of DoT for NIVO and PEMBRO from DUSC review. <sup>c</sup>	█ days  IPI: █ infusions Q3W <sup>e</sup>  NIVO: Induction: █ infusions Q3W Continuing: █ infusions Q2W or █ infusions Q4W <sup>f</sup>  As data for NIVO+IPI combination was not available from the DUSC review, IPI DoT was sourced from CA209-067 (ITT population), and NIVO DoT was assumed to be 239 days, based on DoT for NIVO monotherapy in the DUSC review.	279 days  Based on DUSC review

BRAFi = BRAF inhibitor; DAB = dabrafenib; DoT = duration of therapy; DUSC = Drug Utilisation Sub-Committee; IPI = ipilimumab; ITT = intention to treat; MEKi = MEK inhibitor; NA = not available; NIVO = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; TRAM = trametinib.

<sup>a</sup> Time on first drug regimen. Source: Table 7, p25 of the May 2018 DUSC review

<sup>b</sup> Source: p323 CA067\_AD hoc report\_CA067 3 year. Minimum follow-up 36 months

<sup>c</sup> The DUSC review included 607 patients receiving PD-1 inhibitor monotherapy: 586/607 (96.5%) pembrolizumab, and 21/607 (3.5%) nivolumab

<sup>d</sup> Assuming 3.3 infusions administered Q3W in the induction phase, and 22.7 infusions of NIVO administered Q2W in the maintenance phase.

<sup>e</sup> Source: Excel spreadsheet 'Admin costs', Section 3 Excel workbook 'Elec doc\_Section 3\_CMA model'

<sup>f</sup> The Excel workbook assumed an average of █ infusions administered every 3 weeks in the induction phase, and █ infusions administered every 2 weeks in the continuing treatment phase. These assumptions give an approximate treatment duration of █ days<sup>f</sup>

Source: compiled during the evaluation, based on data reported in Table 7, p25 of the May 2018 DUSC review of medicines for the treatment of melanoma, Excel spreadsheet 'Admin costs', p323 CA067\_AD hoc report\_CA067 3 year, Section 3 Excel workbook 'Elec doc\_Section 3\_CMA model', and Section 3.2.1.2 pp125-127 of the submission.

6.36 The mean duration of treatment for NIVO monotherapy and NIVO+IPI in CA209-067 was considerably longer than assumed in the CMA. The duration of therapy for DAB+TRAM was also likely to be underestimated. Given that the clinical claim of non-inferiority in terms of effectiveness was based on the outcomes of the trials, during the evaluation it was considered appropriate to use the duration of therapy from the trials, as these are the durations of therapy on which these outcomes were obtained. The PSCR stated that the data from the DUSC report provided information regarding the relative usage of the treatments, was representative of use in the Australian setting and avoided the transitivity issues associated with extracting data from the clinical trials. Although time on therapy was calculated using a cohort of patients who initiated PBS therapy between January to June 2016 with a follow-up until December

2017, the ESC noted that pembrolizumab was listed on the PBS on 1 September 2015, DAB+TRAM on 1 April 2016 and NIVO monotherapy on 1 May 2016. The ESC noted that the DUSC review was based on immature data and likely provided an underestimate of true time on each of the therapies. The pre-PBAC response stated that although it would have been more appropriate to base the duration of therapy estimates on trial data, the mean duration of therapy for DAB+TRAM was not publically reported and therefore, this was not possible.

- 6.37 The PBAC, noting the limitations of the clinical trial data for DAB+TRAM, accepted that the data from the DUSC review provided reasonable durations of therapy for NIVO monotherapy and DAB+TRAM, but considered that, in comparison to the trial data, the duration of therapy for NIVO+IPI was underestimated. The PBAC noted that the mean duration of NIVO in the trial as monotherapy (■■■ days), was shorter than when used in combination with IPI (■■■ days), but that in the cost analysis the duration of NIVO as monotherapy was longer (■■■ days) than when in combination with IPI (■■■ days). The PBAC noted that to maintain proportionally consistent estimates between the trial data and the cost analysis, the duration of NIVO when used in combination with IPI in the cost analysis would need to be ■■■ days (■■■/■■■ x ■■■).
- 6.38 Costs associated with the intravenous administration of NIVO and IPI were included. In addition, the incremental cost of managing additional Grade 3-4 AEs occurring in at least 5% of patients, associated with the inferior safety profile of NIVO+IPI, were included in the CMA of NIVO+IPI versus DAB+TRAM. The submission stated that the 5% frequency of AE occurrence was chosen as a cutoff due to having the greatest impact on the average cost of therapy. This was unlikely to capture the true extent of the increase in toxicity associated with NIVO+IPI compared with DAB+TRAM.
- 6.39 As the submission did not know the effective prices of dabrafenib or trametinib, for the purposes of the CMA, they were assumed to be ■■■% of the current published dispensed price for maximum quantity (DPMQ). The cost analysis should have been based on the approved ex-manufacturer prices (AEMPs) as pricing agreements are made by Government under the National Health Act 1953 at the ex-manufacturer level and, as such, the prices would be agreed on this basis. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine. This was corrected in the PSCR.
- 6.40 The results of the cost analysis, based on the assumed effective AEMP for DAB and TRAM are summarised below.

**Table 9: Results of the cost analysis (assumed effective price of DAB+TRAM<sup>a</sup>)**

Component	NIVO	NIVO+IPI		DAB+TRAM
		NIVO	IPI	
Total 1 <sup>st</sup> -line medicine cost per course	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED] PSCR: \$ [REDACTED]
Administration costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	-
Incremental AE costs	-	\$ [REDACTED]	\$ [REDACTED]	-
Total 1 <sup>st</sup> -line costs per course	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED] PSCR: \$ [REDACTED]
Difference in cost per course	\$ [REDACTED] PSCR: -\$ [REDACTED]	\$ [REDACTED] PSCR: -\$ [REDACTED]	\$ [REDACTED] PSCR: -\$ [REDACTED]	-

AE = adverse event; AEMP= approved ex-manufacturer price; DAB = dabrafenib; IPI = ipilimumab; NIVO = nivolumab; PSCR = Pre-Sub-Committee Response; TRAM = trametinib

\* PSCR assumed effective price of DAB (\$ [REDACTED]/day) and TRAM (\$ [REDACTED]/day) was [REDACTED]% of the AEMP; The current effective approved ex-manufacturer price for nivolumab (\$ [REDACTED] for 100 mg vial) and ipilimumab (\$ [REDACTED].00 for a 50 mg vial) were used in the calculation of second-line treatment costs.

<sup>a</sup> For the purposes of the analyses, it was assumed that the safety of IPI monotherapy was similar to that of DAB+TRAM as no comparative data were available

<sup>b</sup> Total cost per patient x % of patients receiving 2L treatment

Source: Table 54, p 130 of the submission; Excel workbook 'Elec doc\_Section 3\_CMA model and Table 3 and Attachment 1\_Updated Section3 CMA model – Excel of the PSCR

6.41 The PSCR provided a supplementary analysis that provided a comparison when the second-line treatment costs were added to the cost-minimised first-line costs (see Table 10 below). The ESC noted that the second-line treatments received by patients who had received NIVO monotherapy in the first-line (BRAf: 2%, BRAf+MEK: 98%) did not match the second-line treatments proposed in the clinical management algorithm (BRAf: 0%, BRAf+MEK: 65.6%, PD-1: 4.8%, NIVO+IPI: 29.6%), which was based on the results of a clinician survey. In addition, the ESC noted that the current PBS restrictions prevent the use of NIVO+IPI following PD-1 inhibitor monotherapy (IPI monotherapy is allowed). Although the use of BRAf±MEK inhibitor therapy following progression on NIVO monotherapy was consistent with current Australian and international guidelines\*, the ESC proposed two alternate scenarios for second-line therapy following NIVO monotherapy: (i) 65.6% BRAf+MEK inhibitor therapy plus 34.4% IPI monotherapy; and (ii) 100% IPI monotherapy.

