

**Addendum to the August 2017 Minutes:**

**13 PEMBROLIZUMAB,  
Powder for I.V. infusion, 50 mg and 100 mg vials,  
Keytruda<sup>®</sup>, Merck, Sharp & Dohme (Australia) Pty Limited**

**1 Purpose of application**

- 1.1 To inform the PBAC of a revised proposal from the sponsor on the basis of the cost-minimisation of pembrolizumab to brentuximab vedotin (BV), following a deferral based partially on this matter from the PBAC at its July 2017 meeting.

**2 Background**

- 2.1 At its July 2017 meeting, the PBAC deferred making a recommendation on whether pembrolizumab should be listed on the PBS for the treatment of relapsed or refractory classical Hodgkin's Lymphoma (rrcHL) pending a positive TGA Delegate's overview, and further discussion with the sponsor on determining the basis of cost-minimisation against BV. In deciding to defer, the PBAC had considered that pembrolizumab treatment showed promising overall response rates in a heavily pre-treated, refractory patient population, and that the clinical claim of non-inferiority compared with BV was supported by the evidence provided.
- 2.2 A revised proposal was received from the sponsor in response to the July 2017 PBAC minutes, addressing the issues raised in the minutes about the restriction, the basis for cost-minimisation, utilisation estimates and the proposed Risk Sharing Arrangement (RSA). *See Section 3 for details of the sponsor's proposal.*
- 2.3 A positive TGA delegate's overview and the ratified resolution of the TGA's Advisory Committee on Medicines (ACM) meeting was available to the Committee prior to the August 2017 Special PBAC meeting.
- 2.4 The clinical evidence was unchanged from the July 2017 submission.

*For more detail on PBAC's view, see section 5 "PBAC outcome".*

**3 Current proposal**

**Restriction**

- 3.1 The sponsor agreed with the PBAC's advice to remove the separation according to autologous stem cell transplant (ASCT) status in the proposed PBS restrictions,

resulting in a single initial and a single continuation restriction. The sponsor also agreed to the removal of the reference to CD30+ and multi-agent chemotherapy in the requested restriction.

#### Cost-minimisation

- 3.2 The sponsor accepted the PBAC's suggestion that the cost-minimisation analysis be based on estimated mean modelled durations of therapies of [REDACTED] cycles for BV and pembrolizumab, respectively, and on estimated mean number of vials per administration of 3.14 and 4 (of 50 mg each) for BV and pembrolizumab, respectively. Based on these estimates, the sponsor stated that the ex-manufacturer's price for pembrolizumab would therefore be \$ [REDACTED] per 50 mg vial.
- 3.3 The sponsor acknowledged that the above price estimate was based on the published price of BV, and that the final price of pembrolizumab would have to be determined using the effective price of BV, under the above dose and duration estimates.

#### Estimated PBS usage and financial implications

- 3.4 The sponsor's proposal assumed a [REDACTED]% share of the third-line market for pembrolizumab, and claimed that listing of pembrolizumab in the third-line setting would be cost neutral to the Commonwealth.
- 3.5 The sponsor also acknowledged that it was difficult to estimate the financial impact with the use of pembrolizumab and BV in the fourth-line setting. Therefore, in order to calculate the number of patients who were alive and progressed to the fourth-line setting to receive treatment with either pembrolizumab or BV depending on their previous therapy, the difference between the extrapolated OS and PFS rates in each year for patients treated with pembrolizumab or BV was calculated separately and applied to the third-line treatment population in the sponsor's proposal. In addition, a higher treatment uptake rate of [REDACTED]% was assumed for pembrolizumab in these estimates, claiming that this was consistent with the uptake rate observed for targeted therapies and immunotherapies in other cancer indications in the current clinical setting.
- 3.6 Based on the above assumptions, the sponsor claimed that the net cost to the PBS for the usage of pembrolizumab in the fourth-line setting would be less than \$10 million in the first year of listing, with a total of \$30 - \$60 million in the first six years of listing.

**Table 1: Estimated PBS usage and financial implications in the fourth-line of treatment**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients with rrCHL treated in 4L therapy	■	■	■	■	■	■
Pembrolizumab	\$■	\$■	\$■	\$■	\$■	\$■
Brentuximab vedotin	\$■	\$■	\$■	\$■	\$■	\$■
Estimated cost to the PBS and RPBS	\$■	\$■	\$■	\$■	\$■ I	\$■

Source: sponsor's proposal prior to the August 2017 PBAC Special meeting

### Risk Sharing Arrangement

- 3.7 The sponsor proposed a ■% rebate of costs above the agreed annual subsidisation caps for use beyond the agreed utilisation estimates, noting that:
- a ■% rebate above expenditure caps was consistent with the other RSAs that are currently in place between the sponsor and the Commonwealth;
  - given the unmet clinical need and small patient population as seen with the recent PBS listing of vorinostat for the treatment of cutaneous T-cell lymphoma (CTCL), the sponsor claimed that it was unlikely that the agreed subsidisation cap would be exceeded, and if it does, the financial impact would be minimal;
  - the sponsor considered that this would compensate for the sponsor's additional administration costs in having an RSA.

*For more detail on PBAC's view, see section 5 "PBAC outcome".*

## **4 PBAC outcome**

- 4.1 The PBAC recommended the Authority Required listing of pembrolizumab for the treatment of rrCHL, on a cost-minimisation basis against BV.
- 4.2 In making this recommendation, the PBAC considered that pembrolizumab treatment showed promising overall response rates in a heavily pre-treated, refractory patient population, and that the clinical claim of non-inferiority compared with BV was supported by the evidence provided.
- 4.3 The PBAC noted the sponsor's agreement to its previous advice on the proposed restriction criteria (paragraph 7.3, pembrolizumab minutes, July 2017 PBAC meeting). The PBAC also advised that the maximum number of repeats for the initial prescription should be increased from 5 to 6, while the maximum number of repeats for each continuing therapy prescription should be decreased from 7 to 6, so that the total corresponds to the maximum number of cycles (35) allowed overall.

