

7.9 BRENTUXIMAB VEDOTIN, injection, 50 mg, Adcetris[®], Takeda Pharmaceuticals Australia Pty Ltd

1 Purpose of Application

- 1.1 To propose a re-specified economic model following the March 2014 PBAC recommendation to list brentuximab vedotin for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) who are suitable for further systemic curative-intent salvage therapy.

2 Requested listing

- 2.1 The requested listing is the same as that requested in the March 2014 major submission. Separate restrictions were sought for initial and continuing treatment.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BRENTUXIMAB VEDOTIN Injection 50 mg	200 mg	3	Adcetris [®] TK

SECTION 100 (EFFICIENT FUNDING OF CHEMOTHERAPY) AUTHORITY REQUIRED (+/- STREAMLINED)

PRIVATE HOSPITAL/PUBLIC HOSPITAL

TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA (sALCL) WHO ARE SUITABLE FOR FURTHER SYSTEMIC CURATIVE INTENT SALVAGE THERAPY

NOTE:

PATIENTS SHOULD NOT BE CONTINUED IF THEY ARE IN A PROGRESSIVE DISEASE STATE AFTER THE FIRST ASSESSMENT OF RESPONSE.

- 2.2 At its meeting in March 2014, the PBAC considered that there “was considerable risk of use of brentuximab vedotin outside the requested restriction, with leakage into Hodgkin Lymphoma and first-line treatment of sALCL. To address this risk, the PBAC considered that a written Authority would be appropriate for brentuximab vedotin, to be administered by the Department of Human Services in Tasmania. The written Authority should include, amongst other things, appropriate histology results and details of prior therapy.” (Ratified Minutes March 2014)
- 2.3 The restriction will need to be finalised in consultation with the sponsor, the Department of Human Services and the Restrictions Working Group.
- 2.4 Listing was requested on the basis of a cost-utility analysis versus multi-agent salvage chemotherapy.

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

3 Background

- 3.1 Brentuximab vedotin was TGA registered on 20 December 2013 for the following indications:
- Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):
 1. following autologous stem cell transplant (ASCT); or
 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
 - Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).
- 3.2 This is the PBAC's second consideration of brentuximab vedotin for this condition.
- 3.3 The March 2014 PBAC meeting recommended listing brentuximab vedotin as a Section 100 (Efficient Funding of Chemotherapy Program) Authority required benefit for the treatment of adult patients with relapsed or refractory sALCL who are suitable for further systemic curative intent salvage therapy.
- 3.4 At this meeting, the PBAC noted a number of issues with the economic model and re-specified the base case to provide a more realistic estimate of the cost effectiveness of brentuximab vedotin. The respecified base case resulted in an ICER in the range of \$75,000/QALY to \$105,000/QALY. The PBAC considered that brentuximab vedotin would be cost-effective at a reduced price that produced an ICER, derived from the respecified base case, in a narrower range of \$45,000/QALY to \$75,000/QALY.
- 3.5 The re-submission proposed a lower price and a revised estimate of the post-progression disease management costs used in the economic evaluation.

4 Clinical place for the proposed therapy

- 4.1 The proposed place in therapy for brentuximab vedotin is unchanged from the previous submission - as a first-line salvage agent for first time relapsing patients with sALCL, although initial usage is also expected to be later in the treatment algorithm amongst sALCL patients in second- or later-line salvage therapy. The proposed first-line salvage therapy patient population will not have received a prior stem cell transplant.

5 Comparator

- 5.1 The comparator, multi-agent salvage chemotherapy, is unchanged from the March 2014 submission.

6 Consideration of the evidence

Sponsor hearing

- 6.1 As a minor submission, there was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from two organisations, the Private Cancer Physicians of Australia and the Medical Oncology Group of Australia. The comments outlined that treatment with brentuximab vedotin meets an unmet need in the small number of patients with relapsed sALCL. The PBAC noted that this advice was supportive of the evidence provided in the submission.

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

Clinical trials

- 6.3 No new clinical trials were presented in the re-submission.

Comparative effectiveness

- 6.4 No new information on comparative effectiveness was presented in the re-submission.

Comparative harms

- 6.5 No new information on comparative harms was presented in the re-submission.

