

7.06 BRENTUXIMAB VEDOTIN

Powder for I.V infusion 50 mg,

Adcetris[®],

Takeda Pharmaceuticals Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor resubmission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of refractory or relapsed (RR) CD30 positive cutaneous T-cell lymphomas (CTCL). In July 2018 the PBAC did not recommend the listing of brentuximab vedotin for this indication due to major reservations regarding the naïve comparison with vorinostat, which meant that cost-effectiveness against vorinostat was unable to be assessed. The PBAC also considered that brentuximab vedotin was not cost-effective compared with methotrexate at the proposed price (Paragraph 7.1, brentuximab vedotin Public Summary Document (PSD), July 2018 PBAC). The minor resubmission provided a revised price for brentuximab vedotin along with a revised proposal for the PBS restriction and additional information to support the listing including lymphomatoid papulosis (LyP) and Sézary syndrome (SS).

2 Requested listing

- 2.1 The minor resubmission requested the following new listing for the treatment of patients with CD30 positive CTCL. Separate listings were proposed for initial and continuing treatment.
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	Nº.of Rpts	Dispensed Price for Max. Qty ¹	Proprietary Manufacturer	Name and
BRENTUXIMAB VEDOTIN 50 mg injection, 1 vial	200 mg	3	Published Public: \$21,283.83 Private: \$21,619.27 Effective Public: \$ Private: \$	Adcetris	Takeda

¹ DPMQ calculated using 'Impact-Pub' and 'Impact-EFF' worksheets from 2018-0306_Takeda_brentuximab vedotin_utilisation and cost model RR CTCL_Section 4.xlsx.

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Category / program	Section 100 – Efficient Funding of Chemotherapy
Episodicity:	Chronic
Severity:	NA
Condition:	CD30 positive cutaneous T-cell lymphoma
PBS Indication:	CD30 positive cutaneous T-cell lymphoma
Treatment phase:	Initial treatment
Restriction:	<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
Treatment criteria:	N/A
Clinical criteria:	<p>Patient must have confirmed The condition must be CD30 positive disease, AND Patient must have had received prior systemic treatment for this condition, AND Patient must demonstrate relapsed or refractory disease, The condition must be relapsed or chemotherapy-refractory AND The treatment must not exceed 4 cycles Patient must not receive more than 4 cycles of treatment under this restriction, AND The treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must not have previously received PBS-subsidised treatment with vorinostat for this condition.</p>
Population criteria:	N/A
Foreword	N/A
Definitions	N/A
Prescriber Instructions	<p>The authority application must be made in writing 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 cutaneous T-cell lymphoma (CTCL) brentuximab vedotin PBS Authority Application Supporting Information Form which includes the following:</p> <p>(i) Evidence of CD30 positivity, either from a histology report on the tumour sample or from a flow cytometric analysis of the blood; <i>and</i></p> <p>(ii) Date of commencement and completion of the most recent prior systemic treatment.</p> <p>(iii) 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>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
Cautions	N/A

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty ²	Proprietary Manufacturer	Name and
BRENTUXIMAB VEDOTIN 50 mg injection, 1 vial	200 mg	11	Published Public: \$21,283.83 Private: \$21,619.27 Effective Public: \$ Private: \$	Adcetris	Takeda

Category / program	Section 100 – Efficient Funding of Chemotherapy
Episodicity:	Chronic
Severity:	NA
Condition:	CD30 positive cutaneous T-cell lymphoma
PBS Indication:	CD30 positive cutaneous T-cell lymphoma
Treatment phase:	Continuing treatment
Restriction:	<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
Treatment criteria:	N/A
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND <i>The condition must be CD30 positive,</i> AND Patient must not have develop progressive disease progression while receiving PBS-subsidised treatment with this drug for this condition, AND <i>The treatment must be the sole PBS-subsidised therapy for this condition.</i> AND <i>The treatment must not exceed Patient must not receive more than 12 cycles of treatment under this restriction.</i>
Population criteria:	N/A
Foreword	N/A
Definitions	N/A
Prescriber Instructions	The treatment must not exceed a lifetime total of 16 cycles.
Administrative Advice	<i>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.</i>
Cautions	N/A

² DPMQ calculated using 'Impact-Pub' and 'Impact-EFF' worksheets from 2018-0306_Takeda_brentuximab vedotin_utilisation and cost model RR CTCL_Section 4.xlsx.

- 2.3 The minor resubmission requested a special pricing arrangement (SPA) where the current published ex-manufacturer price of \$5,300 per vial is maintained, resulting in published dispensed prices for maximum amount of \$21,283.83 (public) and \$21,619.27 (private). The proposed effective approved ex-manufacturer price (AEMP) is \$ [REDACTED] per vial. Compared with the previous submission for the treatment of RR CD30 positive CTCL, this represented a [REDACTED] % reduction to the AEMP (the previous submission proposed an AEMP of \$ [REDACTED] per vial). The minor resubmission stated that the proposed effective AEMP is contingent on the PBS listing covering all four CTCL subtypes and acceptance of the sponsor's request for a SPA.
- 2.4 In the July 2018 consideration of brentuximab vedotin the PBAC noted that no explicit definition of CD30 positivity in CTCL was included in the proposed restriction and considered that a clear definition was desirable. The PBAC considered that the proposed restrictions should include a requirement for the provision of a histology report showing evidence of CD30 positivity (Initial) and for patients to have achieved an appropriate response to therapy (Continuing) (Paragraph 7.4, brentuximab vedotin PBAC PSD, July 2018).
- 2.5 The PBAC noted that the proposed initial restriction was consistent with that presented in the July 2018 submission with two exceptions. Firstly, reference to 'histologically' confirmed CD30 positive disease was removed from the first clinical criterion. Secondly, three information requirements included in the CTCL brentuximab vedotin PBS Authority Application Supporting Information form were detailed in the prescriber instruction section of the proposed restriction.
- 2.6 The minor resubmission stated that in some patients with blood involvement in Mycosis fungoides (MF) or SS, atypical T-cells - Sézary cells – may circulate in the peripheral blood (which affect internal organs such as the spleen and lungs) but may not always have detectable lymphomatous T cells on a routine skin biopsy (despite a rash). Hence, histological assessment alone may not render a diagnosis or clear CD30 expression. The minor resubmission noted that flow cytometry of the blood is the methodology by which CD30 expression is assessed in these patients. Therefore, the minor resubmission argued that evidence of CD30 positivity should be obtained from either a histology report of the tumour biopsy or from a flow cytometric analysis of the blood. The minor resubmission detailed this requirement in the prescriber instruction section of the proposed restriction and removed reference to 'histologically' confirmed CD30 positive disease from the clinical criteria. The PBAC considered that a diagnosis of CD30 positive disease was required, and noted that this is usually via a histology report. However, the PBAC considered that the inclusion of evidence of CD30 positivity from flow cytometric analysis, as an alternative to evidence from a histology report on a tumour sample, was appropriate for patients with SS.

