7.03 BRENTUXIMAB VEDOTIN, Powder for I.V. infusion 50 mg, Adcetris®, Takeda Pharmaceuticals Australia Pty Ltd.

1 Purpose of Application

1.1 The resubmission requested Section 100 – Efficient Funding of Chemotherapy – listing for brentuximab vedotin for the treatment of patients with relapsed or refractory CD30+ Hodgkin lymphoma following autologous stem cell transplant (ASCT).

2 Proposed listing

2.1 The PSCR (p1) argued that a biopsy (to obtain tissue for $CD30^+$ testing) is an invasive procedure, and having to repeat this (per the Secretariat's suggestion: "A histology report including evidence of the tumour's CD30 positivity subsequent to the most recently delivered prior therapy") may be not be in the patients' best interest. Furthermore, $CD30^+$ status does not change over the course of the disease. The ESC agreed, and advised that this criterion be removed from the restriction.

2.2 The ESC considered that the continuation treatment should also have a written Authority restriction, given the requirement of providing several declarations at the time of request.

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. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
BRENTUXIMAB VEDOTIN 50 mg vial for IV infusion, 1	200 mg	3	$[redacted] (Published) $[redacted] (Effective)	Adcetris® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐ Optometrists ☐Midwives
Severity:	*Relapsed or Refractory*
Condition:	*Hodgkin lymphoma*
PBS Indication:	*Relapsed or Refractory Hodgkin lymphoma*
Treatment phase:	Initial treatment

Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Clinical criteria:	*Patient must have undergone a primary autologous stem cell transplant (ASCT)* *AND* *Patient must have experienced a relapsed CD30+ Hodgkin lymphoma post ASCT; OR* *Patient must have experienced a refractory CD30+ Hodgkin lymphoma post ASCT* *AND* *Patient must not receive more than 4 cycles of treatment under this restriction* ~~The patient must have undergone appropriate prior front-line curative intent chemotherapy and at least one prior line of curative intent salvage therapy including a first autologous stem cell transplant (ASCT)~~ ~~AND~~ ~~The patient must demonstrate relapsed or refractory Hodgkin lymphoma disease after their ASCT~~
Prescriber Instructions	Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed Hodgkin lymphoma Brentuximab ~~vedotin~~ PBS Authority Application - Supporting Information Form which includes the following: I. A histology report including evidence of the tumour's CD30 positivity from a biopsy at time of diagnosis~~, or subsequent to the most recently delivered prior treatment with radiation, chemotherapy, biologics, immunotherapy or other agents~~; II. The date of the primary ASCT *performed* III. A declaration of whether the disease is classified as relapsed or refractory *post ASCT* IV. A declaration of whether the patient is planned to have an *allogeneic* ~~second~~ SCT~~, and the type of transplant procedure planned, i.e., autologous or allogeneic~~.
Administrative Advice	~~A maximum quantity and number of repeats to provide for an initial course of brentuximab vedotin of 4 cycles will be authorised as part of the initiating restriction.~~ No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised.

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
BRENTUXIMAB VEDOTIN 50 mg vial for IV infusion, 1	200 mg	11	$[redacted] (Published) $[redacted] (Effective)	Adcetris®	Takeda Pharmaceuticals Australia Pty Ltd

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	*Relapsed or Refractory*
Condition:	*Hodgkin lymphoma*
PBS Indication:	*Relapsed or Refractory Hodgkin lymphoma*
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must not have progressive disease AND Patient must have previously been issued with an authority prescription for this drug AND *Patient must not receive more than 12 cycles of treatment under this restriction*
Prescriber Instructions	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The treatment must not exceed a lifetime total of 16 cycles. ~~Patients should be assessed for response after 4 cycles of brentuximab vedotin treatment.~~ ~~Patients should not be continued on brentuximab vedotin treatment if they are in a progressive disease state after the first assessment of response.~~ ~~The following information is to be provided at time of request for continuation of treatment:~~ ~~The date of initial treatment with brentuximab vedotin;~~ ~~The date and means by which the patient's disease was assessed as being responsive or not to brentuximab vedotin treatment;~~ ~~A declaration of the patient's response to initial treatment (categorised by type of response), and~~ ~~A declaration of whether the patient has had, or is planned to have, a transplant.~~
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

2.3 The resubmission presented a cost-utility analysis compared with salvage chemotherapy (represented by gemcitabine+vinorelbine).