Clinical claim

- 6.6 No new information was presented.

Economic analysis

- 6.7 The re-submission presented a cost-utility analysis that resulted in an incremental cost per quality adjusted life year (QALY) in the range of \$45,000/QALY to \$75,000/QALY. This was based on the March 2014 PBAC's respecified base case with the exception that revised post-progression disease management costs were proposed.
- 6.8 The re-submission used the same source to estimate the post-progression disease management costs as was used previously (*Lee et al, 2008*¹), but used a different method to calculate this parameter. However, the method used in the re-submission may not have applied the patient numbers and treatment duration from *Lee et al 2008* appropriately. Therefore, the evaluation provided an alternative approach, based on the same costing study, which considered palliative care, second- and third-line treatment costs from patients who had progressed after first-line salvage therapy.
- 6.9 The pre-PBAC response argued that the post-progression disease management costs calculated in the evaluation were inappropriate because they were based on the overall first-line salvage population in the costing study, rather than the relevant population (that is, patients who experienced a second progression). However, the weightings applied in the evaluation were limited to patients that received palliative care, or second- or third-line salvage treatment. That is, patients in the 'cure/surveillance/end of treatment' group were not included in the weighting analysis used in the evaluation because these costs were already included in the economic model, as part of the costs associated with progression-free patients.

¹ Lee R, Zou D, Demetrick D et al. Costs Associated with Diffuse Large B-Cell Lymphoma Patient Treatment in a Canadian Integrated Cancer Care Centre. *Value in Health*. 2008. 11(2), 221-230.

- 6.10 The pre-PBAC response proposed an alternative method of calculating post-progression disease management costs. This method, which was also based on *Lee et al 2008*, used distinct pathways of patient follow-up after first-line salvage. These pathways were:
- Second-line salvage therapy then surveillance;
 - Second-line salvage then palliative care;
 - Second-line salvage then third-line salvage; and
 - Second-line palliative care.
- The pre-PBAC response applied weightings separately on the costs as well as on the length of follow-up for each of these four pathways. The PBAC considered that this resulted in 'double weighting', and therefore over-adjustment of costs.
- 6.11 The PBAC concluded that using a single all-inclusive weighting across each follow-up group would be more appropriate given that each treatment pathway is associated with a unique cost and duration of follow-up. The PBAC noted that this resulted in revised post-progression disease management costs of around \$2,300 per 21-day cycle. The PBAC concluded that this cost was the most reasonable interpretation of *Lee et al 2008* and thus should be used in the revised base case for the economic evaluation.
- 6.12 The PBAC noted that this revised base case resulted in an ICER of around \$45,000/QALY to \$75,000/QALY. The PBAC considered that this was the most realistic estimate of the cost-effectiveness of brentuximab vedotin in the indication requested. The PBAC therefore considered that at the price proposed in the submission, brentuximab vedotin was not acceptably cost-effective. The PBAC considered that a price reduction would be required to give an ICER with in the range of \$45,000/QALY to \$75,000/QALY in the respecified base case.
- 6.13 The study used to derive the post-progression disease management costs was undertaken in Canada in patients with diffuse large B-cell lymphoma. The pre-PBAC response argued that this source may not be applicable to the intended patient population for brentuximab vedotin and may overestimate costs, due to differences in disease characteristics, patient demographics and resource costs. For example, the pre-PBAC response cited that ICE (ifosfamide, carboplatin, etoposide) is less expensive in Australia, however this calculation omitted the costs for G-CSF.

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

Drug cost/patient/course; [REDACTED]

- 6.14 The cost per course of brentuximab vedotin, at the price requested by the sponsor, is [REDACTED]. This is based on an average treatment duration of 6.95 cycles (20.9 weeks); Patients are treated once every 3 weeks.

Estimated PBS usage & financial implications

- 6.15 The utilisation estimates in the pre-PBAC response were largely based on the patient numbers accepted by the March 2014 PBAC, which included an uptake of 90% in all years, a 50% increase in the number of patients in years one and two to account for pent up demand, and incorporation of G-CSF costs (Para 6.32, March 2014 Minutes).
- 6.16 The Pre-PBAC response proposed a different distribution of brentuximab vedotin cycles over the five years. One of the reasons for this was because some patients in the 'pent up' demand pool may not be treated in the first year or two of listing of

brentuximab vedotin, but rather in later years. The PBAC did not consider that this assumption was reasonable given the high clinical need for this drug.