6.42 The ESC identified additional areas of uncertainty with the determination of second-line treatment options, including:

- The proportions of patients receiving second-line therapies were based on the results of a survey 143 medical oncologists, in which 32 (22%) clinicians responded. The PSCR considered that the survey was representative of the treating population as survey respondents anticipated that they would treat a total of approximately 900 patients per year, which the PSCR calculated to equate to approximately 38% of the total likely patient population. The ESC was concerned that the low response rate to the survey (22%) affected the representativeness of the sample and the generalisability to inform market shares or provide a reliable estimate of future second-line clinical treatment practices; and

- The treatment duration of each second-line therapy was sourced from the May 2018 DUSC review (Table 8). This analysis included 197 patients who were receiving a second drug regimen with immunotherapy, by the prior drug regimen supplied, between January and June 2016. The ESC considered that the generalisability of the treatment duration of second-line therapy results were highly uncertain.

6.43 The results of the cost analysis, incorporating second-line treatment costs and based on the assumed effective AEMP for DAB and TRAM, are summarised below.

**Table 10: Results of the cost analysis, incorporating second-line treatment costs (assumed effective price of DAB+TRAM<sup>a</sup>)**

Component	NIVO			NIVO+IPI	DAB+TRAM
<b>First-line treatment costs</b>					
Total 1 <sup>st</sup> -line costs per course	\$ [REDACTED]			\$ [REDACTED]	\$ [REDACTED]
<b>Second-line treatment costs</b>					
Patients receiving 2 <sup>nd</sup> -line therapy (%)	46%			31%	46%
2 <sup>nd</sup> -line treatment received	PSCR: BRAf: 2% BRAf+MEK: 98%	ESC scenario 1: BRAf+MEK: 65.6%, IPI: 34.4%	ESC scenario 2: IPI: 100% (4 doses/patient)	BRAf: 2% BRAf+MEK: 98%	PD-1: 41% NIVO+IPI: 59%
Weighted EMP per 2 <sup>nd</sup> -line treatment (per patient)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Administration costs (per patient)	\$0	\$ [REDACTED]	\$ [REDACTED]	\$0	\$ [REDACTED]
Incremental AE costs (per patient)	\$0	\$0 <sup>a</sup>	\$0 <sup>a</sup>	\$0	\$ [REDACTED]
Total costs per 2 <sup>nd</sup> -line course <sup>b</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Total cost of therapy (1<sup>st</sup> and 2<sup>nd</sup> line)</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

AE = adverse event; DAB = dabrafenib; EMP = ex-manufacturer price; ESC = Economic Sub-Committee; IPI = ipilimumab; NIVO = nivolumab; PBS = Pharmaceutical Benefits Scheme; PSCR = Pre-Sub-Committee Response; Rx = restrictions; TRAM = trametinib; Tx = treatment; 1L = first-line; 2L = second-line

\* PSCR assumed effective price of DAB (\$ [REDACTED]/day) and TRAM (\$ [REDACTED]/day) was [REDACTED] % of the AEMP; The current effective approved ex-manufacturer price for nivolumab (\$ [REDACTED] for 100 mg vial) and ipilimumab (\$ [REDACTED] for a 50 mg vial) were used in the calculation of second-line treatment costs.

<sup>a</sup> For the purposes of the analyses, it was assumed that the safety of IPI monotherapy was similar to that of DAB+TRAM as no comparative data were available

<sup>b</sup> Total cost per patient x % of patients receiving 2L treatment

Source: Table 54, p 130 of the submission; Excel workbook 'Elec doc\_Section 3\_CMA model and Table 3 and Attachment 1\_Updated Section3 CMA model – Excel of the PSCR

6.44 The ESC considered that, although not robust, the supplementary analysis incorporating second-line treatment costs provided support that the cost analysis based on first-line treatments only was a reasonable approach. The PBAC agreed.

### **Drug cost/patient/course**

Public Summary Document – November 2019 PBAC Meeting

6.45 Drug cost/patient/course (assumed dispensed effective price): NIVO monotherapy \$ [REDACTED] and NIVO+IPI \$ [REDACTED]. The effective prices for NIVO and IPI were derived in the cost analysis, based on the assumed effective prices of DAB+TRAM. The derivation of these costs is presented in Table 11. This was compared with an estimated price of \$ [REDACTED]/patient/course for DAB+TRAM (based on the assumed dispensed effective price).

6.46 The PBAC noted that the cost/patient/course for each agent was sensitive to the difference between the trial-based duration of therapy and the duration of therapy applied in the CMA and financial estimates.

Table 11: Drug cost per patient per course for NIVO monotherapy, NIVO+IPI and DAB+TRAM (assumed effective dispensed prices)

	Trial dose and duration	CMA	Financial estimates
<b>NIVO monotherapy*</b>			
Dose	3mg/kg (240 mg) <sup>a</sup> Q2W	3 mg/kg ([REDACTED] mg) <sup>c</sup> Q2W, 240 mg Q2W or 480 mg Q4W	3 mg/kg ([REDACTED] mg) <sup>c</sup> Q2W, 240 mg Q2W or 480 mg Q4W
Cost per infusion	\$ [REDACTED]	3 mg/kg: \$ [REDACTED] 240 mg: \$ [REDACTED] 480 mg: \$ [REDACTED]	3 mg/kg: \$ [REDACTED] 240 mg: \$ [REDACTED] 480 mg: \$ [REDACTED]
Mean duration	[REDACTED] infusions Q2W	[REDACTED] infusions Q2W, or [REDACTED] infusions Q4W	[REDACTED] infusions Q2W, or [REDACTED] infusions Q4W
Cost/patient//course	\$ [REDACTED]	\$ [REDACTED] <sup>d</sup>	\$ [REDACTED] <sup>d</sup>
<b>NIVO+IPI*</b>			
Dose	Induction: NIVO 1 mg/kg (80 mg) <sup>a</sup> Q3W IPI 3 mg/kg (250 mg) <sup>a</sup> Q3W Maintenance: NIVO 3mg/kg (240 mg) <sup>a</sup> Q2W	Induction: NIVO 1 mg/kg (80 mg) <sup>c</sup> Q3W IPI 3 mg/kg (250 mg) <sup>c</sup> Q3W Maintenance: NIVO 3 mg/kg (237 mg) <sup>c</sup> Q2W, 240 mg Q2W or 480 mg Q4W	Induction: NIVO 1 mg/kg (80 mg) <sup>c</sup> Q3W IPI 3 mg/kg (250 mg) <sup>c</sup> Q3W Maintenance: NIVO 3 mg/kg (237 mg) <sup>c</sup> Q2W, 240 mg Q2W or 480 mg Q4W
Cost per infusion	Induction: NIVO \$ [REDACTED] IPI \$ [REDACTED] Maintenance NIVO \$ [REDACTED]	Induction: NIVO \$ [REDACTED] IPI \$ [REDACTED] Maintenance (NIVO) 3 mg/kg: \$ [REDACTED] 240 mg: \$ [REDACTED] 480 mg: \$ [REDACTED]	Induction: NIVO \$ [REDACTED] IPI \$ [REDACTED] Maintenance (NIVO) 3 mg/kg: \$ [REDACTED] 240 mg: \$ [REDACTED] 480 mg: \$ [REDACTED]
Mean duration	IPI: [REDACTED] infusions NIVO: [REDACTED] infusions Q2W <sup>b</sup>	Induction (NIVO+IPI): 3.2 infusions Maintenance (NIVO): [REDACTED] infusions Q2W or [REDACTED] infusions Q4W	Induction (NIVO+IPI): 3.2 infusions Maintenance (NIVO): [REDACTED] infusions Q2W or [REDACTED] infusions Q4W
Cost/patient//course	IPI: \$ [REDACTED] NIVO: \$ [REDACTED] TOTAL: \$ [REDACTED]	IPI: \$ [REDACTED] NIVO: \$ [REDACTED] TOTAL: \$ [REDACTED] <sup>d</sup>	IPI: \$ [REDACTED] NIVO: \$ [REDACTED] TOTAL: \$ [REDACTED] <sup>d</sup>
<b>DAB+TRAM**</b>			
Dose	DAB 150 mg BID TRAM 2 mg SID	DAB 150 mg BID TRAM 2 mg SID	DAB 150 mg BID TRAM 2 mg SID
Cost per 30 days	DAB: \$ [REDACTED] TRAM: \$ [REDACTED]	DAB: \$ [REDACTED] TRAM: \$ [REDACTED]	DAB: \$ [REDACTED] TRAM: \$ [REDACTED]
Mean duration	354 days (11.8 scripts) <sup>e</sup>	279 days (9.3 scripts)	279 days (9.3 scripts)
Cost/patient//course	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