2.4 The proposed restriction did not limit use to first-line post ASCT (i.e. listing was sought in any line post ASCT) and use was not restricted to patients whose treatment had a curative intent. This was consistent with the PBAC Minutes from March 2015. Further, the resubmission proposed that patients could continue treatment beyond four cycles if they were progression free (but not necessarily in complete remission). This was less stringent than proposed in the previous submission, which would have restricted continued use to only those patients with a complete response. The ESC considered that these changes were appropriate.

2.5 In March 2015, the PBAC considered that there were other groups of patients with Hodgkin lymphoma who had a high clinical need for treatment options. Thus, in November 2016, a separate submission for brentuximab vedotin (item 6.01) will also be considered, for patients who failed at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option (i.e. ASCT naïve patients).

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

3 Background

3.1 TGA status for Hodgkin lymphoma: brentuximab vedotin was TGA registered on 19 December 2013 for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma:

- Following ASCT; or
- Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

3.2 This item was previously considered at the March 2015 PBAC meeting. The PBAC considered the following issues would need to be addressed in the resubmission:

- Incorporate changes to the proposed restriction (i.e. could provide 'continuation rule' for use of brentuximab vedotin);
- Use the combined data from Kaloyannidis and British Columbia registries to inform the effectiveness of salvage chemotherapy in the economic model;
- Use an eight year time horizon in the base case model;
- Provide more reliable data for rates of consolidation with allogeneic SCT;
- The ICER of the re-specified base case be from $50,000 and $60,000 per QALY; and
- Update the financial estimates to include a more appropriate uptake rate (Paragraph 7.14, PBAC PSD, March 2015).

3.3 Table 1 summarises the differences between the previous submission and the resubmission, and provides comment on how the PBAC issues were addressed.

Table 1: Summary of the previous submission and current resubmission

	Brentuximab vedotin (March 2015)	Current resubmission
Requested PBS listing	Relapsed or refractory Hodgkin lymphoma after ASCT that is suitable for systemic curative salvage therapy. Various options were proposed including restricting: use to first-line post ASCT; use to patients intended for an allogeneic SCT; and continuation beyond the fourth cycle to patients with Complete Response. **PBAC Comment:** The proposed restrictions would exclude certain patient groups who could benefit. The restriction should allow use at any line post ASCT. A continuation rule based on a complete response could be included if adequately justified, but the PBAC noted it would disadvantage some patients (Para 7.2-7.6).	Consistent with the PBAC Minutes listing was proposed in <u>any line</u> of treatment after ASCT failure; there was no requirement for treatment to have a curative intent. A separate submission was made for the PBAC's consideration at the November 2016 for ASCT naïve patients There was no requirement for patients to have a complete response to continue treatment beyond 4 cycles.
Requested price	Public/Private Effective AEMP: $[redacted] (1 vial)	Public/Private Effective AEMP: $[redacted] (1 vial, $[redacted] increase). The resubmission stated the price aligned with price in sALCL.
Main comparator	Gemcitabine+vinorelbine salvage chemotherapy and best supportive care/palliative care as a supportive comparator. **PBAC Comment:** Gemcitabine+vinorelbine were appropriate comparators (Para 7.7).	The resubmission expanded the agents for best supportive care / palliative care to include single chemotherapy agents and anti-tumour steroid regimens.
Clinical evidence	A naïve comparison in first-line post ASCT setting between: <u>Brentuximab vedotin:</u> first-line post ASCT subgroup from the single-arm Study 0003 (n = 45). <u>Salvage chemotherapy:</u> the Kaloyannidis study and British Columbia registry (pooled n = 109). **PBAC Comment:** Naïve comparison using data of poor quality with a high risk of bias (Para 7.8). Combining the Kaloyannidis and British Columbia datasets was appropriate (Para 7.14).	Also a naïve comparison, but with more patients: <u>Brentuximab vedotin:</u> Longer follow-up from Study 0003; plus new follow-up data for [redacted] patients who relapsed in the placebo arm of the AETHERA trial and received brentuximab vedotin as their 1st salvage post progression (pooled n = [redacted]). <u>Salvage chemotherapy:</u> Kaloyannidis data unchanged; additional 22 patients from British Columbia registry due to the expanded comparator; plus new follow-up data for [redacted] patients who relapsed in the placebo arm of AETHERA trial and received salvage chemotherapy (pooled n = [redacted]).
Key effectiveness data	Median PFS, months (95% CI): Brentuximab vedotin: [redacted], -) Salvage therapy: [redacted] HR: [redacted] Median OS, months (95% CI): Brentuximab vedotin: - ([redacted], -) Salvage therapy: [redacted] HR: [redacted] **PBAC Comment:** Brentuximab appears to be effective but the magnitude of survival benefit is difficult to quantify due to the poor quality of the evidence. (Para 7.9)	Median PFS, months (95% CI): Brentuximab vedotin: [redacted] Salvage therapy: [redacted]* HR: [redacted] Median OS, months (95% CI): Brentuximab vedotin: - ([redacted], -) ^ Salvage therapy: [redacted] HR: [redacted] * BC registry only ^ Removal of censoring for subsequent therapies