- 6.17 The Pre-PBAC response proposed a Risk Share Arrangement (RSA) with a series of tiered caps, using sequential discounts for excess vials above set caps, up to a final cap. It also proposed that if the final cap were to be exceeded and data showed that 90% or more of patients met the PBS eligibility criteria, the sponsor would ask the PBAC to reconsider its recommendation that the price of brentuximab vedotin revert to the price of chemotherapy (ICE).
- 6.18 The PBAC considered, among other matters, that its assessment that the cost-effectiveness of brentuximab vedotin would be acceptable if the measures below were implemented to contain risks associated with the cost of the drug to the PBS:
- A RSA between the sponsor and the Government.
 - The PBAC reiterated its recommendation from March 2014, that the RSA should include a hard cap based on the estimate of extent of use outlined in the March 2014 minutes, with the price of brentuximab vedotin to revert to the price of chemotherapy (ICE) should the cap be exceeded. The PBAC reiterated that such a RSA was required to manage total cost and non-cost-effective use, and would address the risk arising from uncertainty in the incremental clinical benefit. The PBAC considered that neither a tiered cap nor reconsideration on the basis of 90% of patients meeting the PBS eligibility criteria would appropriately manage the risks outlined.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of brentuximab vedotin for the treatment of relapsed or refractory systemic anaplastic large cell lymphoma in patients who are suitable for further systemic curative intent salvage therapy on the basis that it should be available only under special arrangements under the Section 100 Efficient

Funding of Chemotherapy (EFC). The PBAC considered that a written Authority, administered by the Department of Human Services in Tasmania would be appropriate for brentuximab vedotin, to prevent leakage into first-line use and treatment of Hodgkin Lymphoma. The PBAC recommended that the circumstances under which brentuximab vedotin should be made available on the Section 100 EFC should be finalised by the Department in consultation with the sponsor, the Restrictions Working Group and the Department of Human Services.

- 7.2 The PBAC reiterated its advice from March 2014 that the Authority application should include the following information:
- A histology report including evidence of the tumour's CD30 positivity from a biopsy subsequent to the most recently delivered prior treatment with radiation, chemotherapy, biologics, immunotherapy or other agents;
 - The date of initial diagnosis of anaplastic large cell lymphoma;
 - Dates of commencement and completion of front-line curative intent chemotherapy;
 - A declaration of whether the patient's disease is relapsed or refractory, and the date and means by which the patient's disease was assessed as being relapsed or refractory;
 - A declaration of whether the patient has had, or is planned to have, a transplant.
- 7.3 The PBAC considered that the restriction for brentuximab vedotin should include the following aspects:
- separate restrictions for initial and continuing treatment, as requested by the sponsor;
 - patients should be assessed for response after 4 cycles of brentuximab vedotin;
 - continuing therapy after 4 cycles may be authorised, by phone authority, for patients who are not in a progressive disease state;
 - the maximum number of PBS-subsidised cycles of brentuximab vedotin should be 16 per patient, comprised of a maximum of 3 repeats in initial treatment and 11 repeats in continuing treatment.
- 7.4 The PBAC re-iterated that there is a high clinical need for treatments for sALCL, and welcomed the input received from organisations in support of the submission for brentuximab vedotin. The comments included descriptions of the high unmet in the small number of patients with relapsed sALCL.
- 7.5 As previously, the PBAC was satisfied that brentuximab vedotin provides, for some patients, a significant improvement in efficacy over multi-agent salvage chemotherapy.
- 7.6 The PBAC noted that the key matter in the re-submission was the revised post-progression disease management costs. Although a number of methods for deriving post-progression costs were presented in the submission, the evaluation and the pre-PBAC response, they were all based on *Lee et al 2008*. The PBAC considered that the most appropriate way to derive costs from *Lee et al 2008* was through the use of a single all-inclusive weighting across each treatment pathway. This resulted in post-progression disease management costs of around \$2,300 per 21-day cycle.
- 7.7 *Lee et al 2008* was a micro-costing study undertaken in Canada in patients with diffuse large B-cell lymphoma. Therefore, the PBAC considered that any further revision to the post-progression disease management costs (beyond the value accepted in the paragraph above) would need to be justified through a costing study

in a relevant group of patients in Australia or by use of a robust method of weighting costs. Evaluation of these data would require a major re-submission.