## Public Summary Document – November 2019 PBAC Meeting

BID = twice daily; CMA = cost-minimisation analysis; DAB = dabrafenib; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SID = once daily; TRAM = trametinib

<sup>a</sup> The mean patient weight in the trial was 82kg. For the purposes of calculating the cost/patient/course, it was assumed that patients received an average of 240 mg NIVO per infusion for monotherapy and maintenance, 80 mg NIVO per infusion for induction (NIVO+IPI), and 250 mg IPI per infusion.

<sup>b</sup> When deriving the cost/patient/course, it was assumed that patients received 3.3 infusions of NIVO in the induction phase, and 22.7 infusions in the maintenance phase.

<sup>c</sup> Average patient body-weight assumed to be 79 kg.

<sup>d</sup> Weighted average price assuming the following utilisation of the 3 doses for NIVO monotherapy/maintenance: 3% 3 mg/kg, 9% 200 mg Q2W, 88% 400 mg Q4W.

<sup>e</sup> Based on median duration from the COMBI-D trial

\* These drug prices are based on the effective prices for NIVO and IPI derived in the cost-minimisation analyses, and the assumed effective prices for DAB and TRAM. Assumed effective ex-manufacturer price: NIVO 40 mg vial \$ [REDACTED], 100 mg vial \$ [REDACTED]; IPI 50 mg vial \$ [REDACTED].

\*\* The submission used an assumed effective dispensed price for maximum quantity (DPMQ) of \$ [REDACTED] for DAB 75 mg (120 tablets), and \$ [REDACTED] and for TRAM 2 mg (30 tablets), assuming a [REDACTED]% reduction in the published DPMQ.

Figures in italics were calculated during the evaluation.

Source: Table 54 p130; Table 57 p133; Excel workbooks 'Elec doc\_Section 3\_CMA model' and 'Elec doc\_Section 4\_BIM', Folder 4 of the submission.

### **Estimated PBS usage & financial implications**

- 6.47 Noting that the reconsideration of the July 2019 deferral of NIVO as adjuvant therapy was also considered at the November 2019 meeting, and that both submissions proposed a RSA which incorporated use in both the adjuvant and unresectable or metastatic settings, the PBAC considered that the adjuvant and unresectable or metastatic populations should be calculated in a consistent manner across the submissions.
- 6.48 This submission was not considered by DUSC. The submission used a mixed market share/epidemiology approach to estimating the financial implications associated with the proposed listing of first-line NIVO monotherapy and NIVO+IPI for treatment of unresectable Stage III or Stage IV BRAF mutation positive melanoma.
- 6.49 The base case analysis only included costs associated with first-line treatment; sensitivity analyses incorporating second-line therapies, and the availability of adjuvant therapies, were provided. The ESC considered that the failure to include changes in the utilisation of second-line therapies in the base case of the financial estimates was not appropriate, given these will be directly impacted.
- 6.50 The submission used data from the May 2018 DUSC review of medicines for the treatment of melanoma to estimate the eligible population, and assumed that all use of NIVO monotherapy and NIVO+IPI would substitute for use of BRAF±MEK inhibitors.
- 6.51 The estimated eligible population was based on a linear projection of data from the May 2018 DUSC review of medicines for the treatment of melanoma. The PBAC noted that the incidence of melanoma in Australia over the last 10 years was increasing at an annual rate of between 0.9% and 5.2% (National Cancer Control Indicators, see Table 12), and considered that a growth rate of 4.56%, which was the growth rate applied in the BRAF/MEK inhibitor population in the July 2019 minor resubmission for

adjuvant NIVO and which was based on PBS data, would be appropriate for projecting the number of patients.

**Table 12: Incidence of melanoma in Australia**

Year	Incident cases	Growth
2010	11,509	-
2011	11,663	1.34%
2012	12,270	5.20%
2013	12,892	5.07%
2014	13,215	2.51%
2015	13,694	3.62%
2016	13,816	0.89%
2017	14,241	3.08%
2018	14,778	3.77%
2019	15,229	3.05%
<b>Average growth</b>		<b>3.17%</b>

Source: National Cancer Control Indicators for melanoma, published 13 Sep 2019. Available from: <https://ncci.cancer australia.gov.au/diagnosis/cancer-incidence/cancer-incidence>

- 6.52 The submission estimated that, in the absence of the listing of NIVO monotherapy and NIVO+IPI for first-line treatment of unresectable Stage III or Stage IV melanoma, there would be less than 10,000 patients treated with BRAF targeted therapy as first-line treatment in the Year 1, increasing to less than 10,000 patients in Year 6. The PBAC noted that the submission estimated that 31% of patients were BRAF mutant and would therefore receive BRAF targeted therapy first-line. The PBAC considered that it would be more reasonable to assume that 37.7% of patients were BRAF mutant, based on the results of an Australian cohort study<sup>††</sup>. In addition, the PBAC considered that the July 2019 recommendation for DAB+TRAM adjuvant treatment of completely resected melanoma (DAB+TRAM was listed on the PBS as adjuvant therapy on 1 November 2019) would affect the number of patients diagnosed with Stage IIIB, IIIC or IIID resectable melanoma who subsequently progress to unresectable or metastatic disease (see paragraph 6.56).
- 6.53 The proportion of patients receiving each treatment option, at each line of therapy, was based on the clinician survey. The ESC considered that the survey results were unreliable (see paragraph 6.42). The survey questions assumed that BRAF±MEK inhibitors would be available as a second-line treatment option following progression on first-line immunotherapy.
- 6.54 The ESC considered that the estimated market share of each treatment option when both NIVO monotherapy and NIVO+IPI are available for first-line therapy for patients with BRAF mutation positive melanoma, was a major source of uncertainty in the financial analysis. In particular, the assumption that 43% of patients would receive

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<sup>††</sup> Lyle M, Haydu LE, Menzies AM, et al. The molecular profile of metastatic melanoma in Australia. 2016; 48(2): 188-193

NIVO+IPI as first-line therapy, while 30% would receive PD-1 inhibitor monotherapy and 27% would receive BRAF+MEK inhibitors, was not adequately justified, given that the NCCN treatment guidelines for cutaneous melanoma indicate that PD-1 inhibitor monotherapy and BRAF targeted therapy are the preferred first-line regimes for patients with BRAF mutation positive disease<sup>§§</sup>. The PBAC considered that the submission's estimate that 73% (i.e. 43% + 30%) of BRAF mutant patients would receive either PD-1 inhibitor monotherapy or NIVO+IPI as first-line treatment in the unresectable or metastatic setting was overestimated.