	Brentuximab vedotin (March 2015)	Current resubmission
Key safety data	The most common treatment related adverse events were neutropenia and peripheral neuropathy. **PBAC Comment:** Brentuximab vedotin is less toxic than salvage therapy. (Para 7.10)	Unchanged
Clinical claim	Brentuximab vedotin is superior in terms of comparative effectiveness and superior in terms of comparative safety over salvage chemotherapy. **PBAC Comment:** The claim was reasonable, however the magnitude of survival benefit was difficult to quantify due to the poor quality of the evidence. The PBAC considered that brentuximab vedotin was less toxic than salvage therapy (Para 7.10)	Brentuximab vedotin is superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over salvage chemotherapy.
Economic evaluation	Cost-utility analysis based on a naïve comparison of non-randomised studies. - 13-year time horizon - Proportion of patients receiving allogeneic SCT was assumed at 30% ICER: $75,000 - $105,000 per QALY **PBAC Comment:** The cost-effectiveness analysis was not reliable. Eight-year time horizon would be more appropriate than the submission's 13-year horizon. Proportion of patients receiving allogenic SCT (30% in each arm) in the model was not sufficiently justified.	- Cost-utility analysis based on a naïve comparison of non-randomised studies. - 13-year time horizon. This was not appropriate; the PBAC requested an 8 year time horizon - Proportion of patients receiving allogeneic SCT was obtained from key evidence studies ([redacted]% for brentuximab vedotin vs [redacted]% for salvage chemotherapy). This appeared reasonable - ICER: $45,000 - $75,000 per QALY - revised ICER in PSCR: $75,000 - $105,000 per QALY
Number of treated patients	Less than 10,000 in Year 1 decreasing to less than 10,000 in Year 5. **PBAC Comment:** Reasonable except uptake was likely to be higher than estimated ([redacted]%) (Para 7.13)	Less than 10,000 in Year 1 decreasing to less than 10,000 in Year 5. Uptake was increased to [redacted]%, which might be reasonable.
Estimated cost to PBS/RPBS	Less than $10 million in Year 1 decreasing to less than $10 million in Year 5 for a total of $10 - $20 million over the first 5 years of listing. **PBAC Comment:** Reasonable	Less than $10 million in Year 1 decreasing to less than $10 million in Year 5 for a total of $10 - $20 million over the first 5 years of listing. The increase was due to an extra less than 10,000 patients being included over 5 years, plus correction of the calculation of G-CSF costs.
PBAC decision	Rejected because the clinical place was not adequately defined, the cost-effectiveness estimate was not reliable, and the proposed restrictions would exclude groups of patients who would benefit from the drug.	-

Source: Compiled during the evaluation

AEMP = approved ex-manufacturer price; ASCT = autologous stem cell transplant; BC = British Columbia; G-CSF = granulocyte-colony stimulating factor; ICER = incremental cost-effectiveness ratio; PAR = paragraph; QALY = quality-adjusted life-year; SCT = stem cell transplant; sALCL = systemic anaplastic large cell lymphoma

3.4 Brentuximab vedotin was recommended for listing by the PBAC in March 2014 for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) and was listed on the PBS on 1 December 2014.