2.7 A definition of CD30 positivity was not included in the revised initial treatment restriction. The minor resubmission argued that there is no requirement for an explicit definition for CD30 expression in the current Authority application for brentuximab vedotin in systemic anaplastic large cell lymphoma (sALCL). In addition, the minor resubmission suggested that the use of trastuzumab for the treatment of locally advanced HER2 positive breast cancer provided another example of an Authority Required PBS-listed oncology drug for which an explicit definition of biomarker expression was not required.³ The resubmission also argued that there were difficulties associated with developing a clear and precise definition for CD30 positivity in the RR CTCL indication, specifically:

- Heterogeneity of CD30 expression between tumour sites and within an individual tumour,
- The evidence demonstrating the treatment effect seen with brentuximab vedotin appears to be independent of a particular percentage of CD30 expression (see paragraph 4.20 and 4.21),
- The subjective nature of the immunohistochemistry (IHC) assay employed for CD30 testing in current Australian pathology practice, where the method depends on the quality of the biopsy tissue, size, necrosis, fixations, and laboratory processes, all of which can introduce variability in the test, and
- Non-standardised reporting of CD30 positivity among pathologists.

In addition, the minor resubmission proposed that the setting of an arbitrary cut-off may lead to inequity of access for some patients. The pre-PBAC response argued that the terminology in the PBS restriction should be 'any CD30 positivity'.

2.8 The PBAC noted the arguments put forward in the minor resubmission and the pre-PBAC response against the inclusion of an explicit definition for CD30 positivity. However, the PBAC noted that a large proportion of patients with CTCL do not express CD30. In addition, the PBAC noted that the evidence for cost-effectiveness of brentuximab vedotin was based on the ALCANZA trial, which only recruited patients whose biopsy had 10% or more target cells with CD30 staining. The PBAC acknowledged that on review, evidence of activity was seen at levels below 10%, and that the disease is heterogeneous, meaning that repeat biopsies may be required. On balance, the PBAC considered it necessary to specify a cut-off, but to make it less stringent than the ALCANZA trial entry criteria given the data provided in both the July 2018 submission and in the minor resubmission.

³ Locally advanced HER2 positive breast cancer Authority Form pb094-1807en-f.pdf states that for a patient to qualify for PBS authority approval, a "Pathology report from an Approved Pathology Authority confirming the presence of HER2 gene amplification by in situ hybridisation (ISH)" must be provided. Source: <https://www.humanservices.gov.au/organisations/health-professionals/forms/pb094>

- 2.9 The proposed continuing restriction remained unchanged from that presented in the July 2018 submission and hence did not include a requirement for patients to have achieved an appropriate response to therapy. In addition to recommending the inclusion of a requirement regarding response to therapy, at the July 2018 meeting the PBAC considered that further advice was required on how response assessment can be pragmatically included as part of a restriction that is amenable to use in clinical practice (Paragraph 2.4, brentuximab vedotin PBAC PSD, July 2018).
- 2.10 The minor resubmission noted that Global Response Score (GRS) was used in the ALCANZA and MAVORIC randomised controlled trials (RCTs) based on the 2011 consensus guidelines on response definitions in MF and SS (Olsen et al, 2011). The minor resubmission stated that expert clinical advice provided by two haematologists and one dermatologist indicated that assessment of response per the methodology used in the Phase III trials in a PBS restriction was not appropriate. The minor resubmission argued that use of the GRS would impose a burden in routine clinical practice as a result of additional costs to the healthcare system, administrative and resource commitments. The minor resubmission argued that the clinical criterion in the proposed restriction stating ‘Patient must not have progressive disease...’ is consistent with the continuing criteria for vorinostat in RR CTCL and with the other PBS listings for brentuximab vedotin.
- 2.11 The PBAC noted the information and opinions provided around the need for, and the details of, response assessment. The PBAC considered that continuing use of brentuximab vedotin would not be cost-effective in the absence of an objective response given the economic evaluation presented the results as a cost per responder and the potential toxicity with continuing treatment. Nevertheless, the PBAC did note concerns related to the complexity of re-staging and agreed that a pragmatic approach to ensuring that continuing treatment only occurs in responders would be appropriate given that the treating clinicians will have expertise in assessing skin response.
- 2.12 In the July 2018 consideration of brentuximab vedotin the PBAC considered that there was a substantial risk of use of brentuximab vedotin outside the restriction. This included use as a first line systemic therapy, retreatment of patients and in combination treatment with other CTCL therapies (Paragraph 6.59, brentuximab vedotin PBAC PSD, July 2018). The minor resubmission proposed the DHS Authority Form require information about the most recent prior systemic treatment received by the patient to address concerns regarding use as a first line therapy. The PBAC considered the inclusion of this information requirement, detailed in the prescriber instruction section of the restriction, was appropriate. The PBAC also considered the addition of the clinical criterion ‘The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition’ was appropriate to address concerns regarding use in combination treatment with other CTCL therapies.

- 2.13 The PBAC advised that inclusion of the criterion “Patient must not have previously received PBS-subsidised treatment with vorinostat for this condition” in the proposed restriction was not appropriate as treatment with brentuximab vedotin would likely displace rather than replace vorinostat.
- 2.14 The vorinostat restriction states that the patient must demonstrate ‘chemotherapy-refractory disease’, whereas the proposed restriction states the patient must demonstrate ‘refractory disease’. The PBAC considered it was not appropriate to specify that the condition must be refractory to chemotherapy in the proposed brentuximab vedotin restriction.

For more detail on PBAC’s view, see section 5 PBAC outcome.

3 Background

- 3.1 CTCLs are a group of non-Hodgkin lymphomas (NHLs) in which malignant T-cell clones accumulate in the skin. The symptoms and prognosis of CTCL are highly varied and depend on the subtype and stage of disease. CTCL may cause skin lesions, tumours, pruritus and erythroderma and may affect the blood and visceral organs. Patients with advanced disease may have extensive skin disease that is disfiguring.
- 3.2 MF is the most common form of CTCL. It results in plaques and patches on the skin, in addition to lesions and tumours in the more advanced stages. Patients diagnosed with advanced stage disease (stages IIB, III and IVA) or visceral involvement (other organs affected, stage IVB) have median overall survivals (OS) of five years and 2.5 years, respectively. SS is a leukemic form of CTCL that affects the blood and causes erythroderma. It has a poor prognosis with a median OS of five years.
- 3.3 Primary cutaneous anaplastic large cell lymphoma (pcALCL) is an indolent lymphoma that causes raised red skin lesions, nodules or tumours. Ten-year survival with pcALCL is approximately 77% (Liu (2003)). LyP is a benign, chronic skin condition that causes skin lesions that can self-resolve. It does not affect life expectancy (Liu (2003)). LyP is not consistently considered to be a cancer.
- 3.4 Early stage CTCL is managed using skin-directed therapies. This includes topical corticosteroids, phototherapy and total skin electron beam therapy. Systemic therapy is used by patients who do not respond to, or are refractory to, initial skin-directed therapies. Systemic therapies include low dose methotrexate, interferon-alpha, retinoids, histone deacetylase inhibitors, chemotherapy and extracorporeal photopheresis, where available. Radiotherapy is also used for pcALCL. For LyP, methotrexate may be used chronically or episodically (Newland (2015)). The approach to treatment is based on CTCL subtype, disease severity and prior treatments. Previously used therapies may be re-used for subsequent lines of therapy.
- 3.5 On 23 May 2018 the TGA approved registration of brentuximab vedotin for the treatment of adult patients with CD30 positive CTCL after at least 1 prior systemic

therapy. Brentuximab vedotin also has TGA registered indications for:

- Treatment of adult patients with RR CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
- Treatment of adult patients with CD30+ HL at higher risk of relapse or progression following ASCT; and
- Treatment of adult patients with RR systemic sALCL.

- 3.6 Brentuximab vedotin was previously considered by the PBAC in July 2018 for use in the treatment of RR CD30 positive CTCL. The intervention in this setting was brentuximab vedotin administered at the recommended dosage of 1.8 mg/kg (maximum 180 mg) via intravenous (IV) infusion every three weeks. Each three-weekly brentuximab vedotin dose constitutes a treatment cycle. Initial treatment consists of four cycles of brentuximab vedotin (four doses). Patients without disease progression may receive a further 12 cycles of treatment for a total of 16 cycles. Vorinostat was nominated as the primary comparator with low-dose methotrexate nominated as a supplementary comparator.
- 3.7 The July 2018 submission proposed that brentuximab vedotin would be used after first-line systemic therapy and will displace current treatment options, such as vorinostat.
- 3.8 The PBAC did not recommend the listing of brentuximab vedotin in RR CD30 positive CTCL in patients who have previously used systemic therapy, due to major reservations regarding the naïve comparison with vorinostat, which meant that cost-effectiveness against vorinostat was unable to be assessed. The PBAC also considered that brentuximab vedotin was not cost-effective compared with methotrexate at the proposed price. The PBAC noted that the ICER presented was unacceptably high based on previous PBAC decisions, even in the context of difficult to treat and relatively rare diseases (Paragraph 7.1, brentuximab vedotin PBAC PSD, July 2018).
- 3.9 The PBAC acknowledged the rarity of CTCL and the difficulty of conducting phase III trials in the heterogeneous subgroups of CTCL but considered that the naïve comparison of brentuximab vedotin and vorinostat did not provide good evidence for the cost-effectiveness of brentuximab vedotin compared with vorinostat. The PBAC noted that the comparison with methotrexate was based on more robust data but based on this comparison brentuximab vedotin had an unacceptably high ICER. Nevertheless, in this uncommon and incurable disease where there is a high unmet need and significant impacts on patient quality of life, the PBAC considered that brentuximab vedotin appears effective for some time in patients with proven CD30 positive disease and more effective than methotrexate in patients with MF. As such, and consistent with the approach taken with vorinostat, the PBAC considered a cost per responder assessment of cost-effectiveness may be appropriate in any future

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submission. The PBAC noted that a considerable price reduction would be required in order to show that brentuximab vedotin is cost-effective compared with methotrexate (Paragraph 7.18, brentuximab vedotin PBAC PSD, July 2018).

Key changes versus the previous submission

3.10 The minor resubmission stated that no further clinical trial data for brentuximab vedotin are forthcoming for this indication. Therefore, the minor resubmission submitted a cost effectiveness analysis versus methotrexate based on a cost per responder (ORR) with a revised price for brentuximab vedotin.

3.11 The key changes are outlined in the table below.

Table 1: Summary of the previous submission and current resubmission

	July 2018 submission	Current resubmission
Requested PBS listing	PBAC Comment: (paragraph 7.4) The PBAC noted that no explicit definition of CD30 positivity in CTCL was included in the proposed restriction and considered that a clear definition was desirable. The PBAC considered that the proposed restrictions should include a requirement for the provision of a histology report showing evidence of CD30 positivity (Initial) and for patients to have achieved an appropriate response to therapy (Continuing).	The resubmission provided proposed restrictions that remained largely unchanged from those considered in July 2018.
Requested effective DPMQs	DPMQ: Effective Private \$ [REDACTED] Public \$ [REDACTED] Published Private \$21,427.47 Public \$ 21,283.83 The submission requested a SPA where the current published approved ex-manufacturer price (AEMP) of \$5,300 per vial is maintained. The proposed effective AEMP is \$ [REDACTED] per vial. The pre-PBAC response proposed a reduced AEMP of \$ [REDACTED] per vial.	The resubmission proposed a revised AEMP of \$ [REDACTED] per vial. This represents a [REDACTED]% price reduction on the AEMP proposed in the July 2018 submission. The resubmission stated that the offer is contingent on: - The PBS listing covering all four CTCL subtypes, namely, MF, SS, pcALCL and LyP subtypes; and - Granting of the sponsors request for a SPA.
Comparator	Vorinostat (primary comparator). PBAC comment: (paragraph 7.5) The PBAC agreed with the ESC that this was appropriate for the MF and SS subtypes of CTCL only as patients with pcALCL and LyP were not included in the vorinostat trial. The PBAC considered that it was unclear whether vorinostat is used to treat pcALCL and LyP in Australian clinical practice although the vorinostat PBS listing also allows use in these subtypes. The PBAC also considered that the use of vorinostat as a comparator in this submission was limited by the fact that, unlike brentuximab vedotin, its use was not restricted to CD30 positive CTCL. Methotrexate (supplementary comparator). PBAC comment: (paragraph 7.6) The PBAC considered that the best comparative evidence available in this submission was for patients treated with methotrexate, which the PBAC accepted as one of the standard therapies in Australia for this rare condition.	Unchanged.

