

## 7.13 PEMBROLIZUMAB

### **Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda, Merck Sharp & Dohme (Australia) Pty Ltd**

#### **1 Purpose of Application**

- 1.1 Following a deferral at the November 2019 PBAC meeting, this minor resubmission sought:
- a recommendation for pembrolizumab for the adjuvant treatment of resected Stage IIIB, IIIC and IIID melanoma; and
  - to highlight the sponsor’s concerns regarding weighting and market share with the proposed cost-minimised price to nivolumab and with the existing melanoma Risk Sharing Arrangement (RSA).

#### **2 Background**

- 2.1 Pembrolizumab for the adjuvant treatment of Stage IIIB, IIIC and IIID melanoma was deferred at the November 2019 PBAC meeting, with the Committee noting that a listing for pembrolizumab would be unable to proceed until a listing for nivolumab was agreed. This was because the PBAC considered it appropriate for pembrolizumab to be listed on a cost minimisation basis versus nivolumab (paragraph 6.4, pembrolizumab minutes, Nov 2019).
- 2.2 Nivolumab for the adjuvant treatment of Stage IIIB, IIIC, IIID and Stage IV melanoma was recommended at the November 2019 PBAC meeting. Nivolumab was listed on the PBS for this indication on 1 March 2020.
- 2.3 A major submission to extend the restrictions of pembrolizumab to allow its use as first-line treatment in BRAF mutant patients in the unresectable or metastatic setting was also considered at the March 2020 PBAC meeting (Item 6.03). This restriction extension was recommended by the PBAC.
- 2.4 Nivolumab monotherapy and nivolumab plus ipilimumab combination therapy were recommended for use as first-line treatment options in BRAF mutant patients in the unresectable or metastatic setting at the November 2019 PBAC meeting. Nivolumab was listed on the PBS for this indication on 1 March 2020.

*For more detail on PBAC’s view, see Section 4 PBAC outcome.*

#### **3 Consideration of the evidence**

- 3.1 No changes were made to the clinical, economic or financial claims outlined in the November 2019 submission.

- 3.2 A minor change was made to the financial estimates to reflect recent changes to the pembrolizumab list price. The neutral budget impact compared with nivolumab was maintained. The PBAC considered that this was appropriate.

### ***Sponsor hearing***

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

### ***Consumer comments***

- 3.4 The PBAC noted and welcomed the input from an organisation (1) via the Consumer Comments facility on the PBS website.
- 3.5 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the pembrolizumab submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the KN054 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab as an adjuvant treatment for Stage III melanoma, which was a Grade A, which is the highest grade (out of C, and where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies), based on a comparison with placebo in the KN054 trial.<sup>1</sup>

### ***Pricing considerations***

- 3.6 The sponsor noted that in its consideration of nivolumab in July 2019, the PBAC stated that the effective price of nivolumab should be weighted across the adjuvant and ‘unresectable or metastatic settings (paragraph 4.48, nivolumab PSD, July 2019). The same approach was accepted by the PBAC for dabrafenib + trametinib (paragraph 5.9, dabrafenib + trametinib PSD, July 2019).
- 3.7 The sponsor presented a number of concerns relating to a weighed melanoma price for pembrolizumab including:
- the price in the adjuvant setting is expected to be lower than in the metastatic setting and any underweighting of the metastatic share or overweighting of the adjuvant share will pose a commercial risk;
  - the market share splits will not be equal for pembrolizumab and nivolumab across the adjuvant and metastatic settings, given the market share of pembrolizumab in the metastatic setting was approximately █% in the most recent RSA year. The sponsor states that an overall PD-1 inhibitor weighted price would assume a 50%/50% market share split in both settings, undervaluing pembrolizumab;

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<sup>1</sup> Cherny N, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefits scale, version 1.1. *Annals of Oncology*. 2017; 28: 2340-2366.

