

## 14.03 PEMBROLIZUMAB

**Powder for injection 50 mg, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda<sup>®</sup>, Merck Sharp & Dohme (Australia) Pty Ltd**

### 1 Purpose of Application

- 1.1 The minor submission requested removal of the weight-based dosing option for pembrolizumab for the treatment of unresectable Stage III or Stage IV malignant melanoma.

### 2 Requested Listing:

- 2.1 The submission requested removal of weight based dosing to the existing listings to align with requested changes to the TGA product information.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	DPMA	Proprietary Name and Manufacturer
PEMBROLIZUMAB				
Powder for injection 50 mg	200 mg	5 (initial) 7 (continuing)	\$9,186.18 (private)	Keytruda <sup>®</sup>
Solution concentrate for I.V. infusion 100 mg in 4 mL			\$9,023.22 (public)	Merck Sharp & Dohme (Australia) Pty Ltd

Public Summary Document – November 2018 PBAC Meeting

**Treatment phase: Initial treatment 1**

<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
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be positive for a BRAF V600 mutation,</p> <p>AND</p> <p>The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) unless contraindicated or not tolerated according to the TGA approved Product Information,</p> <p>AND</p> <p>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>The treatment must not exceed a total of 6 doses administered every 3 weeks, with each maximum dose either at 2 mg per kg for patients &lt;100 kg or 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 of repeats will be authorised.</p> <p>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>

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**Treatment phase: Initial treatment 2**

<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 2
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The condition must be negative for a BRAF V600 mutation,</p> <p>AND</p> <p>Patient must not have received prior treatment with ipilimumab or a PD-1 (programmed cell death-1) inhibitor for this condition,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition,</p> <p>AND</p> <p>The treatment must not exceed a total of 6 doses administered every 3 weeks, with each maximum dose either at 2 mg per kg for patients &lt;100 kg or fixed at 200 mg.</p>
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<b>Administrative Advice</b>	<p>No increase in the maximum number of repeats will be authorised.</p> <p>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>

**Treatment phase: Continuing treatment**

<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
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<b>Clinical criteria:</b>	The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must have stable or responding disease, AND The treatment must not exceed a maximum dose administered every 3 weeks either at 2 mg per kg for patients <100 kg or fixed at 200 mg.
<b>Administrative Advice</b>	No increase in the maximum number of repeats will be authorised.  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.

### 3 Background

- 3.1 At the March 2018 PBAC meeting, the PBAC recommended an amendment to the existing PBS restrictions for pembrolizumab, for the treatment of unresectable Stage III or Stage IV malignant melanoma, to allow either a weight-based dose of 2 mg/kg or a fixed dose of 200 mg, every three weeks. The PBAC recommended that the maximum amount be adjusted to 200 mg.
- 3.2 At the time of consideration, the PBAC noted the sponsor’s claim that there is a flat relationship between pembrolizumab exposure and efficacy or safety within the dose range of 2 to 10 mg/kg. The PBAC therefore concluded that, for patients who are currently on a weight-based dose of less than 200 mg, there is no extra clinical benefit achieved by increasing to the fixed 200 mg dose, but there could potentially be more toxicity (Public Summary Document, March 2018 PBAC Meeting).

- 3.3 The change in dosing also has the effect of increasing wastage on average by 25% of the drug because the fixed dosing results in a higher administered dose without any additional patient benefit. For this reason, the PBAC concluded that a change from the weight-based to fixed dose regimen would not be cost-effective on a per-patient basis, as currently the mean dose of pembrolizumab is significantly less than 200 mg (Public Summary Document, March 2018 PBAC Meeting).
- 3.4 However, the PBAC noted that there is currently a relevant risk sharing arrangement in place, with a [REDACTED] % rebate over the annual expenditure caps. These caps have been exceeded in previous years. If the caps continue to be exceeded, the overall net cost to Government with the restriction amendment would remain the same as it would be contained by the risk sharing arrangement. The PBAC therefore advised that subsequent annual expenditure caps for this melanoma-based Deed of Agreement should be negotiated with the sponsor for pembrolizumab based on the weight-based dosing regimen, to ensure that the PBS listing remains acceptably cost-effective (Public Summary Document, March 2018 PBAC Meeting).

#### 4 Other relevant factors

[REDACTED]

[REDACTED]

#### 5 Pricing Considerations

- 5.1 At the time of its March 2018 consideration the PBAC had noted that the average benefit paid by the Commonwealth would increase as patients move from a weight based to a flat dosing regimen. The following information was considered by the PBAC at the March 2018 meeting.

Table 1: Comparison of the average benefit paid for pembrolizumab between 2016 – 2017 and the price requested by the minor submission

Setting	Average benefit paid 2016-17	Minor submission requested DPMA	Difference
Private hospital	\$8,468.96	\$9,186.18	\$698.59
Public hospital	\$8,418.39	\$9,023.22	\$587.17

#### 6 Secretariat comments

[REDACTED]

- 6.1 The Secretariat noted a final decision on timelines for amending the approved Product Information has not been made by the TGA, which may impact the timing of implementation of this request.

## 7 PBAC Outcome

- 7.1 The PBAC agreed with the impending change to the dose regimens in the Product Information and also noted the changes to be processed by the Secretariat following finalisation of TGA matters in relation to this change. The Committee noted its standing recommendation to add the fixed-dose regimen option to the current weight-based dosing listing and noted the sponsor had not proceeded with listing at this time.
- 7.2 The PBAC also noted that, while the current cap arrangement limited any increase in expenditure, future deeds would need to include a price reduction to pembrolizumab to ensure no net effect on the cost of pembrolizumab on a per patient basis for the treatment of melanoma, and therefore its cost-effectiveness, should all patients be required to switch to a flat dose regimen.

## 8 Recommended listing

- 8.1 Amend item as follows:

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## 9 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.

## 10 Sponsor's Comment

The sponsor had no comment.