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	July 2018 submission	Current resubmission
Clinical evidence	<p>The submission's primary comparison was a naïve comparison of the brentuximab vedotin arm of the Phase III, open-label ALCANZA randomised controlled trial (n=131) with the vorinostat arm of the Phase III, open-label MAVORIC RCT (n=372).</p> <p>PBAC comment: (paragraph 7.7) The PBAC considered the comparison was flawed with the major transitivity issues being the different mix of disease subtypes/stages and the difference in CD30 positive selection between the two trials. The PBAC considered that due to differences in CD30 positivity between patients included in the trials the efficacy of vorinostat in a CD30 positive subset of CTCL patients was unknown. The PBAC considered that because of these differences this comparison could not currently be accepted as the basis for decision-making regarding the cost-effectiveness of brentuximab vedotin.</p> <p>The submission's supplementary comparison with methotrexate compared the brentuximab vedotin arm of the ALCANZA trial with the methotrexate subgroup (n=26) of the physician's choice arm of the trial.</p> <p>PBAC comment: (paragraph 7.9) The PBAC noted that the ALCANZA trial included patients with MF and pcALCL only, with the majority of patients having MF.</p>	<p>The trial results for the primary and supplementary comparisons remain unchanged.</p> <p>The minor resubmission provided updated data from the CSRs for the Duvic (2015) and Kim (2015) to support the use of brentuximab vedotin in SS and LyP. In addition, data from the ALCANZA trial on ORR and PFS outcomes by CD30 expression and from the Duvic (2015) and Kim (2015) trials on ORR by CD30 expression were provided as evidence of the correlation between CD30 expression and response.</p>
Clinical claim	<p>In patients with relapsed or refractory CD30+CTCL, brentuximab vedotin is more effective than vorinostat or methotrexate at improving clinical response (higher objective response rate) and has a longer PFS.</p> <p>PBAC comment: (paragraph 7.8) The PBAC considered that the claim of superior comparative effectiveness to vorinostat was not adequately supported by the data. (paragraph 7.11) The PBAC considered that the claim of superior comparative effectiveness to methotrexate was reasonable for the MF and pcALCL subtypes only and was not adequately supported by the data in LyP and SS subtypes.</p> <p>Brentuximab vedotin has a different, non-inferior safety profile to both vorinostat and methotrexate that is considered tolerable and manageable.</p> <p>PBAC comment: (paragraph 7.8) The PBAC considered that the claim of non-inferior comparative safety to vorinostat was reasonable. (paragraph 7.12) The PBAC considered that the claim of non-inferior comparative safety to methotrexate was not adequately supported by the data.</p>	Unchanged.
Economic evaluation	<p>The submission presented several modelled economic evaluations of brentuximab vedotin based on the cost per responder (ORR), cost per $\geq 25\%$ mSWAT responder, and a cost utility analysis based on PFS.</p> <p>PBAC comment: (paragraph 7.18) The PBAC noted that the comparison with methotrexate was based on more robust data but based on this comparison brentuximab vedotin had an unacceptably high ICER. (paragraph 7.18) As such, and consistent with the approach taken with vorinostat, the PBAC considered a cost per responder assessment of cost-</p>	<p>The resubmission provided revised cost per responder and cost per PFS LYG for brentuximab vedotin versus methotrexate based on a revised AEMP of \$ [REDACTED] per vial.</p>

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	July 2018 submission	Current resubmission
	effectiveness may be appropriate in any future submission. The PBAC noted that a considerable price reduction would be required in order to show that brentuximab vedotin is cost-effective compared with methotrexate.	
Number of patients	The submission estimated that less than 10,000 patients would be treated in Year 1, decreasing to less than 10,000 in Year 6.	Unchanged.
Estimated net cost to PBS	The submission estimated the overall net cost to government was less than \$10 million in Year 1, decreasing to less than \$10 million in Year 6, resulting in a net cost of \$10 – \$20 million for the Australian Government health budget over the first six years of listing.	Based on the revised AEMP of \$ [redacted] per vial, the resubmission estimated the overall net cost to government was less than \$10 million in Year 1, decreasing to less than \$10 million in Year 6.
Risk sharing arrangement (RSA)	RSA proposed.	The resubmission provided additional detail in regard to the proposed RSA.

Source: Compiled during the evaluation. Paragraph references for July 2018 refer to the brentuximab vedotin PSD.

For more detail on PBAC’s view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

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

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

4.3 The July 2018 submission’s primary comparison was a naïve comparison of the brentuximab vedotin arm of the Phase III, open-label ALCANZA RCT (n=131) with the vorinostat arm of the Phase III, open-label MAVORIC RCT (n=372). The submission also presented two single-arm studies of brentuximab vedotin: Duvic (2015) (N=48) and Kim (2015) (N=32); and two single-arm studies of vorinostat: P001 (n=74) and P005 (n=33).

4.4 The July 2018 submission’s supplementary comparison with methotrexate was based on one head-to-head randomised trial (ALCANZA) that compared brentuximab vedotin with methotrexate or bexarotene (physician’s choice) (N = 131). The submission compared the brentuximab vedotin arm of the study with the methotrexate subgroup of the physician’s choice arm (n = 26). An additional single-arm, retrospective, Australian study (Newland 2015) of methotrexate in the CTCL subtype LyP was included during the evaluation.

4.5 In July 2018 the PBAC noted that the ALCANZA trial included patients with MF and pcALCL only, with the majority of patients having MF. The PBAC noted the Newland

(2015) study provided information on the use of methotrexate in patients with LyP but considered it was of limited relevance to the submission overall given the indolent nature of LyP, the common watch and wait approach used in its management, and the ability to use other therapies such as topical steroids or oral retinoids in this condition. The PBAC considered that overall, data on methotrexate was suboptimal in robustness. However, the PBAC noted that the ALCANZA trial did provide data on the efficacy of methotrexate, although underpowered, in a CD30 positive subset of CTCL (Paragraph 7.9, brentuximab vedotin PBAC PSD, July 2018).

- 4.6 The minor resubmission provided updated data from the CSRs for the Duvic (2015) and Kim (2015) Phase II studies to support the use of brentuximab vedotin in SS and LyP. In addition, the minor resubmission provided data from the ALCANZA trial on ORR and PFS outcomes by CD30 expression and from the Duvic (2015) and Kim (2015) trials on ORR by CD30 expression as evidence of the correlation between CD30 expression and response. As a minor resubmission the additional data provided were not evaluated.

Comparative effectiveness

- 4.7 The key effectiveness outcomes were response, either objective response rate (ORR) or $\geq 25\%$ improvement in mSWAT, and PFS.
- 4.8 The trial results for the primary and supplementary comparisons remain unchanged from the previous major submission considered in July 2018 (See Table 1).
- 4.9 The results for the brentuximab vedotin versus methotrexate comparison and for ORR by CTCL subtype are provided below. This is followed by information on CD30 expression and response.

Brentuximab vedotin vs. methotrexate

- 4.10 Table 2 presents the response outcomes from the ALCANZA trial that compared

brentuximab vedotin with physician’s choice of methotrexate or bexarotene.