- 7.8 Advice to the Minister under subsection 101(3BA) of the *National Health Act 1953*
 In accordance with subsection 101(3BA) of the *National Health Act 1953*, the PBAC advised that it is of the opinion that, on the basis of the material available to it at its July 2014 meeting, brentuximab vedotin should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).
- 7.9 The PBAC advised that brentuximab vedotin is not suitable for inclusion in the list of medicines for prescribing by nurse practitioners, noting that chemotherapy agents are currently considered out of scope for prescribing by nurse practitioners.
- 7.10 The Safety Net 20 Day Rule should not apply.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration form	Max. Amt	No. of Rpts
--	-------------	----------------

BRENTUXIMAB VEDOTIN

Injection	200 mg	3
-----------	--------	---

Available brands:

Adcetris

(brentuximab vedotin 50mg injection, 1 x 50mg vial)

Category /Program	Chemotherapy items for Public/Private Hospital Use
Condition:	CD30 positive systemic anaplastic large cell lymphoma
Indication	CD30 positive systemic anaplastic large cell lymphoma
Treatment phase:	Initial treatment
Restriction:	Authority required (Public/Private Hospital) – WRITTEN ONLY
Clinical criteria:	The treatment must be for curative intent AND The patient must have undergone appropriate prior front-line curative intent chemotherapy AND The patient must demonstrate relapsed or chemotherapy-refractory disease

<p>Prescriber Instructions</p>	<p>Applications for authorisation of initial treatment must be in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Systemic anaplastic large cell lymphoma Brentuximab PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes the following:</p> <p>(i) a histology report including evidence of the tumour’s CD30 positivity from a biopsy subsequent to the most recently delivered prior treatment with radiation, chemotherapy, biologics, immunotherapy or other agents; ;</p> <p>(ii) The date of initial diagnosis of systemic anaplastic large cell lymphoma;</p> <p>(iii) Dates of commencement and completion of front-line curative intent chemotherapy ;</p> <p>(iv) a declaration of whether the patient’s disease is relapsed or refractory, and the date and means by which the patient’s disease was assessed as being relapsed or refractory;</p> <p>(v) a declaration of whether the patient has had, or is planned to have, a transplant</p> <p>A maximum quantity and number of repeats to provide for an initial course of brentuximab vedotin of 4 cycles will be authorised as part of the initiating restriction.</p>
<p>Administrative advice</p>	<p><u>NOTE:</u> 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 www.humanservices.gov.au</p> <p>Written 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> <p><u>NOTE:</u> No increase in the maximum number of repeats may be authorised.</p> <p><u>NOTE:</u> No increase in the maximum quantity or number of units may be authorised.</p> <p><u>NOTE:</u> Special pricing arrangements apply.</p>

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts
BRENTUXIMAB VEDOTIN		
Injection	200 mg	11

Available brands:

Adcetris

(brentuximab vedotin 50mg injection, 1 x 50mg vial)

Category/Program	Chemotherapy items for Public/Private Hospital Use
Condition:	CD30 positive Systemic anaplastic large cell lymphoma
Indication	CD30 positive systemic anaplastic large cell lymphoma
Treatment phase:	Continuing treatment
Restriction:	Authority required (Public/Private Hospital) – telephone
Clinical criteria:	Patient must not have progressive disease AND Patient must have previously been issued with an authority prescription for this drug.
Prescriber Instructions	The treatment must not exceed a lifetime total of 16 cycles.
Administrative advice	<u>NOTE:</u> No increase in the maximum number of repeats may be authorised. <u>NOTE:</u> No increase in the maximum quantity or number of units may be authorised. <u>NOTE:</u> Special pricing arrangements apply.

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 thanks the PBAC for their positive recommendation for the listing of brentuximab vedotin on the PBS for the treatment of patients with sALCL, which is an orphan indication.