- nivolumab has a large patient access program in the adjuvant setting, which will result in the market share being heavily weighted towards nivolumab in the first years of the new RSA, and which is expected to continue throughout the RSA; and
  - the adjuvant nivolumab listing includes Stage IV patients which will also increase its expected market share. The nivolumab submission estimated that 14% of the eligible adjuvant population would have Stage IV disease (paragraph 6.43, nivolumab PSD, March 2019).
- 3.8 Therefore, the sponsor requested that the weighted price for pembrolizumab be product specific and represent an accurate forecast of the market share split between pembrolizumab and nivolumab.
- 3.9 The PBAC recalled that when considering nivolumab in November 2019, it recommended that the weightings be based on estimated volumes, rather than estimated indication-specific expenditure as that would result in a higher weighting for indications with higher effective prices. In addition, the weighted price for nivolumab included use in the first-line unresectable or metastatic setting for BRAF mutant patients.

### ***Risk sharing arrangements***

- 3.10 The sponsor stated that they agree in principle to a joint RSA consisting of PD-1 inhibitor subsidisation caps across both the adjuvant and metastatic settings; however, raise the following concerns:
- the current caps do not appropriately account for existing PBS use and it is estimated that they will be exceeded in Year 5 of the deed within the financial range of less than \$10 million;
  - any new caps should include an adequate uplift to account for first-line use in the BRAF positive unresectable or metastatic population (considered by PBAC for nivolumab in November 2019 and for pembrolizumab in March 2020); and
  - any new caps should also account for adequate uplift due to adjuvant PD-1 usage.
- 3.11 The Secretariat notes that the PBAC reviewed the financial estimates and proposed a revised RSA for the PD-1 inhibitors as part of its consideration of the November 2019 submissions for nivolumab as adjuvant melanoma treatment and nivolumab monotherapy and nivolumab in combination with ipilimumab for the first-line treatment of BRAF mutant patients with unresectable or metastatic melanoma.

*For more detail on PBAC's view, see Section 4 PBAC outcome.*

## **4 PBAC Outcome**

- 4.1 The PBAC recommended the listing of pembrolizumab as adjuvant treatment for patients who have had completely surgically resected Stage IIIB, IIIC or IIID malignant

melanoma. The PBAC had previously deferred making a recommendation as it considered it appropriate for pembrolizumab to be listed on a cost-minimisation basis versus nivolumab. The PBAC noted that nivolumab was listed on the PBS on 1 March 2020. The PBAC considered that the uncertainty surrounding uptake in the adjuvant setting and changes to use in the unresectable or metastatic setting (see item 6.03, March 2020 PBAC meeting) could be managed by subsidisation caps through a risk sharing arrangement and recommended that pembrolizumab join the arrangement agreed for nivolumab for melanoma, which reflected likely use across both settings.

- 4.2 The PBAC considered that the equi-effective doses of pembrolizumab and nivolumab in the cost-minimisation analysis would be:

Pembrolizumab 200 mg every 3 weeks = Nivolumab 360 mg every 3 weeks

- 4.3 The PBAC considered that as adjuvant therapy with both treatment is a fixed 12 month course, it was reasonable for the equi-effective doses to not reflect the mean treatment duration from the trials.
- 4.4 The PBAC recalled that in considering the nivolumab submissions in November 2019 it recommended that the weighted price of nivolumab be based on the estimated volume for each indication, and that the weighted price be updated to include extended use in the first-line unresectable or metastatic setting for BRAF mutant patients. As the recommended weighted nivolumab price was based on the total number of patients expected to be treated with a PD-1 inhibitor in each setting (BRAF mutant adjuvant, BRAF wild type adjuvant, BRAF mutant unresectable and BRAF wild type unresectable) it did not incorporate differences in market share by setting for each specific PD-1 inhibitor. Noting that the extension of the restriction for pembrolizumab to include BRAF mutant patients in the unresectable or metastatic setting was recommended at the March 2020 meeting, the PBAC recommended that pembrolizumab be cost-minimised to the weighted price of nivolumab.
- 4.5 The PBAC recalled that it reviewed the RSA of the PD-1 inhibitors across the adjuvant and unresectable or metastatic melanoma settings as part of its consideration of the November 2019 nivolumab submissions. The PBAC noted that the accepted RSA encompassed the entire melanoma market and consisted of subsidisation caps beyond which 100% rebates would apply. The PBAC recommended that pembrolizumab join the revised RSA.
- 4.6 The PBAC recommended that a grandfather listing be in operation for a period of 12 months to transition private patients to PBS-subsidised use.
- 4.7 The PBAC, noting that its recommendation was on a cost-minimisation basis, advised that as pembrolizumab was not expected to provide a substantial and clinically relevant improvement in efficacy or reduction in toxicity over nivolumab and not expected to address a high and urgent unmet clinical need, the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