Table 2: Results of response outcomes from the ALCANZA trial (brentuximab vedotin vs. methotrexate)

Outcome and assessor	BV	PC (BEX or MTX)	Risk difference BV vs PC (95% CI)	MTX	BEX
ORR4 (primary outcome)					
IRF	36/64 (56%)	8/64 (13%)	44% (29, 58)	2/26 (8%)	6/38 (16%)
Investigator	38/64 (60%)	5/64 (8%)	52% (35, 66)	2/26 (8%)	3/38 (8%)
ORR (CR + PR)					
IRF	43/64 (67%)	13/64 (20%)	47% (32, 62)	1/26 (4%)	1/38 (3%)
Investigator	44/64 (69%)	14/64 (22%)	47% (32, 62)	1/26 (4%)	1/38 (3%)
PR					
IRF	33/64 (52%)	12/64 (19%)	NR	1/26 (4%)	1/38 (3%)
Investigator	32/64 (50%)	14/64 (22%)	NR	1/26 (4%)	1/38 (3%)
CR					
IRF	10/64 (16%)	1/64 (2%)	14% (-4, 32)	1/26 (4%)	0/38 (0%)
Investigator	12/64 (19%)	0/64 (0%)	19% (1, 36)	1/26 (4%)	1/38 (3%)
≥ 25% mSWAT reduction					
Investigator	1/64 (2%)	0/64 (0%)	NR	0/26 (0%)	0/38 (0%)

Source: Table 6 brentuximab vedotin PBAC minutes, July 2018.

BEX = bexarotene; BV = Brentuximab vedotin; CI = confidence interval; CR = complete response; IRF = independent review facility; MTX = methotrexate; NR = not reported; ORR = objective response rate; ORR4 = objective global response lasting 4 months; PC = Physician’s Choice; PR = partial response; **Bold** = statistically significant

4.11 Table 3 presents the PFS outcomes from the ALCANZA trial.

Table 3: Results of PFS from the ALCANZA trial

Comparison	Brentuximab vedotin		Comparator		Difference in median	P value (log rank test)	Hazard ratio (95% CI)
	Events	Median PFS	Events	Median PFS			
Brentuximab vedotin vs. physician’s choice (methotrexate or bexarotene)							
IRF	36/64 (56%)	16.7 months (14.9, 22.8)	50/64 (78%)	3.5 months (2.4, 4.6)	13.2 months	< 0.001 ^a	0.27 (0.17, 0.43)
Investigator	40/64 (63%)	15.7 months (11.7, 17.2)	51/64 (80%)	3.6 months (2.5, 4.5)	12.1 months	< 0.001 ^a	0.32 (0.21, 0.50)
Brentuximab vedotin vs. methotrexate							
IRF	36/64 (56%)	16.7 months (14.9, 22.8)	22/26 (85%)	2.3 months (1.2, 3.5)	14.4 months	NR	0.17 (0.09, 0.31)
Investigator	40/64 (63%)	15.7 months (11.7, 17.2)	1/26 (4%)	1.2 months (0.5, 2.1)	1.2 months	NR	NR

Source: Table 7 brentuximab vedotin PBAC PSD, July 2018

BEX = bexarotene; BV = Brentuximab vedotin; CI = confidence interval; IRF = independent review facility; MTX = methotrexate; NR = not reported; PC = Physician’s Choice; PFS = progression-free survival;

^a Log rank test stratified by baseline disease diagnosis (MF or pcALCL)

4.12 In July 2018 the PBAC noted that the results of the ALCANZA trial indicated that patients in the brentuximab vedotin arm had higher ORR, ORR4 and complete response than patients in the methotrexate arm. The PBAC also noted that patients treated with brentuximab vedotin had a median PFS of 16.7 months, which was significantly longer than the median 2.3 months PFS experienced by patients treated with methotrexate. Acknowledging the limitations of the data, the PBAC considered that brentuximab vedotin appears to be effective over an extended duration in

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patients with proven CD30 positive CTCL and more effective than methotrexate in patients with MF (Paragraph 7.10, brentuximab vedotin PBAC PSD, July 2018).

Outcomes by CTCL subtype

4.13 The minor resubmission provided updated ORR data by CTCL subtype from the CSRs of the Duvic (2015) and Kim (2015) Phase II studies. Table 4 presents ORR outcomes by CTCL subtype with the updated data provided in the minor resubmission shaded.

Table 4: Results of ORR across the studies by CTCL subtype

CTCL subtype and study	Brentuximab vedotin	Vorinostat	Methotrexate
MF			
ALCANZA	31/48 (65%)	-	█ (█%)
Duvic (2015)	15/28 (54%)	-	-
Duvic (2017)	22/41 (54%)		
Kim (2015)	17/22 (77%)	-	-
Kim (2017)	21/32 (66%)		
MAVORIC	-	7/99 (7%)	-
P001	-	12/44 (27%)	-
P005	-	4/22 (18%)	
pcALCL			
ALCANZA	12/16 (75%)	-	█ (█%)
Duvic (2015)	2/2 (100%)	-	-
Duvic (2017)	2/3 (67%)		
SS			
Duvic (2017)	1/2 (50%)		
Kim (2015)	2/3 (67%)	-	-
Kim (2017)	2/4 (50%)		
MAVORIC	-	2/87 (2%)	-
P001	-	10/30 (33%)	-
P005	-	4/11 (36%)	-
LyP			
Duvic (2015) LyP only	9/9 (100%)	-	-
Duvic (2015) LyP + MF or pcALCL	8/8 (100%)	-	-
Duvic (2017)	12/13 (92%)		
Newland (2015) LyP	-	-	22/25 (88%)

Source: Table 8 brentuximab vedotin PBAC PSD, July 2018, Table 7 p17 minor resubmission (Shaded rows)

CTCL = cutaneous T-cell lymphoma; LyP = lymphomatoid papulosis; MF = mycosis fungoides; ORR = objective response; pcALCL = primary cutaneous anaplastic large cell lymphoma; SS = Sézary syndrome

4.14 In July 2018 the PBAC noted that the evidence base to support the comparative effectiveness of brentuximab vedotin over vorinostat and methotrexate in patients with SS was very limited because the data were based on three patients (Paragraph 6.22, brentuximab vedotin PBAC PSD, July 2018). The minor resubmission provided

ORR data on an additional 3 patients with SS (Table 4) and stated the ORR was 50% (3 of 6 patients), with an averaged PFS of 7.7 months⁴.

- 4.15 In terms of patients with SS, the minor resubmission also noted that the inclusion criteria for the Phase III ALCANZA study did allow patients with blood involvement⁵. The minor resubmission stated that as the brentuximab vedotin arm of the ALCANZA trial included nine MF patients (19%) with Stage IVA₂ and Stage IVB disease it is possible these patients may have had sézary cells in their blood. The minor resubmission stated that regardless of stage, patients achieved a better response with brentuximab vedotin (Prince 2017). The minor resubmission also noted that one Australian patient with SS had received brentuximab vedotin via the sponsors subsidised access program.
- 4.16 The minor resubmission proposed that the evidence from the updated CSR for the Duvic (2015) study supported the use of brentuximab vedotin in LyP (Table 4). An ORR was achieved in 12/13 (92%) of patients with the minor resubmission stating the median PFS was 11.7 months. The minor resubmission also noted that data from the Australian Cutaneous Lymphoma Network (ACLN) database indicated that ■ of ■ Australian patients with a confirmed CD30 positive LyP diagnosis received treatment with various systemic therapies.
- 4.17 The pre-PBAC response reiterated the difficulties in conducting a clinical trial program which will comprehensively cover all the subtypes in this rare cancer (CTCL represents approximately 2% of all cancers). The pre-PBAC response also noted that the number of patients with these specific subtypes is very small, with the expected total of SS and LyP patients being approximately ■ in Year 1, and declining to ■ patients in Year 6.
- 4.18 The PBAC noted the arguments that patients with CD30 positive SS, a poor prognosis cancer, appeared to benefit from treatment with brentuximab vedotin to a similar degree as those with MF. The PBAC considered that given the poor prognosis of SS, the very low patient numbers and the evidence of potential benefit provided it may be appropriate to allow PBS subsidy of brentuximab vedotin for patients with this CTCL subtype.
- 4.19 The PBAC also noted the arguments that some patients with LyP appear to benefit from treatment with brentuximab vedotin. However, the PBAC recalled that the LyP subtype is not consistently defined as a cancer, can resolve without treatment and does not affect life-expectancy. The PBAC considered that as the majority of patients

