PUBLIC SUMMARY DOCUMENT

Product: BRENTUXIMAB VEDOTIN, 50 mg injection, 1 x 50 mg vial Adcetris®
Sponsor: Takeda Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

To seek an Efficient Funding of Chemotherapy – Section 100 listing 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. Background

This was the first consideration of brentuximab vedotin (BV) by the PBAC. There are no other medications that are specifically listed on the PBS for the treatment of relapsed or refractory sALCL.

3. Registration Status

The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluation Report, TGA Delegate's Overview, and ACPM outcome were available, and the product was included on the Australian Register of Therapeutic Goods (ARTG).

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).

4. Listing Requested and PBAC's View

Section 100 (Efficient Funding of Chemotherapy)
Public Hospital Authority Required (STREAMLINED)
Private Hospital/Private Clinic Authority Required

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.

The submission also proposed optional additional wording in order to facilitate the auditing of the requested restriction, partially based on the inclusion criteria of the pivotal study (Study 0004):

1. The patient must have undergone appropriate prior front-line curative intent chemotherapy. The prescriber must also provide details of the time to relapse after front-line treatment (or refractory status), Eastern Cooperative Oncology Group (ECOG) score, age and any other relevant patient history that indicates the patient's eligibility for further treatment, rather than palliative care. The inclusion criteria from Study 0004 required patients to have an ECOG performance status of 0 or 1.
2. Despite appropriate prior treatment, the patient must demonstrate refractory or relapsed disease by one of the following clinical-pathological assessments or imaging modalities:
    a. Histologically documented CD30 positive systemic ALCL from a biopsy subsequent to the most recently delivered prior treatment with radiation, chemotherapy, biologics, immunotherapy and/or other investigational agents.
    b. Interval tumour growth documented between two successive CT evaluations with the second evaluation occurring at least 4 weeks after delivery of any radiation, chemotherapy, biologics, immunotherapy and/or other investigational agents.
    c. Fluorodeoxyglucose (FDG)-avidity by PET in a new tumour mass on CT that is unlikely to have an alternative explanation
    d. Recurrent FDG-avidity by PET in a previously identified FDG-avid tumour mass on CT that had become negative.
    e. FDG-avid tumour mass by PET in conjunction with sALCL related symptoms (e.g. pruritus, B symptoms (fever, night sweats, or weight loss >10%), after infectious causes have been excluded.

(Diagnostic biopsies/laparotomy for the grading of lymphoma is funded through MBS item: 30075, 30078, 30384 and examination of the biopsy is funded by MBS item 72838. *Additionally, MBS items 72846, 72849 and 72850 cover immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques.* CT scans are covered through MBS items 56001 to 57356; Whole body FDG PET study for restaging following confirmation of recurrence of HL or non-Hodgkin's lymphoma is covered through MBS Item 61628)

The PBAC considered that there was considerable risk of use of BV 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 BV, 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.

The PBAC agreed with the Secretariat that a separate grandfather restriction for patients currently receiving treatment with BV was unnecessary. Since the estimated number of patients currently receiving non-PBS subsidised BV is small (estimated at approximately two or three), any requests for grandfathering of patients could be managed by DHS. Such patients would be required to meet the PBS eligibility criteria.

The restriction will need to be finalised in consultation with the sponsor, the Department of Human Services and the Restrictions Working Group.

Listing was requested on the basis of a cost-utility analysis versus multi-agent salvage chemotherapy.

The PBAC accepted that the requested maximum amount (200 mg) and number of repeats (three) were appropriate and would provide sufficient supply for four cycles of treatment, following which assessment would occur to determine therapeutic effect.

The PBAC considered that it was likely that BV would be used in later line salvage, but that the majority of use would be in first line salvage. The PBAC considered that it was appropriate for the restriction to allow use in second- and later-line salvage therapy.

5. Clinical Place for the Proposed Therapy

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma, which is made up of either malignant T-lymphocytes or null lymphocytes. The presence of the CD30 antigen on the surface of lymphoma cells is the hallmark of disease pathology. ALCL occurs in two forms: systemic ALCL and primary cutaneous ALCL. Brentuximab vedotin is a treatment for the systemic form.

sALCL is a high grade lymphoma which accounts for 2-8% of all cases of adult non-Hodgkin lymphomas. sALCL is categorised into two subtypes: ALK-positive and ALK negative. 40% to 65% of patients with systemic ALCL subsequently develop recurrent disease. The 5 year OS of ALK-positive sALCL is 70-80% versus 15%-46% for ALK negative patients (Falini 1999; Gascoyne 1999; Shiota 1995). Data from the British Columbia (BC) Cancer Registry, which formed the basis of the comparative data in the submission, indicates that median OS for all patients after first progression (entire dataset inclusive of those too frail for treatment at time of first progression; n=67) was 4 months.

