

## 6.11 IPILIMUMAB

### 50 mg/10 mL injection, 10 mL, 200 mg/40 mL injection, 40 mL, Yervoy<sup>®</sup>, Bristol-Myers Squibb Australia Ltd

#### 1 Purpose of Application

- 1.1 The minor submission requested an amendment to the restriction wording for the PBS listing of ipilimumab for unresectable stage III or stage IV malignant melanoma from “the treatment must be as monotherapy” to “the treatment must be the sole PBS-subsidised therapy for this condition”.

#### 2 Requested listing

- 2.1 The submission requested the following changes to the existing listing. An abridged version is presented below, with the submission’s proposed deletion marked in strikethrough and submission’s proposed additions in italics.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
IPILIMUMAB 50 mg/10 mL injection, 10 mL 200 mg/40 mL injection, 40 mL	360 mg	3	\$48159.70	Yervoy <sup>®</sup> BQ

<b>Category / Program</b>	Section 100 – Efficient funding of chemotherapy (Public and Private)
<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>PBS Indication:</b>	Unresectable Stage III or Stage IV malignant melanoma
<b>Treatment phase:</b>	Induction treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<del>The treatment must be as monotherapy;</del> <i>The treatment must be the sole PBS-subsidised therapy for this condition;</i>  AND  Patient must not have received prior treatment with ipilimumab;  AND  The treatment must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.

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<b>Treatment phase:</b>	Re-induction treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<del>The treatment must be as monotherapy;</del> The treatment must be the sole PBS-subsidised therapy for this condition;  AND  Patient must have progressive disease after achieving an initial objective response to the most recent course of ipilimumab treatment (induction or re-induction)  AND  The treatment must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.

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<b>Treatment phase:</b>	Completion of induction treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<del>The treatment must be as monotherapy;</del> The treatment must be the sole PBS-subsidised therapy for this condition;  AND  The treatment must be for completion of induction treatment in a patient who commenced induction treatment with ipilimumab prior to 1 August 2013.  AND  The treatment must not exceed a total of 4 doses (combined PBS-subsidised and non-PBS subsidised) at a maximum dose of 3 mg per kg every 3 weeks.

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<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p><del>The treatment must be as monotherapy;</del>                      The treatment must be the sole PBS-subsidised therapy for this condition;</p> <p>AND</p> <p>Patient must have progressive disease after achieving an initial objective response to the most recent course of ipilimumab treatment (induction or re-induction);</p> <p>AND</p> <p>The treatment must be for completion of re-induction treatment in a patient who commenced re-induction treatment with ipilimumab prior to 1 August 2013;</p> <p>AND</p> <p>The treatment must not exceed a total of 4 doses (combined PBS-subsidised and non-PBS subsidised) at a maximum dose of 3 mg per kg every 3 weeks.</p>

- 2.2 The submission stated that the proposed change to the restriction wording would be consistent with the current approved wording for nivolumab and pembrolizumab, both PBS-listed for metastatic melanoma, and would allow the use of ipilimumab through the PBS when used in combination with nivolumab (provided free-of-charge by the sponsor) to enable a commitment to the TGA for a safety study of the combination.
- 2.3 The Pre-PBAC response agreed that the grandfather restrictions could be deleted at this time as all patients requiring this provision should have now completed their initial treatment course.

*For more detail on PBAC's view, see section 6 "PBAC outcome"*

### 3 Background

- 3.1 Ipilimumab is registered by the TGA as monotherapy for the treatment of patients with unresectable or metastatic melanoma.
- 3.2 Ipilimumab received a positive PBAC recommendation in November 2012 and has been PBS listed for metastatic melanoma as monotherapy since 1 August 2013.