⁴ Duvic (2017) = The 1 SS patient with a response had an estimated PFS of 5.5 months. Kim (2017) = 2 SS patients with a response had an estimated PFS of 7.8 months and 9.7 months respectively.

⁵ MF patients in ALCANZA were allowed to have circulating SS cells in their blood of up to 1000 Sezary cells/mm³.

with LyP do not require this type of therapy it is appropriate to exclude this CTCL subtype from PBS subsidised access to brentuximab vedotin.

CD30 expression and response

- 4.20 An inclusion criterion of the ALCANZA trial was a positive CD30 expression on biopsy, with patients being scored CD30 positive if one or more biopsies had $\geq 10\%$ CD30 positive lymphoid cells. The minor resubmission stated that in an analysis of outcomes per CD30 expression published by Kim (2017)⁶ the MF ALCANZA patients could be further grouped into: CD30 min<10% (defined as patients with ≥ 1 biopsy with < 10% CD30 positive); and CD30 max>10% (defined as patients with ≥ 1 biopsy with > 10% CD30 positive). These data are shown in Table 5. The minor resubmission stated that these findings indicate that clinical response (ORR4) and PFS are demonstrated in MF patients regardless of CD30 min expression.

Table 5: ALCANZA trial - ORR and PFS by CD30 expression in MF patients who received brentuximab vedotin

BV arm (ALCANZA)	ORR4, n/N(%)	Median PFS (months) [95% CI]
CD30 min <10%	9/22 (40.9)	27.9 [8.6, 27.9]
CD30 min $\geq 10\%$	16/28 (57.1)	17.2 [9.8, NE]

Source: Table 3 p8 minor resubmission

- 4.21 The minor resubmission proposed that the evidence from Duvic (2015) and Kim (2015) presented in Table 6 supported these findings. The Secretariat noted that in Kim (2015) the CD30 high group (>10%) is divided into 10-50% and > 50% expression with ORR, n/N(%) reported as 11/14 (79%) and 3/3 (100%) respectively. The commentary on the July 2018 submission stated the results of Kim (2015) appeared to show higher ORR with higher levels of CD30 positivity.

Table 6: ORR by CD30 expression in MF/SS patients who received BV - supplementary evidence from Phase II trials

MF/SS	Duvic et al (2015)	Kim et al (2015)
ORR, n/N (%)		
CD30 low (<10%)	5/10 (50%)	7/13 (54%)
CD30 high (>10%)	10/18 (56%)	14/18 (78%)

Source: Table 4 p9 minor resubmission

Economic analysis

- 4.22 The July 2018 submission presented several modelled economic evaluations of brentuximab vedotin based on the cost per responder (ORR), cost per $\geq 25\%$ mSWAT responder, and a cost utility analysis based on PFS.
- 4.23 In July 2018 the PBAC noted that the economic evaluations were based on a clinical comparison with vorinostat that was unreliable due to differences between the trial

⁶ Kim et al (2017) "Outcomes by CD30 expression in patients with CTCL receiving brentuximab vedotin (BV) vs physician's choice (PC) in the Phase 3 ALCANZA study." J. Clin. Oncol. Abstract 7517
http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.7517

populations. The comparison with methotrexate was considered more reliable as it was based on the results of a RCT; however the comparison with methotrexate was not applicable to patients with the SS or LyP subtypes. In addition the PBAC considered that the economic evaluations did not fully capture the benefits and harms of brentuximab vedotin and the comparators, specifically:

- The cost per responder analyses did not capture the length of response which may be relevant to patients;
- The cost-utility analyses were based on PFS; in CTCL, patients can be progression-free and not have a skin response to treatment; and
- There were no costs or disutilities associated with the AEs due to brentuximab vedotin and vorinostat treatment (Paragraph 7.14, brentuximab vedotin PBAC PSD, July 2018).

4.24 For the comparison of brentuximab vedotin with methotrexate, the July 2018 submission presented an incremental cost per responder (ORR) of \$105,000 – \$200,000 and an ICER of more than \$200,000/QALY. The PBAC considered that the ICER presented was unacceptably high based on previous PBAC decisions, even in the context of difficult to treat and relatively rare diseases. The PBAC noted that in the pre-PBAC response the sponsor offered a reduced price of \$ [REDACTED] per vial. The PBAC considered that the revised ICER with the reduced price remained very high and uncertain (Paragraph 7.15, brentuximab vedotin PBAC PSD, July 2018).

4.25 The minor resubmission provided a cost-effectiveness analysis versus methotrexate based on cost per responder (ORR) using a revised price of \$ [REDACTED] per vial for brentuximab vedotin for the indication of RR CTCL (Table 7). The revised ICER for cost per responder (ORR) was \$45,000 - \$75,000 and for cost per additional year without progression was \$15,000 - \$45,000. The PBAC considered that the revised ICER for cost per responder (ORR) was acceptable based on previous PBAC decisions in the context of difficult to treat and relatively rare diseases.

Table 7: Cost-effectiveness analysis of brentuximab vedotin versus methotrexate based on cost per responder (ORR) and cost per PFS LYG

	BV effective price / vial	Cost per responder (ORR-based CEA)	Cost per additional year without progression
July 2018 Submission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
July 2018 Pre-PBAC response	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
November 2018 minor resubmission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

BV = brentuximab vedotin; MTX = methotrexate; ICER = incremental cost effectiveness ratio; PFS = Progression Free Survival; LYG = Life Year Gained; ORR = Overall Response Rate; CEA = Cost Effectiveness Analysis
Source: Table A1, p23 of the minor resubmission

Estimated PBS usage & financial implications

4.26 The minor resubmission updated the financial estimates to include the revised price of \$ [REDACTED] per vial for brentuximab vedotin in the indication of RR CTCL. The PBAC

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noted that the estimated number of patients with RR CTCL being treated with brentuximab vedotin remained unchanged from the July 2018 submission.