- 4.4 The PBAC noted that estimates presented in the July 2017 submission included [REDACTED] grandfather patients. The PBAC recommend a grandfather arrangement be added to the listing of pembrolizumab for rrcHL. The PBAC noted that a grandfather provision would provide equity of access for a small number of patients who meet the PBS criteria but are receiving non-PBS subsidised treatment with a PD-1 inhibitor via another source (such as self-funding). Further, any patients not identified by the submission as grandfathered patients, would be captured as part of the estimated eligible population.
- 4.5 The PBAC noted the sponsor's agreement to its previous advice on the appropriate basis of cost-minimisation against BV, based on estimated mean modelled durations of therapies of [REDACTED] cycles for BV and pembrolizumab, respectively, and on estimated mean number of vials per administration of 3.14 and 4 (of 50 mg each) for BV and pembrolizumab, respectively. Additionally, the PBAC advised the price of the 100 mg pembrolizumab vials should be estimated on the same principles.
- 4.6 The PBAC considered that the sponsor's estimates of a [REDACTED] market share, in favour of pembrolizumab, in the fourth line of therapy, was reasonable.
- 4.7 Noting its previous views on the uncertainty in the financial estimates due to displacement of BV, the PBAC maintained that a RSA would be required to mitigate the risks associated with the additional utilisation of pembrolizumab (paragraph 7.11, pembrolizumab minutes, July 2017 PBAC meeting). The PBAC considered that given the uncertainty around the potential for sequential use of BV and pembrolizumab, a sizeable rebate on costs above the agreed annual subsidisation caps should be put in place to manage the risk of use beyond the agreed utilisation estimates.
- 4.8 The PBAC advised that the Early Supply Rule should apply not to the listing of pembrolizumab.
- 4.9 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* that pembrolizumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 4.10 The PBAC advised that pembrolizumab is not suitable for prescribing by nurse practitioners.
- 4.11 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

**Outcome:**

Recommended

## 5 Recommended listing

### 5.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed price for maximum amount (DPMA)	Proprietary Name and Manufacturer
PEMBROLIZUMAB 50 mg vial for infusion, 1 100 mg vial for infusion, 1	200 mg	6	To be confirmed	Keytruda® Merck Sharp and Dohme Pty Ltd

<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>	Relapsed or refractory
<b>Condition:</b>	Hodgkin lymphoma
<b>PBS Indication:</b>	Relapsed or refractory Hodgkin lymphoma
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must have undergone an autologous stem cell transplant (ASCT) for this condition OR Patient must not be suitable for ASCT for this condition; AND Patient must have relapsed Hodgkin lymphoma following at least two prior treatments for this condition; OR Patient must have refractory Hodgkin lymphoma following at least two prior treatments for this condition; AND Patient must not have received prior treatment with a PD-1 inhibitor for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition
<b>Prescriber Instructions</b>	Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; (b) a completed Hodgkin lymphoma pembrolizumab PBS Authority Application; and (c) a signed patient acknowledgement form.

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<b>Administrative Advice</b>	<p>No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing arrangements apply.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</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>Severity:</b>	Relapsed or Refractory
<b>Condition:</b>	Hodgkin lymphoma
<b>PBS Indication:</b>	Relapsed or Refractory Hodgkin lymphoma
<b>Treatment phase:</b>	Initial treatment – Grandfather patients
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Clinical criteria:</b>	<p>Patient must have received non-PBS-subsidised treatment with a programmed cell death 1 (PD-1) inhibitor for this condition prior to 1 May 2018 AND Patient must have undergone an autologous stem cell transplant (ASCT) for this condition and have experienced relapsed or refractory disease post ASCT prior to receiving treatment with a PD-1 inhibitor for this condition; OR Patient must have not been suitable for ASCT for this condition and have experienced relapsed or refractory disease following at least 2 prior treatments for this condition prior to receiving treatment with a PD-1 inhibitor for this condition AND Patient must not have developed disease progression while receiving treatment with a PD-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 35 cycles in a lifetime.</p>

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<b>Prescriber Instructions</b>	<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> <p>Applications for authorisation of initial treatment must be in writing and must include:                  (a) a completed authority prescription form;                  (b) a completed Hodgkin lymphoma pembrolizumab PBS Authority Application for Grandfathered patients.</p>
<b>Administrative Advice</b>	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a>.</p> <p>Applications for authority to prescribe should be forwarded to:                  Department of Human Services                  Complex Drugs                  Reply Paid 9826                  HOBART TAS 7001</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed price for maximum amount (DPMA)	Proprietary Name and Manufacturer
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<b>Severity:</b>	Relapsed or refractory			
<b>Condition:</b>	Hodgkin lymphoma			
<b>PBS Indication:</b>	Relapsed or refractory Hodgkin lymphoma			
<b>Treatment phase:</b>	Continuing treatment			
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			

<b>Clinical criteria:</b>	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.
<b>Prescriber Instructions</b>	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).  The treatment must not exceed a total of 35 cycles in a lifetime.
<b>Administrative Advice</b>	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised Special Pricing Arrangements apply

## 6 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.

## 7 Sponsor's Comment

The sponsor had no comment.