6.55 The PBAC noted that in the November 2019 reconsideration of the July 2019 deferral for adjuvant NIVO, it was assumed that 74.1% of patients would receive a PD-1 inhibitor in the adjuvant setting, which the PBAC considered reasonable. The clinician survey estimated that 63% to 70% (as opposed to 73%) of the BRAF mutant population would also receive a PD-1 inhibitor (either as monotherapy or as NIVO+IPI) as first-line treatment in the unresectable or metastatic setting. The PBAC considered an estimate that 50% to 60% of BRAF mutant unresectable or metastatic patients would receive a PD-1 inhibitor as monotherapy or NIVO+IPI first-line would be more appropriate.

6.56 In addition, the PBAC considered that the number of patients eligible for treatment in the unresectable or metastatic setting should be revised to account for:

- Patients who no longer require treatment after receiving adjuvant therapy, i.e. those who are cured:
  - In reconsidering the NIVO as adjuvant therapy deferral, the PBAC determined that █████% to █████% of patients would avoid unresectable or metastatic recurrence (local and/or distant), and that this would translate into a reduction of approximately █████% to █████% of unresectable or metastatic patients receiving treatment.
- Patients who are ineligible to receive further treatment due to recurring whilst on, or within six months of completing, adjuvant therapy:
  - In reconsidering the NIVO as adjuvant therapy deferral, the PBAC noted that it was assumed that approximately 61% of patients complete 12 months of adjuvant therapy, i.e. 30% to 40% would relapse whilst on or within six months of completing adjuvant treatment. It was also assumed that 66% of patients in the unresectable or metastatic setting would have received adjuvant treatment, 37.7% of those would be BRAF mutant and 74.1% of BRAF mutant patients would have received a PD-1 inhibitor. Thus, the PBAC determined that

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<sup>§§</sup> National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 2.2019. Available from: <https://www.nccn.org/>.

■■■■% to ■■■■% of the unresectable or metastatic PD-1 inhibitor population would be ineligible for treatment.

- 6.57 The mean effective price per infusion for NIVO monotherapy and NIVO+IPI were derived using the methodology outlined in Table 11, above. The PBAC considered that the nivolumab dosage assumptions applied in the submission that 3% of patients would receive 3 mg/kg every two weeks, 9% would receive 240 mg every two weeks and 88% would receive 480 mg every four weeks were appropriate.
- 6.58 The estimated duration of treatment for each regimen was the same as in the economic analysis (see Table 7).
- 6.59 The estimated use and financial implications of listing NIVO monotherapy and NIVO+IPI for the first-line treatment of unresectable Stage III or Stage IV BRAF mutation positive melanoma presented in the submission are summarised below. The PBAC considered that revised estimates based on the recommendations above would also result in a minimal cost to the PBS/RPBS/MBS.

Table 13: Estimated use and financial implications (based on the assumed effective prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use of NIVO monotherapy and NIVO+IPI</b>						
No. of patients treated						
NIVO monotherapy						
NIVO+IPI						
<b>Number of infusions</b>						
NIVO monotherapy <sup>a</sup>						
NIVO+IPI <sup>b</sup>						
IPI						
NIVO induction						
NIVO maintenance						
<b>Estimated financial implications of listing NIVO and NIVO+IPI</b>						
<b>Cost to PBS/RPBS</b>						
NIVO monotherapy	\$	\$	\$	\$	\$	\$
NIVO +IPI	\$	\$	\$	\$	\$	\$
Total cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for utilisation of BRAF and MEK inhibitors</b>						
Cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Copayments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less copayments	-\$	-\$	-\$	-\$	-\$	-\$
<b>Net financial implications to the PBS/RPBS and MBS</b>						
Net cost to PBS/RPBS	\$	-\$	-\$	-\$	-\$	-\$
Net cost to MBS	\$	\$	\$	\$	\$	\$
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$	\$

IPI = ipilimumab; NIVO = nivolumab

<sup>a</sup> Assuming 19.6 infusions administered every 2 weeks (3 mg/kg Q2W and 200 g Q2W doses) or 9.8 infusions administered every 4 weeks (400 mg dose) per course, as estimated by the submission.

<sup>b</sup> Assuming 3.2 infusions of NIVO+IPI in the induction phase, and either 11.1 infusions of NIVO administered every 2 weeks (3 mg/kg Q2W and 200 g Q2W doses) or 5.5 infusions administered every 4 weeks (400 mg dose) for the maintenance phase, as estimated by the submission.

<sup>c</sup> Includes 25 grandfathered patients

Source: Table 56 p132, Table 57 pp133-4, Table 61 p137, Table 62 p138, Table 66 p140, Table 69 p141 and Table 70 p141 of the submission; Section 4 Excel workbook 'Elec doc\_Section 4\_BIM'.

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

6.60 The ESC considered additional sources of uncertainty in the base case of the financial analysis were:

- The failure to incorporate changes in the utilisation of second-line treatments;
- The likely market share of each treatment option, when both NIVO monotherapy and NIVO+IPI are available for first-line therapy for patients with BRAF mutation positive melanoma; and

- The mean duration of therapy for each of the treatment regimens.
- 6.61 The submission presented a sensitivity analysis including changes in second-line melanoma therapies. There were a number of issues with this sensitivity analysis. In addition, the treatment duration for most of the second-line therapies was highly uncertain: the induction and maintenance phases of NIVO+IPI were based on data for a small number of patients receiving these treatments as monotherapy (IPI: n=37; NIVO: n=14), while the duration of second-line BRAF targeted therapy was assumed to be the same as that for PD-1 inhibitor monotherapy, as reported in the May 2018 DUSC review. The ESC, noting that inclusion of the second-line therapies resulted in cost savings of less than \$10 million per year over the first six years of listing, agreed with the evaluation and considered that there were a number of issues with the analysis. The pre-PBAC response stated that the availability of immunotherapies first-line would result in fewer patients requiring subsequent therapy. A recent analysis of the CA209-067 trial found that 67% of patients treated with NIVO+IPI and 58% of patients treated with NIVO monotherapy were alive at five years and treatment free.

### ***Financial Management – Risk Sharing Arrangements***

- 6.62 The submission raised the following options for a Risk Sharing Arrangement (RSA):
- Include NIVO monotherapy and NIVO+IPI in the existing expenditure cap for currently listed first-line BRAF targeted therapies for unresectable or metastatic melanoma. In this scenario, until the expenditure cap for combined first-line BRAF targeted therapy and immunotherapy was exceeded, the cost of NIVO monotherapy and NIVO+IPI in the first-line setting would be incurred by the PBS. However, the ESC noted that as the total Commonwealth expenditure on PD-1 inhibitors for unresectable or metastatic melanoma is currently above the subsidisation cap<sup>\*\*\*</sup>, any reduction in utilisation of NIVO in the second-line setting would not result in a reduction in costs to the PBS unless the total utilisation of NIVO and pembrolizumab currently covered under the RSA dropped below the subsidisation cap for this therapy group.
  - Join the proposed RSA encompassing the use of BRAF/MEK, PD-1 and programmed cell death ligand-1 (PD-L1) inhibitors in both the adjuvant and the unresectable/metastatic melanoma settings, as proposed by the PBAC in its reconsideration of the deferral for NIVO for adjuvant treatment of melanoma (paragraph 7.14, Nivolumab PSD, March 2019). If this cap was imposed then a cost-minimisation approach should result in cost neutrality to the PBS, regardless of whether the cap is exceeded or not.