- 4.27 The minor resubmission estimated a net cost to the PBS of less than \$10 million in Year 6 of listing, with a total net cost to the PBS of \$10 - \$20 million over the first 6 years of listing. This is summarised in the table below as well as the expected patient/prescription numbers.

Table 8: Estimated use and financial implications

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Estimated extent of use						
Eligible population						
Number of patients treated						
Total scripts dispensed ^a						
Cost to PBS/RPBS ^b	\$	\$	\$	\$	\$	\$
Copayments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Previous submission (July 2018) – estimated financial implications						
Cost to PBS/RPBS						
Copayments						
Cost to PBS/RPBS less copayments						
Net financial implications						
Net cost to MBS ^b						
Net cost to MBS (85% fee)						
Net cost to PBS/RPBS/MBS						
Net cost to PBS/RPBS/MBS (corrected MBS costs)						

Source: Table 14 brentuximab vedotin PBAC PSD, July 2018, Table A4 p24 minor resubmission

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

^a 10.3 prescriptions per patient per course.

^b The DPMA is calculated to be \$ / vial across the public and private settings. The weighted price is based on current utilisation of brentuximab vedotin in the two RR HL indications: 42% in the public setting and 58% in the private.

^c Brentuximab vedotin estimated to require 10 additional IV infusions, 5 additional specialist consultations, and 10 additional blood tests (full blood count and biochemistry).

The redacted table shows that at Year 6 the estimated number of patients would be substantially less than 10,000 per year.

- 4.28 In the July 2018 consideration of brentuximab vedotin the PBAC considered that the overall the estimated budget impact was relatively low, due to the small number of patients eligible for treatment. However, the PBAC considered the estimates to be uncertain as there was a substantial risk of use of brentuximab vedotin outside the restriction particularly for use as a first line therapy (Paragraph 7.16, brentuximab vedotin PBAC PSD, July 2018).

4.29 The PBAC noted the amendments to the proposed restriction (restricting use first line or in combination with other CTCL therapies) and considered that it was now reasonable to accept the financial estimates as the basis of a risk sharing arrangement (RSA). The PBAC considered that a RSA remained appropriate to mitigate any residual uncertainties regarding the potential use of brentuximab vedotin outside the proposed restriction.

Financial management – risk sharing arrangements

4.30 In July 2018 the PBAC considered that a RSA with a substantial rebate above an upper expenditure cap would be required to manage the risks associated with potential use outside the restriction, a decrease in the threshold to commence systemic therapy, and an unclear definition of CD30 positivity (Paragraph 7.17, brentuximab vedotin PBAC PSD, July 2018).

4.31 The PBAC noted that the minor resubmission proposed a rebate of █% for utilisation above the subsidisation cap in the RR CTCL indication. The proposed rebate would result in a price per vial of \$█. The minor resubmission stated that this is in alignment with the price per vial for use above the subsidisation cap for the two RR HL indications (Table 9).

Table 9: Summary of RSA terms for current indications & proposed rebate for use above SC in RR CTCL

Indication	Published price / vial	SPA rebate	Effective price per vial	SC 1 rebate	SC 2 rebate	Above SC 1 price	Above SC 2 price
RR sALCL	\$5,300	█	█	█	█	█	█
RR HL Post ASCT		█	█	█	█	█	█
RR HL ASCT Naïve		█	█	█	█	█	█
RR CTCL		█	█	█	█	█	█

Source: Table A5, p25 of the minor resubmission

ASCT = autologous stem cell transplant, CTCL = cutaneous T-cell lymphoma, HL = Hodgkin lymphoma, RR = refractory or relapsed

For more detail on PBAC’s view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing of brentuximab vedotin for the treatment of refractory or relapsed (RR) CD30 positive cutaneous T-cell lymphomas (CTCL). The PBAC recognised the clinical need for effective treatments in this population. The PBAC was satisfied that brentuximab vedotin provides, for some patients with the mycosis fungoides (MF), Sézary syndrome (SS) and primary cutaneous anaplastic large cell lymphoma (pcALCL) subtypes of CTCL, a significant improvement in efficacy over methotrexate.

5.2 The PBAC’s recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of brentuximab vedotin would be acceptable for the MF, SS and pcALCL CTCL subtypes at the revised price

proposed in the minor resubmission.

- 5.3 The PBAC reaffirmed it considered that there is a need for additional therapies for patients with CTCL who have failed prior systemic therapies. The PBAC considered that a high unmet clinical need was particularly evident for patients with the MF, SS and pcALCL subtypes of CTCL.
- 5.4 The PBAC noted that a definition of CD30 positivity was not included in the revised initial treatment restriction. The PBAC noted the arguments put forward in the minor resubmission and the pre-PBAC response against the inclusion of an explicit definition for CD30 positivity. However, the PBAC noted that a large proportion of patients with CTCL do not express CD30. In addition, the PBAC noted that the evidence for cost-effectiveness of brentuximab vedotin was based on the ALCANZA trial, which only recruited patients whose biopsy had 10% or more target cells with CD30 staining. The PBAC acknowledged evidence of activity was seen at levels below 10%, and that the disease is heterogeneous, meaning that repeat biopsies may be required. On balance, the PBAC considered it necessary to specify a cut-off, but to make it less stringent than the ALCANZA trial entry criteria given the data provided in both the July 2018 submission and in the minor resubmission. The PBAC recalled that the Pre-Sub-Committee Response (PSCR) for the July 2018 submission stated that a response to brentuximab vedotin in the ALCANZA trial was seen across a range of baseline CD30 expression from 3% to 100%, for all biopsy samples of each patient. The PBAC therefore advised that the proposed restriction should include a requirement for CD30 positivity of at least 3% of malignant cells.
- 5.5 The minor submission requested that flow cytometric analysis of the blood be included in the proposed restriction as a methodology to assess CD30 expression. The PBAC considered that a definitive diagnosis of CD30 positive disease was required, usually via a histology report. However, the PBAC considered that the inclusion of evidence of CD30 positivity from flow cytometric analysis, as an alternative to evidence from a histology report on a tumour sample, was appropriate for patients with SS.
- 5.6 The PBAC noted that the proposed continuing restriction did not include a requirement for patients to have achieved an appropriate response to therapy. The PBAC noted the information and opinions provided around the need for, and the details of, response assessment. The PBAC considered that continuing use of brentuximab vedotin would not be cost-effective in the absence of an objective response given the economic evaluation presented the results as cost per responder and the potential toxicity with continuing treatment. Nevertheless, the PBAC did note some of the concerns related to the complexity of re-staging and agreed that a pragmatic approach to ensuring that continuing treatment only occurs in responders would be appropriate given that the treating clinicians will have expertise in assessing skin response. The PBAC recommended that documentation of a skin response or a

nodal response, in the absence of progressive disease in any compartment, be included in the continuing restriction.