The submission proposed that the place in therapy for BV is 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 (SCT).

The PBAC considered that there is potential for use of BV in second-line (or later-line) salvage therapy in the initial stages of listing of BV. Additionally, the PBAC noted that clinicaltrials.gov lists two trials currently recruiting patients that are investigating the use of BV in patients with newly diagnosed sALCL ('Brentuximab Vedotin or Crizotinib and Combination Chemotherapy in Treating Patients With Newly Diagnosed Stage II-IV Anaplastic Large Cell Lymphoma' ClinicalTrials.gov Identifier: NCT01979536; and ECHELON-2: A Comparison of Brentuximab Vedotin and CHP With Standard-of-care CHOP in the Treatment of Patients With CD30-positive Mature T-cell Lymphomas. ClinicalTrials.gov Identifier: NCT01777152). Given the potential for use of more targeted therapies and aggressive regimens at first diagnosis of sALCL, the PBAC agreed with the ESC that it is possible that the future use of BV may be earlier in the treatment algorithm at patient diagnosis.

The PBAC considered that there is a high clinical need for treatment for relapsed or refractory sALCL, noting that the prognosis is poor for patients who have relapsed following first line treatment.

6. Comparator

The submission nominated multi-agent salvage chemotherapy (ICE: ifosfamide, carboplatin, etoposide; DHAP: dexamethasone, cytarabine, cisplatin; ESHAP: etoposide, methylprednisolone, cytarabine, cisplatin) as the main comparators. The first line salvage therapies in the comparator BC lymphoid cancer registry study (platinum, etoposide, and cytarabine based regimens) were not consistent with the nominated main comparators (ICE, DHAP, and ESHAP). However, the PBAC agreed with the ESC that these therapies were unlikely to differ in efficacy or toxicity compared with the therapies currently used in Australian clinical practice. Thus, the comparators used in the submission were considered appropriate by the PBAC.

7. Clinical Trials

No direct randomised trials were identified in the literature search comparing BV to multi-agent salvage chemotherapy for sALCL. In the absence of head to head trials, the submission presented a non-randomised comparison based on:

- BV: One pivotal single arm prospective cohort study: Study 0004 (n=58)
- Multi-agent salvage chemotherapy: the sponsor commissioned an extraction of a sample of relapsed or refractory sALCL patients from the British Columbia (BC) lymphoma registry: BC lymphoid cancer registry study (n=48)

The efficacy analysis from Study 0004 was conducted in various subgroups. The non-randomised comparison was reliant on a subgroup analysis of NS0 patients from Study 0004, which are defined as patients who have received BV as first line salvage therapy without a prior history of SCT. Results from this subgroup directly informed the economic analysis. The NS0 subgroup patient characteristics correlate with the sponsor's intention that BV would be introduced as a first line salvage agent. Nevertheless, the use of BV may initially occur further down the treatment algorithm.

The inclusion/exclusion criteria governing the BC lymphoid cancer registry was dictated by the sponsor-commissioned request for patients that had progressed following primary treatment (n=22). This restricted the non-randomised comparison to the NS0 population from Study 0004.

Although the submission contended that analysis at later steps of the algorithm was not possible due to lack of available resources for data collection, estimates of OS at the second line salvage stage were calculated during the evaluation using the dataset provided by the submission. This enabled a comparison with the NS1 subgroup (patients who have received BV after one prior salvage therapy without a prior history of SCT, i.e. second-line salvage) from Study 0004.

The PBAC noted the ESC's concerns regarding the validity of the non-randomised single-arm comparison:

- There were significant differences in the baseline characteristics of the single arm study populations (ALK status, disease stage at diagnosis, extra-nodal disease, and prior front line chemotherapy regimens used). The ESC considered that, while it is difficult to estimate the direction of bias, these differences are likely to favour the comparator.
- As indicated in the Guidelines (p190), 'Data from other types of quasi-experimental non-randomised designs (e.g. 'before and after' studies, case series with historical controls, comparisons of results of two or more single arm studies), are subject to major and (often) non-quantifiable biases'.
- It is not known whether the registry data provides an accurate reflection of the natural history of patients with sALCL.