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<sup>\*\*\*</sup> Paragraph 6.37, 7.05 Nivolumab plus ipilimumab PSD, July 2018 PBAC Meeting

- 6.63 In its consideration of the July 2019 resubmissions for nivolumab monotherapy and DAB+TRAM for adjuvant treatment of patients with completely resected Stage III or Stage IV melanoma, the PBAC considered that there should be separate subsidisation caps for PD-1 inhibitors and DAB+TRAM, each encompassing use in both the adjuvant and the unresectable/metastatic settings (paragraph 4.36, Nivolumab PSD, July 2019). The PSCR stated that the Sponsor would be willing to revise the current PD-1 inhibitor subsidisation caps to include the extension of use in the first-line setting for BRAF positive patients. The PSCR stated that, consistent with the pricing proposal associated with the reconsideration of the NIVO as an adjuvant treatment deferral, the weighted nivolumab melanoma price would be revised across the three patient populations (adjuvant melanoma, current metastatic melanoma and extended use in the first-line setting for BRAF positive patients). The PBAC considered that this would be the most implementable form of RSA.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC outcome**

- 7.1 The PBAC recommended the extension of the PBS listings for nivolumab (NIVO) monotherapy and nivolumab in combination with ipilimumab (NIVO+IPI) to allow their use as first-line therapies in the treatment of BRAF V600 mutant positive Stage III or Stage IV unresectable or metastatic melanoma, noting the strong clinical support to allow individualised treatment. The PBAC considered that nivolumab (NIVO) monotherapy and nivolumab in combination with ipilimumab (NIVO+IPI) would be cost-effective in this population if they were cost-minimised to dabrafenib plus trametinib (DAB+TRAM).
- 7.2 The PBAC noted the strong support provided by individuals, health care professionals and organisations describing the clinical and quality of life benefits of allowing patients to be proactive in determining their treatment sequence. The PBAC also noted the high clinical and consumer demand, which was supported by current Australian and international guidelines.
- 7.3 In terms of the clinical place in therapy, the PBAC recalled that it previously restricted the use of NIVO monotherapy and NIVO+IPI in patients with BRAF mutant unresectable or metastatic melanoma to those patients who had progressed following treatment with a BRAF±MEK inhibitor. The PBAC noted that current Australian and international guidelines recommended NIVO monotherapy and NIVO+IPI combination therapy as alternative first-line therapies for these patients. The PBAC noted that guidelines state that first-line systemic therapy should be individualised, with clinical factors dictating preference for use of BRAF-targeted treatment or immunotherapy.
- 7.4 The PBAC considered that DAB+TRAM was the appropriate comparator for NIVO monotherapy and NIVO+IPI as first-line therapy in BRAF mutant unresectable or metastatic melanoma.

- 7.5 The PBAC noted that the submission was based on a naïve side-by-side comparison of BRAF mutation positive melanoma patients from the NIVO monotherapy and NIVO+IPI arms of the CA209-067 randomised controlled trial (RCT) and the DAB+TRAM arms of the COMBI-V and COMBI-D trials. The PBAC considered that the evidence provided in the resubmission was of low quality due to the nature of the side-by-side comparison, the considerable potential for confounding inherent to the comparison and the potential transitivity issues.
- 7.6 The PBAC also noted two recently published network meta-analyses of therapies for the treatment of advanced BRAF mutant melanoma. An and Lui, 2019 did not find a significant difference in progression free or overall survival between BRAF+MEK and PD-1 inhibitors. Zoratti et al, 2019 found that BRAF+MEK inhibitors were more favourable in terms of progression free survival, whereas NIVO+IPI was likely to be more efficacious in terms of overall survival.
- 7.7 The PBAC considered that, in totality, the evidence did not provide a compelling signal of difference in the efficacy of NIVO monotherapy or NIVO+IPI compared to DAB+TRAM in terms of progression free and overall survival, or the optimal sequence of BRAF targeted therapies and immunotherapies in patients with unresectable or metastatic BRAF mutant melanoma. Overall, the PBAC considered that the claim of non-inferior efficacy between NIVO monotherapy, NIVO+IPI combination therapy and DAB+TRAM was likely to be supported by the data.
- 7.8 The PBAC agreed with the ESC in that there was genuine clinical equipoise amongst clinicians as to the optimal sequence of therapies in BRAF mutant metastatic melanoma. The PBAC noted that two international RCTs comparing the effects on overall survival of BRAF-targeted therapy and immunotherapy (DREAMseq and SECOMBIT) were in progress and requested that the results of these trials be made available to the PBAC once they are completed.
- 7.9 In terms of comparative harms, the PBAC considered that NIVO monotherapy was no worse than DAB+TRAM. Due to high rates of serious adverse events, grade 3 and 4 adverse events and adverse events resulting in discontinuation associated with NIVO+IPI, the PBAC considered that NIVO+IPI had an inferior safety profile compared to DAB+TRAM.
- 7.10 The PBAC noted that the submission proposed a cost-neutral approach to listing NIVO monotherapy and NIVO+IPI compared with the cost of DAB+TRAM in the first-line setting. The PBAC, noting that the economic evaluation incorporated costs of administration for NIVO monotherapy and NIVO+IPI and adverse events associated with NIVO+IPI, considered that the approach was consistent with that presented for NIVO+IPI in the treatment of unresectable or metastatic melanoma in July 2018.
- 7.11 The PBAC noted that the durations of treatment for NIVO monotherapy, NIVO+IPI and DAB+TRAM were based on a DUSC review. Noting that the DUSC data were likely to be immature, due to the comparability issues between the trials the PBAC considered

that the durations of therapy applied in the cost analysis were acceptable for NIVO monotherapy and DAB+TRAM, but considered that the duration of NIVO+IPI was underestimated. The PBAC noted that the mean duration of NIVO when used as monotherapy was shorter in the trial, but longer in the cost analysis compared with when used in combination with IPI. However, the PBAC also noted that in the July 2018 submission the duration of NIVO when used as monotherapy was longer than when used in combination with IPI.

- 7.12 The PBAC considered that the durations of therapy for NIVO monotherapy and NIVO+IPI should be proportionally more consistent between the trial data and that applied in the cost analysis. Therefore, the PBAC proposed that the equi-effective durations of therapy were (paragraph 6.37):

Nivolumab monotherapy (■■■ days) =

Nivolumab + ipilimumab (■■■ to ■■■ days) =

Dabrafenib + trametinib (279 days)

- 7.13 The PBAC noted that the economic analysis did not incorporate second-line treatment costs, but that a supplementary analysis which added the costs of second-line therapy to cost-minimised first-line therapies was provided in the pre-Sub-Committee Response. The PBAC considered that due to the unclear assumptions regarding second-line treatments this analysis introduced additional uncertainty. The PBAC considered that, although not robust, the supplementary analysis incorporating second-line treatment costs provided support that the analysis based on first-line treatments only was a reasonable approach.