- 5.7 The PBAC recalled that in its July 2018 consideration of brentuximab vedotin it had previously considered that the claim of superior comparative effectiveness to methotrexate was reasonable for the MF and pcALCL subtypes only and was not adequately supported by the data in the LyP and SS subtypes (Paragraph 7.11. brentuximab vedotin PBAC PSD, July 2018). The PBAC also recalled that it had considered that brentuximab vedotin may have an inferior safety profile compared with methotrexate (Paragraph 7.12. brentuximab vedotin PBAC PSD, July 2018).
- 5.8 The PBAC noted that the July 2018 submission and minor resubmission presented a cost-effectiveness analysis versus methotrexate based on cost per responder (ORR). Using the revised price proposed in the resubmission, the cost per responder (ORR) was \$45,000 - \$75,000 and the cost per additional year without progression was \$15,000 - \$45,000. The PBAC considered that the revised ICER for cost per responder (ORR) was acceptable based on previous PBAC decisions in the context of difficult to treat and relatively rare diseases. The PBAC noted that, as the largest CTCL subtype in the ALCANZA trial, the resulting ICER was largely based on the benefits seen in patients with MF.
- 5.9 The PBAC noted the additional data provided in the minor resubmission to support the use of brentuximab vedotin in patients with SS. The PBAC also noted the minor resubmission's argument that patients with CD30 positive SS, a poor prognosis cancer, appeared to benefit to a similar degree to those with MF. The PBAC considered that inclusion of a response assessment requirement in the proposed restriction would reduce the uncertainty associated with brentuximab being cost-effective for the treatment of patients with the SS. In these specific circumstances of poor prognosis, very low patient numbers and some evidence of a similar degree of benefit to patients with MF, the PBAC considered the listing should include patients with SS.
- 5.10 The PBAC noted the additional data provided in the minor resubmission to support the use of brentuximab vedotin in patients with LyP. The PBAC noted the minor resubmission's argument that some patients with LyP appear to benefit from treatment with brentuximab vedotin. However, the PBAC recalled that the LyP subtype is not consistently defined as a cancer, can resolve without treatment and does not affect life-expectancy. The PBAC considered that the evidence provided in the minor resubmission did not adequately address the cost-effectiveness of brentuximab for the treatment of LyP given the majority of patients with LyP do not require treatment with this type of therapy. The PBAC recommended that patients with the LyP CTCL subtype be excluded from PBS subsidised access to brentuximab vedotin.
- 5.11 The PBAC considered that amendments to the proposed restriction (restricting use first line or in combination with other CTCL therapies) reduced previous concerns that

the estimates were uncertain due to the risk of use of brentuximab vedotin outside the restriction.

- 5.12 The PBAC noted that, while it had recommended that patients with the LyP CTCL subtype be excluded from PBS subsidised access to brentuximab vedotin, LyP patient numbers were included in the proposed financial estimates. The PBAC considered that it was not possible to accurately split LyP numbers from the combined pcALCL and LyP numbers provided due to different registry requirements for reporting. However, given the overall small number of patients, the overall modest budget impact and the RSA proposed, the PBAC considered it reasonable to accept the numbers as proposed in the minor resubmission as the maximum number of PBS-eligible CD30 positive CTCL patients to be treated per annum.
- 5.13 The PBAC considered that the RSA proposed by the sponsor, with a financial cap set at the level of the estimates utilisation was appropriate to mitigate any residual uncertainties regarding the potential use of brentuximab vedotin outside the proposed restriction.
- 5.14 The PBAC advised that brentuximab vedotin was not suitable for prescribing by nurse practitioners.
- 5.15 The PBAC noted that the Early Supply Rule does not currently apply to Section 100 (Efficient Funding of Chemotherapy) listings.
- 5.16 The PBAC recommended that brentuximab vedotin should not be treated as interchangeable with any other drugs.
- 5.17 The PBAC noted that this submission is not eligible for an Independent Review as it made a positive recommendation.

Outcome:

Recommended

6 Recommended listing

- 6.1 Add new item:

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Name, Restriction, Manner of administration and form	Max. Amt.	No. of Rpts	Proprietary Name and Manufacturer	
BRENTUXIMAB VEDOTIN 50 mg injection, 1 vial	180 mg	3	Adcetris	Takeda
Category / program	Section 100 – Efficient Funding of Chemotherapy			
Condition:	CD30 positive cutaneous T-cell lymphoma			
PBS Indication:	CD30 positive cutaneous T-cell lymphoma			
Treatment phase:	Initial treatment			
Restriction:	<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			
Clinical criteria:	Patient must have pathologically confirmed CD30 positive cutaneous T cell lymphoma, AND Patient must have a diagnosis of mycosis fungoides; OR Patient must have a diagnosis of Sézary syndrome; OR Patient must have a diagnosis of primary cutaneous anaplastic large cell lymphoma; AND Patient must have received prior systemic treatment for this condition, AND The condition must be relapsed or refractory, AND The treatment must not exceed 4 cycles under this restriction, AND The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition.			
Prescriber Instructions	The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Cutaneous T-cell lymphoma (CTCL) Brentuximab vedotin PBS Authority Application Supporting Information Form which includes the following: (i) Evidence of a diagnosis of either mycosis fungoides, Sézary syndrome or primary cutaneous anaplastic large cell lymphoma; and (ii) Evidence of CD30 positivity of at least 3% of malignant cells, either from a histology report on the tumour sample or from a flow cytometric analysis of lymphoma cells the blood; and (iii) Date of commencement and completion of the most recent prior systemic treatment.			
Administrative Advice	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.			

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Name, Restriction, Manner of administration and form	Max. Amt.	No. of Rpts	Proprietary Name and Manufacturer	
BRENTUXIMAB VEDOTIN 50 mg injection, 1 vial	180 mg	11	Adcetris	Takeda
Category / program	Section 100 – Efficient Funding of Chemotherapy			
Condition:	CD30 positive cutaneous T-cell lymphoma			
PBS Indication:	CD30 positive cutaneous T-cell lymphoma			
Treatment phase:	Continuing treatment			
Restriction:	<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			
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must have achieved an objective response with this drug, AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition, AND The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition, AND The treatment must not exceed 12 cycles under this restriction.			
Prescriber Instructions	An objective response is defined as the demonstration of response by clinical observation of skin lesions, or response by positron-emission tomography (PET) and/or computed tomography (CT) standard criteria. The treatment must not exceed a lifetime total of 16 cycles.			
Administrative Advice	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.			

7 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.

8 Sponsor's Comment

Takeda Pharmaceuticals Australia welcomes the PBAC's positive recommendation for the listing of its innovative medicine brentuximab vedotin for patients with relapsed

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or refractory cutaneous T-cell lymphoma. Takeda Australia also acknowledges and thanks the clinical community and the patients / carers who contributed to this outcome via their input to the PBAC.