Details of the studies and associated reports presented in the submission are provided in the table below.

Trial ID	Reports
Brentuximab vedotin	
Study 0004	A Phase 2 study of SGN-35 in treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL). 29 November 2011 Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, Matous J, Ramchandren R, Fanale M, Connors JM, Yang Y, Sievers EL, Kennedy DA, Shustov A. Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma: Results of a Phase II Study. Journal of Clinical Oncology. 2012;30(18):2190-2196 Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, Matous J, Ramchandren R, Fanale M, Connors JM, Yang Y, Sievers EL, Kennedy DA, Shustov A. Long-Term Remissions Observed in an Ongoing Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma. Blood. 2012;120(21):2745 (Conference abstract)
Multi-agent salvage chemotherapy	
BC lymphoid cancer registry	Connor JM. Clinical Characteristics and Outcome for Patients with Relapsed Systemic Anaplastic Large Cell Lymphoma in British Columbia. 3 Sep 2013 (sponsor commissioned unpublished study)

The PBAC noted consumer comments from two healthcare professionals, and three organisations: Lymphoma Australia, the Haematology Society of Australia and New Zealand (HSANZ) and the Medical Oncology Group of Australia (MOGA). The consumer comments highlighted the tolerability of BV, and its high response rate in a clinical setting with few alternatives.

The PBAC noted there was no sponsor hearing for this item.

8. Results of Trials

Non-comparative results for clinical response (complete response, partial response, stable disease or progressive disease) and overall objective response rate (ORR) from Study 0004 for the per patient protocol (PPP) population and the subgroup analyses conducted by the submission were presented. These results were unpublished.

Objective response rates were generally similar across the subgroup analyses and the PPP (>80%), although the proportion of complete responders was higher in patients that had previously received SCT when compared to patients with no prior history of SCT ,with the exception of the NS1 subgroup (1 prior salvage chemotherapy), which reported a lower percentage of patients achieving a CR).

Unpublished results for overall survival (OS) and progression free survival (PFS) from Study 0004 and BC lymphoid cancer registry were also presented in the submission.

From the results of Study 0004, the NS0 subgroup (first line salvage therapy), demonstrated the most favourable OS (median survival yet to be reached, estimating greater than 85% survival at 36 months) and PFS analysis (median PFS yet to be reached, estimating greater than 60% PFS estimate at 36 months).

The (unpublished) BC lymphoid cancer registry study results for median OS and median PFS were also reported.During the evaluation, a non-randomised single arm comparison of OS was also undertaken between the NS1 subgroup in study 0004 (N=11) and second line salvage chemotherapy sALCL patients from the BC registry dataset (N=7). The difference in survival gain at 36 months was markedly less in second line salvage therapy compared to first line salvage therapy.

The PBAC noted the latest published data for Study 0004 reported an ORR of 86% (50/58) with 59% (34/58) CR for all patients. The median duration of objective response for all patients was 13.2 months (95% CI: 5.7-26.3 months) and median progression free survival (PFS) for all patients was 14.6 months. The estimated 3-year survival rate for all patients was 63% (95% CI: 51%, 76%). (*Blood*; November 15, 2013 vol. 122 no. 21 1809).

The PBAC recognised that in the context of a rare disease, obtaining clinical data for the use of BV in sALCL is difficult and that it is likely that the comparative data provided in the submission are the best available. The PBAC also noted the correspondence from the Haematology Society of Australia and New Zealand (HSANZ), which indicated that the control group was valid from a clinical perspective.

Overall, the PBAC accepted that BV represented an advance in therapy for a disease where a high clinical need exists.

A formal comparison of safety with the BC lymphoid cancer registry study was not possible due to the lack of available data. Treatment related adverse event rates were presented from study 0004 in the submission. The most common adverse events in Study 0004 were peripheral sensory neuropathy (very common), nausea (very common), fatigue (very common), diarrhoea (very common) and neutropenia (very common). Overall, over 50% of

patients experienced at least one treatment emergent event associated with peripheral neuropathy (PN) with over 15% reporting severe PN.