Public Summary Document – March 2020 PBAC meeting

- 4.8 The PBAC advised that pembrolizumab is not suitable for prescribing by nurse practitioners.
- 4.9 The PBAC recommended that the Early Supply Rule should not apply to pembrolizumab.
- 4.10 The PBAC noted that this submission is not eligible for an Independent Review as it was a positive recommendation.

**Outcome:**

Recommended

## 5 Recommended listing

5.1 Add new Resected Stage IIIB, IIIC or IIID malignant melanoma listing as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	200 mg	7	Merck Sharp & Dohme (Australia) Pty Ltd
<b>Available brands</b>				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				

<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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic
<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
<b>Indication:</b> Resected Stage IIIB, IIIC or IIID malignant melanoma <b>Treatment Phase:</b> Initial treatment – 3 weekly treatment regimen <b>Clinical criteria:</b> <ul style="list-style-type: none"> <li>▪ The treatment must be adjuvant to complete surgical resection <b>AND</b></li> <li>▪ Patient must have a WHO performance status of 1 or less <b>AND</b></li> <li>▪ The treatment must be the sole PBS-subsidised therapy for this condition <b>AND</b></li> <li>▪ Patient must not have received prior PBS-subsidised treatment for this condition <b>AND</b></li> <li>▪ The treatment must commence within 12 weeks of complete resection <b>AND</b></li> <li>▪ Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy</li> </ul>
<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.

*Public Summary Document – March 2020 PBAC meeting*

<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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic
<p><b>Administrative Advice:</b>            No increase in the maximum amount or number of units may be authorised.            No increase in the maximum number of repeats may be authorised.            Special Pricing Arrangements apply.            Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.</p>
<p><b>Indication:</b> Resected Stage IIIB, IIIC or IIID malignant melanoma  <b>Treatment Phase:</b> Continuing treatment – 3 weekly treatment regimen  <b>Clinical criteria:</b></p> <ul style="list-style-type: none"> <li>▪ Patient must have previously been issued with an authority prescription for this drug for adjuvant treatment following complete surgical resection  <b>AND</b></li> <li>▪ Patient must not have experienced disease recurrence  <b>AND</b></li> <li>▪ The treatment must be the sole PBS-subsidised therapy for this condition  <b>AND</b></li> <li>▪ Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy</li> </ul>

<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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic
<p><b>Administrative Advice:</b>            No increase in the maximum amount or number of units may be authorised.            No increase in the maximum number of repeats may be authorised.            Special Pricing Arrangements apply.            Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.</p>
<p><b>Indication:</b> Resected Stage IIIB, IIIC or IIID malignant melanoma  <b>Treatment Phase:</b> Grandfather treatment – 3 weekly treatment regimen  <b>Clinical criteria:</b></p> <ul style="list-style-type: none"> <li>▪ Patient must have previously received non-PBS-subsidised drug for adjuvant treatment following complete surgical resection prior to 1 Month 20XX  <b>AND</b></li> <li>▪ Patient must have a WHO performance status of 1 or less prior to starting non-PBS treatment with this drug  <b>AND</b></li> <li>▪ Patient must not have evidence of recurrence  <b>AND</b></li> <li>▪ The treatment must be the sole PBS-subsidised therapy for this condition  <b>AND</b></li> <li>▪ Patient must not have received prior PBS-subsidised treatment for this condition  <b>AND</b></li> <li>▪ Patient must have commenced non-PBS-subsidised treatment within 12 weeks of complete surgical resection  <b>AND</b></li> <li>▪ Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy</li> </ul>
<p><b>Prescribing Instructions:</b>            A Grandfathered 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>Administrative Advice:</b> This grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria.