- 7.14 In terms of the utilisation estimates in the unresectable or metastatic setting, the PBAC recommended that:

- Growth in the unresectable or metastatic setting should be estimated at ■■■%, rather than derived from a linear projection of DUSC data, to more closely align with the incidence of melanoma in Australia (paragraph 6.51);
- The proportion of patients with BRAF mutant positive melanoma should be 37.7%, which was based on the results of an Australian cohort study by Lyle 2016, rather than 31% (paragraph 6.52) ;
- The estimate of first-line PD-1 inhibitor use (either as monotherapy or NIVO+IPI) in the unresectable or metastatic setting should be 50% to 60% rather than 73% (paragraph 6.55); and
- The number of unresectable or metastatic patients should be revised downwards (i) from Year 2 to incorporate the estimated ■■■% to ■■■% of patients who remain recurrence free after receiving adjuvant therapy; and (ii) from Year 1 to incorporate the estimated ■■■% to ■■■% of patients who recur whilst on, or within six months of completing, adjuvant therapy (paragraph 6.56).

- 7.15 The PBAC reiterated that the restriction changes should result in no additional costs to the PBS/RPBS.
- 7.16 In terms of the Special Pricing Arrangement for nivolumab, the PBAC advised that the weighted pricing proposal associated with the November 2019 reconsideration of the deferral of NIVO as adjuvant treatment would have to be updated include extended use in the first-line unresectable or metastatic setting for BRAF mutant patients.
- 7.17 The PBAC considered that the proposal of a RSA for the PD-1 inhibitors consisting of subsidisation caps across both the adjuvant and unresectable or metastatic settings, beyond which [REDACTED] rebates would apply, was appropriate to manage the uncertainty around uptake in the adjuvant setting and changes to use in the unresectable or metastatic setting. The PBAC advised that:
- the current subsidisation caps applying to PD-1 inhibitor monotherapies in the unresectable or metastatic setting should be revised based on the recommendations provided in paragraph 7.14 and to include the extension of NIVO use, both as monotherapy and in combination with ipilimumab, in the first-line setting for BRAF mutant patients;
  - the proposed subsidisation caps applying to PD-1 inhibitor monotherapies in the adjuvant setting, as provided in the reconsideration of NIVO as an adjuvant treatment deferral, should be revised as recommended by the PBAC to assume the proportion of patients with BRAF mutant disease was 37.7% and the dosing schedule for NIVO was as per paragraph 6.57.
- 7.18 Noting that nivolumab for the treatment of adjuvant Stage IIIB, IIIC, IIID or Stage IV melanoma was recommended at the November 2019 meeting, the PBAC advised that to minimise the number of restriction changes required, both recommendations should be implemented at the same time.
- 7.19 The PBAC considered that it would be appropriate to remove reference to BRAF mutation status in the restrictions for NIVO and NIVO+IPI in the unresectable or metastatic setting.
- 7.20 For patients who had received a PD-1 inhibitor in the adjuvant setting the PBAC advised that NIVO or NIVO+IPI could only be used as retreatment in the unresectable or metastatic setting if patients had completed 12 months of adjuvant therapy and remained recurrence free for six months following completion of adjuvant therapy.
- 7.21 For BRAF mutant patients who had received BRAF+MEK inhibitor combination therapy in the adjuvant setting, the PBAC advised that NIVO or NIVO+IPI could be used as retreatment in the unresectable or metastatic setting at recurrence.
- 7.22 The PBAC noted the flow-on restriction changes to the current PBS listings for the BRAF and MEK inhibitors in the unresectable or metastatic setting to allow extension of treatment as second-line therapies and considered this was appropriate.

*Public Summary Document – November 2019 PBAC Meeting*

- 7.23 The PBAC advised that NIVO monotherapy and NIVO+IPI combination therapy are not suitable for prescribing by nurse practitioners.
- 7.24 The PBAC recommended that the Early Supply Rule should not apply to the listings of NIVO monotherapy or NIVO+IPI combination therapy.
- 7.25 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* that nivolumab and ipilimumab should not be treated as interchangeable on an individual patient bases with any other drugs.
- 7.26 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because the availability of NIVO monotherapy and NIVO+IPI combination therapy as a first-line treatment option for patients with BRAF mutant unresectable or metastatic melanoma were not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the DAB+TRAM, and not expected to address a high and urgent unmet clinical need, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.27 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

Amend existing/recommended listing as follows:

### Initial treatment (NIVOLUMAB monotherapy)

*Amend as follows:*

**Nivolumab:**            **Restriction summary 9249 / Treatment of Concept: 9320: Authority Streamlined (9320)**  
 PBS item codes: 10764M (Public) & 10775D (Private)

7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
14458	<b>Administrative Advice:</b> 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.
8676	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
edit	<b>Treatment Phase:</b> Initial treatment 2
delete [16650]	<b>Clinical criteria:</b>
[16649]	<del>The condition must be negative for a BRAF V600 mutation</del>
	<b>AND</b>
18686	<b>Clinical criteria:</b>

Public Summary Document – November 2019 PBAC Meeting

edit 18685	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for <del>this condition</del> the treatment of unresectable Stage III or Stage IV malignant melanoma
	<b>AND</b>
insert	<b>Clinical criteria:</b>
new	Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment if treated for resected Stage IIIB, IIIC, IIID or IV melanoma if treated for resected disease
	<b>AND</b>
7890	<b>Clinical criteria:</b>
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
delete 24450	<b>Clinical criteria:</b>
24449	The treatment must not exceed a dose of 3 mg/kg or 240 mg every two weeks or 480 mg every four weeks
8682	<b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
24451	<b>Prescribing Instructions:</b> 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.

Delete the following restriction:

**Nivolumab:** Restriction Summary 9845 / ToC: 9832: Authority Required: Streamlined (9832)  
PBS item codes: 10764M (Public) & 10775D (Private)

[7607]	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
[7608]	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
[14458]	<b>Administrative Advice:</b> 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.
[8676]	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
	<b>Treatment Phase:</b> Initial treatment 1
[9245]	<b>Clinical criteria:</b>
[9244]	The condition must be positive for a BRAF V600 mutation
	<b>AND</b>
[24933]	<b>Clinical criteria:</b>
[24871]	Patient must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) in the unresectable or metastatic setting unless contraindicated or not tolerated according to the TGA approved Product Information; or
[24934]	Patient must have experienced disease recurrence whilst receiving a BRAF inhibitor with MEK inhibitor as an adjuvant treatment for resected Stage IIIB, IIIC or IIID melanoma; or
[24935]	Patient must have experienced disease recurrence within 6 months of completion of adjuvant BRAF inhibitor with MEK inhibitor treatment
	<b>AND</b>
[24876]	<b>Clinical criteria:</b>
[24875]	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma
	<b>AND</b>
[7890]	<b>Clinical criteria:</b>
[7889]	The treatment must be the sole PBS-subsidised therapy for this condition
	<b>AND</b>
[24450]	<b>Clinical criteria:</b>

Public Summary Document – November 2019 PBAC Meeting

[24449]	The treatment must not exceed a dose of 3 mg/kg or 240 mg every two weeks or 480 mg every four weeks
[8682]	<b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
[24451]	<b>Prescribing Instructions:</b> 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.