The post-marketing rate for febrile neutropenia associated with BV-treatment was reported in the periodic safety update report. This rate was lower than what was observed in publications reporting background febrile neutropenia rates for chemotherapy (5% to 12% incidence rate). Although this difference may point towards a benefit for BV, the magnitude of this reduced risk is unclear given that no direct comparative studies have evaluated BV versus salvage chemotherapy in relapsed/refractory sALCL.

The PBAC noted the sponsor's claims in the PSCR and pre-PBAC response in relation to harms. The PSCR (p III) stated that toxicity of combination regimens is generally increased compared to the single agents' individual toxicity profiles. And, unlike efficacy, adverse event profiles with multi-agent salvage chemotherapy regimens in one cancer indication are likely to be generalisable to sALCL. The pre-PBAC response (pp II-III) presented the following summary of grade 3 and 4 adverse event frequencies associated with BV and comparator chemotherapies:

Summary of grade 3 and 4 adverse event frequencies in brentuximab vedotin and comparator chemotherapies

	BV	ICE (42.1%)	ESHAP (26.3%)	DHAP (31.6%)	Weighted % of patients
N (patients)	58	40	32	28	
Source	Pro 2012[8]	Jerkeman 2004	Wang 1999	Abali 2008	
Peripheral Neuropathy	12%	10%	NR	NR	4.2%
Neutropenia	21%	90%	100%	14%	68.6%
Thrombocytopenia	14%	90%	100%	10%	67.4%
Anaemia	7%	NR	NR	15%	4.7%
Nausea/Vomiting	7%	5%	22%	NR	7.9%
Fatigue	5%	NR	NR	NR	0%
Infection/Febrile neutropenia	2%	12%	38%	10%‡	18.1%

The PBAC also noted the input received from health professionals via the consumer comments facility on the PBS website which cited tolerability and a favourable toxicity profile as being benefits of BV therapy.

9. Clinical Claim

The submission described BV as being associated with significant additional OS and patient relevant efficacy as well as less toxicity relative to multi-agent salvage therapy.

The PBAC accepted the submission's claim in relation to comparative efficacy as reasonable in the first line salvage therapy setting for patients that have had no prior SCT.

The PBAC noted that BV is a novel agent, for which long-term safety has yet to be adequately established. The PBAC considered that the submission's claim of less toxicity relative to multi-agent salvage chemotherapy was reasonable with respect most acute toxicity,

but that severe peripheral neuropathy was an important toxicity more likely in BV-treated patients.

10. Economic Analysis

The submission presented a cost-utility analysis that resulted in an incremental cost per quality adjusted life year (QALY) in the range of $45,000 – 75,000 (updated during the evaluation to account for costs associated with pegfilgrastim).

The PBAC noted the following issues with the economic model were raised by the ESC:

- The economic evaluation was based on the BV treatment effect on the NSO sub-group of Study 0004, in which seven patients were alive at 36 months. The ESC considered that it was not reasonable to extrapolate an unknown treatment effect in seven patients at three years over a 20 year time horizon;
- Pre-progression and post-progression costs were built into the economic model, but were not utilised for the derivation of total costs for BV or salvage chemotherapy. The PBAC noted the sponsor's pre-subcommittee response (PSCR, pIV), which argued that these costs are not directly attributable to the study drug. The ESC considered that the likelihood of progression is related to the effectiveness of BV, and thus considered these costs to be relevant.

The PBAC therefore considered a respecified base case for the modelled economic evaluation. The revised base case was based on:

- the most optimistic clinical incremental benefit (i.e., that proposed by the sponsor, which was a comparison of Study 0004 (NS0 subgroup) and the BC lymphoid cancer registry study), with all key costs included;
- acceptance of the sponsor's model of 6.95 treatment cycles;
- acceptance of the sponsor's model of a 20 year time horizon;
- inclusion of disease management costs;
- adjustments to the cost of multi-agent salvage chemotherapy to account for administration in a combination of the inpatient and outpatient settings. The PBAC considered that the submission's assumption that multi-agent salvage chemotherapy would be administered entirely on an inpatient basis was unreasonable. The PBAC noted that the eviQ guidelines indicate that only certain treatment days in the chemotherapy regimen would require patients to be admitted to hospital, but considered that these guidelines reflect the minimum number of inpatient days. Therefore, the PBAC considered that a ratio of 50% inpatient and 50% outpatient administration of chemotherapy represented the most realistic base case.