Public Summary Document – March 2020 PBAC meeting

5.2 Add 6-weekly dosing listing as per recommendation from the minutes of item 6.13 of this meeting as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
PEMBROLIZUMAB Injection	NEW (Public) NEW (Private)	400 mg	3	Merck Sharp & Dohme (Australia) Pty Ltd
<b>Available brands</b>				
Keytruda (pembrolizumab 100 mg/4 mL injection, 4 mL vial)				

<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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic
<p><b>Administrative Advice:</b>            No increase in the maximum amount or number of units may be authorised.            No increase in the maximum number of repeats may be authorised.            Special Pricing Arrangements apply.            Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.</p>
<p><b>Indication:</b> Resected Stage IIIB, IIIC or IIID malignant melanoma  <b>Treatment Phase:</b> Initial treatment – 6 weekly treatment regimen  <b>Clinical criteria:</b></p> <ul style="list-style-type: none"> <li>▪ The treatment must be adjuvant to complete surgical resection <b>AND</b></li> <li>▪ Patient must have a WHO performance status of 1 or less <b>AND</b></li> <li>▪ The treatment must be the sole PBS-subsidised therapy for this condition <b>AND</b></li> <li>▪ Patient must not have received prior PBS-subsidised treatment for this condition <b>AND</b></li> <li>▪ The treatment must commence within 12 weeks of complete resection <b>AND</b></li> <li>▪ Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy</li> </ul>
<p><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.</p>

<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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic
<p><b>Administrative Advice:</b>            No increase in the maximum amount or number of units may be authorised.            No increase in the maximum number of repeats may be authorised.            Special Pricing Arrangements apply.            Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.</p>
<p><b>Indication:</b> Resected Stage IIIB, IIIC or IIID malignant melanoma  <b>Treatment Phase:</b> Continuing treatment – 6 weekly treatment regimen  <b>Clinical criteria:</b>            Patient must have previously been issued with an authority prescription for this drug for adjuvant treatment following complete surgical resection  <b>AND</b>            Patient must not have experienced disease recurrence</p>

*Public Summary Document – March 2020 PBAC meeting*

<p><b>AND</b> The treatment must be the sole PBS-subsidised therapy for this condition</p> <p><b>AND</b> Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy</p>
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<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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Emergency/Electronic
<p><b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.</p>
<b>Indication:</b> Resected Stage IIIB, IIIC or IIID malignant melanoma
<b>Treatment Phase:</b> Grandfather treatment – 6 weekly treatment regimen
<b>Clinical criteria:</b>
<ul style="list-style-type: none"> <li>▪ Patient must have previously received non-PBS-subsidised drug for adjuvant treatment following complete surgical resection prior to 1 Month 20XX</li> </ul>
<b>AND</b>
<ul style="list-style-type: none"> <li>▪ Patient must have a WHO performance status of 1 or less prior to starting non-PBS treatment with this drug</li> </ul>
<b>AND</b>
<ul style="list-style-type: none"> <li>▪ Patient must not have evidence of recurrence</li> </ul>
<b>AND</b>
<ul style="list-style-type: none"> <li>▪ The treatment must be the sole PBS-subsidised therapy for this condition</li> </ul>
<b>AND</b>
<ul style="list-style-type: none"> <li>▪ Patient must not have received prior PBS-subsidised treatment for this condition</li> </ul>
<b>AND</b>
<ul style="list-style-type: none"> <li>▪ Patient must have commenced non-PBS-subsidised treatment within 12 weeks of complete surgical resection</li> </ul>
<b>AND</b>
<ul style="list-style-type: none"> <li>▪ Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy</li> </ul>
<p><b>Prescribing Instructions:</b> A Grandfathered 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>Administrative Advice:</b> This grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria.

5.3 For flow-on changes to pembrolizumab restrictions in unresectable Stage III or Stage IV disease, see restrictions in the minutes of item 6.03 of this meeting.

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

## **6 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the

circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **7 Sponsor's Comment**

MSD is pleased with the positive recommendation by the PBAC for this indication, and is working with the Department to achieve a listing on the PBS as soon as possible.