**Induction treatment (NIVOLUMAB, in combination with ipilimumab)**

Amend as follows:

**Nivolumab: Restriction Summary 8144 / ToC: 8182: Authority Required: Streamlined (8182)**  
PBS item codes: 11532Y (Private) & 11543M (Public)

7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
8676	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
	<b>Treatment Phase:</b> Induction treatment
<del>16650</del>	<b>Clinical criteria:</b>
16649	The condition must be negative for a BRAF V600 mutation
	<b>AND</b>
18686	<b>Clinical criteria:</b>
<del>18685</del>	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition <i>the treatment of unresectable Stage III or Stage IV malignant melanoma</i>
	<b>AND</b>
<del>18685</del>	<b>Clinical criteria:</b> <i>Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment for resected Stage IIIB, IIIC, IIID or IV melanoma if treated for resected disease</i>
	<b>AND</b>
23067	<b>Clinical criteria:</b>
23066	Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	<b>AND</b>
23069	<b>Clinical criteria:</b>
23068	The condition must not be ocular or uveal melanoma
	<b>AND</b>
23107	<b>Clinical criteria:</b>
23106	The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition
23103	<b>Caution:</b> Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.
23070	<b>Prescribing Instructions:</b> Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.
23071	<b>Prescribing Instructions:</b> Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.
8682	<b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

Delete the following restriction:

**Nivolumab: Restriction Summary 9836 / ToC: 9844: Authority Required: Streamlined (9844)**

*Public Summary Document – November 2019 PBAC Meeting*

PBS item codes: 11532Y (Private) & 11543M (Public)

[7607]	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
[7608]	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
[8676]	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
	<b>Treatment Phase:</b> Induction treatment
[9245]	<b>Clinical criteria:</b>
[9244]	The condition must be positive for a BRAF V600 mutation
	<b>AND</b>
[24933]	<b>Clinical criteria:</b>
[24874]	Patient must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) in the unresectable or metastatic setting unless contraindicated or not tolerated according to the TGA approved Product Information; or
[24934]	Patient must have experienced disease recurrence whilst receiving a BRAF inhibitor with MEK inhibitor as an adjuvant treatment for resected Stage IIIB, IIIC or IIID melanoma; or
[24935]	Patient must have experienced disease recurrence within 6 months of completion of adjuvant BRAF inhibitor with MEK inhibitor treatment
	<b>AND</b>
[24876]	<b>Clinical criteria:</b>
[24875]	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma
	<b>AND</b>
[23067]	<b>Clinical criteria:</b>
[23066]	Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	<b>AND</b>
[23069]	<b>Clinical criteria:</b>
[23068]	The condition must not be ocular or uveal melanoma
	<b>AND</b>
[23107]	<b>Clinical criteria:</b>
[23106]	The treatment must be in combination with PBS subsidised treatment with ipilimumab as induction for this condition
[23103]	<b>Caution:</b> Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.
[23070]	<b>Prescribing Instructions:</b> Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.
[23071]	<b>Prescribing Instructions:</b> Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.
[8682]	<b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
[14458]	<b>Administrative Advice:</b> 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.

*Amend nivolumab's current grandfathering restriction in induction treatment of BRAF negative patients to allow continuing treatment in patients (approximately 25) who commenced with nivolumab as first-line therapy through clinical trials/ patient familiarisation programs/ compassionate supply as follows:*

**Nivolumab:** Restriction Summary 8145 / ToC: 8146: Authority Required: Streamlined  
PBS item codes: 11532Y (Private) & 11543M (Public)

7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
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*Public Summary Document – November 2019 PBAC Meeting*

7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
8676	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
<del>edit</del>	<b>Treatment Phase:</b> Induction treatment - Grandfathered patients treated with nivolumab as first-line therapy in unresectable Stage III or Stage IV malignant melanoma prior to [1 Month 20XX – insert listing date here]
<del>delete</del> 16650	<b>Clinical criteria:</b>
16649	The condition must be negative for a BRAF V600 mutation
	<b>AND</b>
<del>delete</del> 23079	<b>Clinical criteria:</b>
<del>delete</del> 23078	Patient must have received combined therapy with ipilimumab and nivolumab as induction for this condition prior to 1 December 2018; or
<del>delete</del> 23111	Patient must have received monotherapy with nivolumab as maintenance for this condition prior to 1 December 2018
	<b>AND</b>
<del>delete</del> 23116	<b>Clinical criteria:</b>
23115	Patient must not have previously received treatment with ipilimumab or a programmed cell death factor 1 (PD-1) inhibitor prior to initiating combined therapy with ipilimumab and nivolumab as induction for this condition
	<b>AND</b>
<del>delete</del> 23081	<b>Clinical criteria:</b>
23080	Patient must not have developed disease progression while being treated with combined therapy with ipilimumab and nivolumab as induction for this condition; or
23117	Patient must not have developed disease progression while being treated with monotherapy with nivolumab as maintenance for this condition
	<b>AND</b>
<del>delete</del> 23112	<b>Clinical criteria:</b>
23120	Patient must have had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 prior to initiating treatment with this drug for this condition
	<b>AND</b>
<del>delete</del> 23069	<b>Clinical criteria:</b>
23068	The condition must not be ocular or uveal melanoma
	<b>AND</b>
<del>delete</del> 23119	<b>Clinical criteria:</b>
23106	The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition; or
23118	The treatment must be as monotherapy as maintenance for this condition
<del>insert</del>	<b>Clinical criteria:</b>
New	Patient must have received non-PBS subsidised supply of this drug as first-line therapy for unresectable Stage III or Stage IV malignant melanoma prior to [1 Month 20XX – insert listing date here]
	<b>AND</b>
<del>insert</del> 7890	<b>Clinical criteria:</b>
7889	The treatment must be the sole PBS-subsidised therapy for this condition
<del>delete</del> 23070	<b>Prescribing Instructions:</b> Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.
<del>delete</del> 23071	<b>Prescribing Instructions:</b> Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.
<del>delete</del> 23108	<b>Prescribing Instructions:</b> Maintenance treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks.

*Public Summary Document – November 2019 PBAC Meeting*

<del>20162</del>	<b>Prescribing Instructions:</b> 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.
<del>8682</del>	<b>Prescribing Instructions:</b> <del>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.</del>
<i>insert</i> 24451	<b>Prescribing Instructions:</b> 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.

*Delete the following nivolumab grandfather restriction in BRAF positive patients (not shown) that is now more than 12 months old:*

**Nivolumab:**            **Restriction Summary 8220 / ToC: 8220: Authority Required: Streamlined**  
PBS item codes: 11543M (Public) / 11532Y (Private)

**Induction treatment (IPILIMUMAB, in combination with nivolumab)**

*Amend as follows:*

**Ipilimumab:**            **Restriction Summary 8206 / ToC: 8206: Authority Required: Streamlined (8206)**  
PBS item codes: 2638W (Private) and 2641B (Public)

7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
8676	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
	<b>Treatment Phase:</b> Induction treatment
<del>16650</del>	<b>Clinical criteria:</b>
<del>16649</del>	<del>The condition must be negative for a BRAF V600 mutation</del>
	<b>AND</b>
18686	<b>Clinical criteria:</b>
<i>edit</i> 18685	Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for <del>this condition</del> <i>the treatment of unresectable Stage III or Stage IV malignant melanoma</i>
	<b>AND</b>
<i>insert</i> New	<b>Clinical criteria:</b> <i>Patient must not have experienced disease progression whilst on adjuvant PD-1 inhibitor treatment or disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment for resected Stage IIIB, IIIC, IIID or IV melanoma if treated for resected disease</i>
	<b>AND</b>
23067	<b>Clinical criteria:</b>
23066	Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	<b>AND</b>
23069	<b>Clinical criteria:</b>
23068	The condition must not be ocular or uveal melanoma
	<b>AND</b>
23102	<b>Clinical criteria:</b>
23101	The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction therapy for this condition
23103	<b>Caution:</b> Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.
23070	<b>Prescribing Instructions:</b>