The PBAC noted that the revised base case resulted in an ICER in the range of $75,000 – 105,000/QALY. The PBAC considered that this was the most realistic estimate of the cost-effectiveness of BV in the indication requested.

Having accepted the base case outlined above, the PBAC also considered that the most informative multi-variate sensitivity analyses included the following:

- 8.2 cycles of BV, which was the average treatment duration in Study 0004;
- 10 and 30 year time horizons,
- an adjusted chemotherapy response rate, based on the results of Mak 2013, which was a database analysis of patients who were not intended to be candidates for transplantation.

This study found a response rate to standard chemotherapy in this group of patients of 26% for complete response and 29% for partial response and stable disease and was used in sensitivity analyses included in the submission;
- administration of multi-agent salvage chemotherapy entirely on an inpatient basis or in line with the eviQ guidelines.

Based on the sensitivity analyses, the PBAC considered the ICER for BV in sALCL could plausibly be in the range of $105,000 – 200,000/QALY.

The PBAC therefore considered that at the price proposed in the submission, BV was not acceptably cost-effective. The PBAC considered that BV would be cost-effective at a reduced price that produced an ICER, derived from the re-specified base case, of between $45,000 and $75,000/QALY.

11. Estimated PBS Usage and Financial Implications

The likely numbers of patients (BV patients 1st line salvage treatment) per year was revised during the evaluation and was estimated to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.
The revised estimates 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

The PBAC did not accept the submission's estimated financial implications. The PBAC considered that the evaluator's revised estimate of extent of use should form the basis of a risk-sharing arrangement to be negotiated with the sponsor. The PBAC recommended a hard cap based on the revised estimate of extent of use, with the price of BV to revert to the price of chemotherapy (ICE) should the cap be exceeded. The PBAC considered that such a risk-sharing arrangement was desirable to manage total cost and non-cost-effective use, and would address the risk arising from uncertainty in the incremental clinical benefit.

12. PBAC Outcome

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

The PBAC recommended that the Authority application should include the following information:
- A histology report including evidence of the tumour's CD30 positivity;
- The date of initial diagnosis;
- A declaration of whether the patient's disease is relapsed or refractory, and the date on 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.

The PBAC considered that there was a high clinical need for treatments for sALCL, noting that the prognosis is poor for patients who have relapsed following first line treatment. The PBAC welcomed and noted the input received via the consumer comments facility on the PBS website from health care professionals and organisations in support of the submission for BV. The comments included descriptions of the high unmet clinical need, and highlighted the chance provided by BV for patients to proceed to potentially curative transplant.

The PBAC was satisfied that BV provides, for some patients, a significant improvement in efficacy over multi-agent salvage chemotherapy.

The PBAC agreed that multi-agent salvage chemotherapy (ICE, DHAP, and ESHAP) was the appropriate comparator.

The PBAC considered that the non-randomised, single-arm comparison of Study 0004 and the BC lymphoid cancer registry, presented in the submission, represented the best case scenario for treatment with BV. The PBAC recognised that it was unlikely that better data would be available given the rare nature of sALCL.

The PBAC accepted that BV represented an advance in therapy for a disease where a high clinical need exists. The PBAC accepted the submission's claim that BV is associated with significant additional OS and patient relevant efficacy in the first line salvage therapy setting for patients that have had no prior SCT. The PBAC considered that the submission's claim of less toxicity relative to multi-agent salvage chemotherapy was reasonable with respect most acute toxicity, but that severe peripheral neuropathy was an important toxicity more likely in BV treated patients.

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 March 2014 meeting, brentuximab vedotin should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

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.

Outcome:
Recommended

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
BRENTUXIMAB VEDOTIN 50 mg injection, 1 x 50 mg vial	200 mg	3	Adcetris	TK

Episodicity:	Relapsed or refractory

Condition:	systemic anaplastic large cell lymphoma
Restriction:	Section 100 (Efficient Funding of Chemotherapy) Public Hospital Authority Required Private Hospital/Private Clinic Authority Required Restriction to be finalised

13. 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.

14. Sponsor's Comment

The sponsor welcomes the positive recommendation, and we look forward to working with Department of Health and the PBAC to agree on a respecified base case cost-utility model to ensure sALCL patients will gain access to brentuximab vedotin therapy.