- 3.3 In making a positive recommendation, the PBAC considered that a mechanism should be implemented to verify the anticipated overall survival benefits of ipilimumab in real world clinical practice in Australia, with the sponsor expected to rebate the cost of difference in performance between observed versus predicted benefits of ipilimumab (Ipilimumab Public Summary Document, November 2012). The “Australian Outcomes Program” (AOP) required that data be collected on the outcomes of patients using ipilimumab as monotherapy. These results are required to be submitted in September 2016 for PBAC consideration, and may potentially affect the cost-effectiveness of ipilimumab. The Pre-PBAC response confirmed that the results of the AOP for ipilimumab as monotherapy have been collected and so these results would not be affected by the requested change to the restriction.
- 3.4 Nivolumab in combination with ipilimumab is registered by the TGA for use in patients with metastatic melanoma with M1c disease or elevated lactic dehydrogenase. As part of the risk management plan accompanying the TGA approval of combination therapy, a commitment was made that Australian sites would participate in a global safety study of combination use. The cost of providing nivolumab is proposed to be covered by the sponsor.
- 3.5 A major submission for nivolumab in combination with ipilimumab was rejected by the PBAC at the November 2015 meeting. In making this recommendation, the PBAC noted that the use of combination immunotherapy was associated with a modest improvement in PFS, but a substantial increase in adverse events. The net clinical benefit of combination treatment was therefore uncertain. The PBAC noted that there were no statistically significant differences in OS between combination nivolumab and ipilimumab treatment, and either pembrolizumab or ipilimumab monotherapy, and no OS data yet officially reported comparing the combination with nivolumab monotherapy (Nivolumab with Ipilimumab Public Summary Document, November 2015).
- 3.6 In April 2016, the Medical Oncology Group of Australia alerted its members to serious adverse events of fatal myocarditis, myositis and rhabdomyolysis in patients receiving ipilimumab and nivolumab. A link with the influenza vaccine was also suspected, and the sponsor was reported to be collecting and analysing further data.

#### **4 Current situation**

- 4.1 The submission stated that an alternative scenario, whereby ipilimumab is provided by the sponsor at no cost and nivolumab is claimed through the PBS is problematic, and would impact upon the current cap arrangements for PD-1 inhibitors and make it difficult to track monotherapy use.
- 4.2 There is a cap in place for ipilimumab; [REDACTED]. The expenditure for ipilimumab has reduced significantly in the last 9 months, likely due to listing of PD-1 inhibitors pembrolizumab and nivolumab. In the first two years of listing, ipilimumab expenditure was [REDACTED] \$ [REDACTED] and \$ [REDACTED] respectively, while the projected expenditure in year 3 is around \$ [REDACTED].
- 4.3 The submission stated that other combination studies are underway with ipilimumab in metastatic melanoma.

- 4.4 The current Special Pricing Arrangement rebate is designed to achieve cost-effectiveness for ipilimumab as monotherapy. The Pre-PBAC response stated that a price reduction was not warranted to continue to maintain cost-effectiveness.
- 4.5 Agreeing to this request would be likely to increase the number of patients for whom a grandfathering clause would need to be considered in the event that the combination of nivolumab and ipilimumab is subsequently PBS-subsidised.

*For more detail on PBAC's view, see section 6 "PBAC outcome"*

## **5 Consideration of the evidence**

### ***Sponsor hearing***

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

### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from one health professional via the Consumer Comments facility on the PBS website, supporting the proposed change in restriction wording.

## **6 PBAC Outcome**

- 6.1 The PBAC recommended the PBS restriction for ipilimumab for the treatment of unresectable stage III or stage IV malignant melanoma be amended to read "*The treatment must be the sole PBS-subsidised therapy for this condition*", on the basis that it would remain as an Authority Required (STREAMLINED) listing only under special arrangements under Section 100 Efficient Funding of Chemotherapy.
- 6.2 The PBAC additionally recommended the removal of the grandfathering restriction for ipilimumab at this time.
- 6.3 The PBAC was satisfied that the proposed change in restriction is consistent with other PBS listed agents currently available for the treatment of unresectable stage III or stage IV malignant melanoma.
- 6.4 The PBAC noted that the change in restriction wording was not likely to increase concomitant multiple PBS listed agents for the treatment of malignant melanoma. However, the PBAC also noted that as patients may access non-PBS therapy concomitantly with PBS-subsidised ipilimumab, this may change the level of utilisation of ipilimumab.
- 6.5 As the submission did not provided estimates of cost, the PBAC advised that the Department should work with the sponsor to determine the likely financial impact of the proposed change over the forward estimates to ensure that it does not have a financial impact for the Government.

**Outcome:**

Recommended

**7 Recommended listing**

7.1 Amend existing listing as follows:

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Delete:

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## 8 Context for Decision

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

## 9 Sponsor's Comment

The sponsor had no comment.