*Public Summary Document – November 2019 PBAC Meeting*

	Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.
23071	<b>Prescribing Instructions:</b> Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.
8682	<b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

*Delete restriction:*

**Ipilimumab: Restriction Summary 9839 / ToC: 9840: Authority Required: Streamlined (9840)**  
PBS item codes: 2638W (Private) & 2641B (Public)

[7607]	<del><b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.</del>
[7608]	<del><b>Administrative Advice:</b> Special Pricing Arrangements apply.</del>
[8676]	<del><b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma</del>
	<del><b>Treatment Phase:</b> Induction treatment</del>
[9245]	<del><b>Clinical criteria:</b></del>
[9244]	<del>The condition must be positive for a BRAF V600 mutation</del>
	<del><b>AND</b></del>
[24933]	<del><b>Clinical criteria:</b></del>
[24871]	<del>Patient must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) in the unresectable or metastatic setting unless contraindicated or not tolerated according to the TGA approved Product Information; or</del>
[24934]	<del>Patient must have experienced disease recurrence whilst receiving a BRAF inhibitor with MEK inhibitor as an adjuvant treatment for resected Stage IIIB, IIIC or IIID melanoma; or</del>
[24935]	<del>Patient must have experienced disease recurrence within 6 months of completion of adjuvant BRAF inhibitor with MEK inhibitor treatment</del>
	<del><b>AND</b></del>
[24876]	<del><b>Clinical criteria:</b></del>
[24875]	<del>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death 1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma</del>
	<del><b>AND</b></del>
[23067]	<del><b>Clinical criteria:</b></del>
[23066]	<del>Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1</del>
	<del><b>AND</b></del>
[23069]	<del><b>Clinical criteria:</b></del>
[23068]	<del>The condition must not be ocular or uveal melanoma</del>
	<del><b>AND</b></del>
[23102]	<del><b>Clinical criteria:</b></del>
[23101]	<del>The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction therapy for this condition</del>
[23103]	<del><b>Caution:</b> Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.</del>
[23070]	<del><b>Prescribing Instructions:</b> Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.</del>
[23071]	<del><b>Prescribing Instructions:</b> Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.</del>
[8682]	<del><b>Prescribing Instructions:</b> The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.</del>
[14458]	<del><b>Administrative Advice:</b> 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.</del>

*Delete the following ipilimumab grandfather restrictions (not shown) that will be more than*

Public Summary Document – November 2019 PBAC Meeting

12 months old:

**Ipilimumab:** Restriction Summary 8178 / ToC: 8178: Authority Required: Streamlined (BRAF negative patients)  
Restriction Summary 8180 / ToC: 8180: Authority Required: Streamlined (BRAF positive patients)  
PBS item codes 2641B (Public) & 2638W (Private)

Flow-on changes to BRAF inhibitors to allow for first or second-line use, but without cycling through different BRAF inhibitors, in unresectable Stage III or Stage IV disease, are shown as follows:

**Restriction summary 9833 / ToC: 9842: Authority Required: Streamlined**

Dabrafenib: PBS item codes: 2846T (75 mg capsules, 120) & 2963Y (50 mg capsules, 120)

Vemurafenib: PBS item code: 11076Y (240 mg tablets, 56)

7606	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
8676	<b>Indication:</b> Unresectable Stage III or Stage IV malignant melanoma
	<b>Treatment Phase:</b> Initial treatment
9245	<b>Clinical criteria:</b>
9244	The condition must be positive for a BRAF V600 mutation
	<b>AND</b>
24863	<b>Clinical criteria:</b>
edit 24865	The condition must not have been treated previously with PBS subsidised <i>BRAF inhibitor</i> therapy for unresectable Stage III or Stage IV disease; or
9248	Patient must have developed intolerance to other BRAF inhibitors of a severity necessitating permanent treatment withdrawal
	<b>AND</b>
24931	<b>Clinical criteria:</b>
edit 24932	Patient must not have experienced disease <i>progression whilst on adjuvant BRAF inhibitor treatment or disease recurrence</i> within 6 months of completion of adjuvant BRAF inhibitor with MEK inhibitor treatment if previously treated with adjuvant BRAF inhibitor with MEK inhibitor for resected Stage IIIB, IIIC or IIID melanoma
	<b>AND</b>
7601	<b>Clinical criteria:</b>
7600	Patient must have a WHO performance status of 2 or less
	<b>Administrative Advice:</b>
9251	A patient who has had progressive disease when treated with another BRAF inhibitor is not eligible to receive PBS-subsidised treatment with this drug.

**Pembrolizumab in the unresectable or metastatic setting**

Flow-on changes to pembrolizumab restrictions for unresectable Stage III or Stage IV disease:

<b>Pembrolizumab</b>	
<b>Category/Program:</b>	Section 100 Efficient Funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Unresectable Stage III or Stage IV
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial treatment 1

Public Summary Document – November 2019 PBAC Meeting

<b>Restriction level:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be positive for a BRAF V600 mutation, AND The condition must have progressed following treatment with a BRAF inhibitor (with or without MEK inhibitor) in the unresectable or metastatic setting unless contraindicated or not tolerated according to the TGA approved Product Information, OR The patient must have experienced disease recurrence whilst receiving a BRAF inhibitor with a MEK inhibitor as an adjuvant treatment for completely resected Stage IIIB, IIIC or IIID melanoma, OR The patient must have experienced disease recurrence within 6 months of completion of adjuvant BRAF inhibitor with MEK inhibitor treatment, AND Patient must not have been treated with an adjuvant programmed cell death-1 (PD-1) inhibitor for resected Stage IIIB, IIIC, IIID or IV melanoma, OR Patient must have experienced disease recurrence after at least 6 months from completion of an adjuvant PD-1 inhibitor for resected Stage IIIB, IIIC, IIID or IV melanoma, followed by disease progression after treatment with a BRAF inhibitor (with or without MEK inhibitor) in the unresectable or metastatic setting unless contraindicated or not tolerated according to the TGA approved Product Information, AND Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The treatment must not exceed a total of 6 doses administered every 3 weeks, with each maximum dose fixed at 200 mg.</p>
<b>Prescriber instructions:</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
<b>Administrative advice:</b>	<p>No increase in the maximum number or repeats may be authorised. Special Pricing Arrangements apply. 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.</p>

<b>Pembrolizumab</b>	
<b>Category/Program:</b>	Section 100 Efficient Funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Malignant melanoma
<b>PBS indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Initial treatment 2
<b>Restriction level:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be negative for a BRAF V600 mutation, AND Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for the treatment of unresectable Stage III or Stage IV malignant melanoma, OR Patient must not have experienced disease recurrence within 6 months of completion of adjuvant PD-1 inhibitor treatment for resected Stage IIIB, IIIC, IIID or IV melanoma, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND The treatment must not exceed a total of 6 doses administered every 3 weeks, with each maximum dose fixed at 200 mg.</p>

*Public Summary Document – November 2019 PBAC Meeting*

<b>Prescriber instructions:</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
<b>Administrative advice:</b>	No increase in the maximum number or repeats may be authorised. Special Pricing Arrangements apply. 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.

*These restrictions may be subject to further review. Should there be any changes made to the restrictions the Sponsor will be informed.*

## **9 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.

## **10 Sponsor's Comment**

The sponsor had no comment.