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

4 Clinical place for the proposed therapy

4.1 The resubmission proposed that the place in therapy was for the treatment of patients with relapsed or refractory CD30+ Hodgkin lymphoma following ASCT. The PBAC previously considered that the restriction should allow use in relapsed/refractory patients at any line post ASCT. The PBAC noted that use in later-lines would diminish once the prevalent population has been treated.

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

5 Comparator

5.1 Consistent with the previous submission, the resubmission nominated both the chemotherapy combination of gemcitabine + vinorelbine and best supportive care/palliative care as the relative main comparators to brentuximab vedotin. This was previously considered appropriate by the PBAC. However, the range of therapies encompassed by best supportive care and palliative care was expanded in the resubmission to include single chemotherapy and anti-tumour steroid regimens. Thus, the resubmission used a mixed comparator of gemcitabine + vinorelbine, single chemotherapy and anti-tumour steroid regimens, which it referred to as "salvage chemotherapy". This was reasonable.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. At the hearing, a haematologist presented clinical case studies to support the effectiveness of brentuximab vedotin in providing a 'bridge' to an allogeneic stem cell transplant for a young patient, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on the benefits of brentuximab vedotin with relapsed HL post ASCT.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (8), health professionals (5) and organisations (3) via the Consumer Comments facility on the PBS website. The comments highlighted the tolerability of brentuximab vedotin in heavily pre-treated patients and its effectiveness in patients post ASCT-failure.

6.3 The PBAC noted advice from both Lymphoma Australia and the Leukaemia Foundation that brentuximab vedotin is well tolerated and provides an improved quality of life to patients with Hodgkin lymphoma. The PBAC also noted Rare Cancer Australia's support for PBS listing of brentuximab vedotin. The PBAC noted that this

advice was of the evidence provided in the submission.

Clinical trials

6.4 No direct randomised trials were identified in the relevant population. The resubmission continued to use a naïve comparison in the first-line post ASCT setting for the key efficacy assessment and to inform the economic model. The sources of evidence for the naïve comparison remained Study 0003, the British Columbia Registry and Kaloyannidis 2012 (Greek registry), with the addition of patient level follow-up data from a new study, AETHERA (Table 2).

Table 2: Key clinical evidence in the resubmission: naïve comparison in the first-line post ASCT population

Study	Previous submission	Resubmission		
	n	This resubmission	Used for	n
Brentuximab vedotin				
Study 0003	45 in subgroup (102 in ITT)	**Updated data-cut.** In the subgroup used, median follow-up was *62 months* [a] vs. 37 months in the previous submission. Per the previous submission, only the 1st line post ASCT subgroup was used.	OS PFS	45
AETHERA trial follow-up	-	**New study**. *Post-hoc* analysis of placebo arm pts who, during long term follow-up, received BV 1st-line post ASCT)	OS	[redacted]
Total	**45**			[redacted]
Salvage chemotherapy				
Kaloyannidis 2012 (Greek Registry)	87	Unchanged	OS PFS	87
British Columbia registry	22	***20* additional pts included**, who received single agents as the comparator was expanded.	OS PFS	42
AETHERA trial follow-up	-	**New study**. *Post-hoc* analysis of placebo arm pts who, during long term follow-up, received chemotherapy 1st-line post ASCT)	OS	[redacted]
Total	**109**			[redacted]

Source: *Compiled during evaluation based on: text on p46; Table B.2-3, pp48 of the resubmission*
ASCT = autologous stem cell transplant; BV = brentuximab vedotin; ITT = intention-to-treat; OS = overall survival; PFS = progression free survival; pts = patients vs = versus
[a] *Based on time from 'start date (first exposure to BV)' until 'last long-term follow-up date' in spreadsheet "12B - 2. Censoring"*

6.5 Similar to the previous submission, the resubmission used individual patient data from the key studies (data provided in the resubmission). The resubmission included new data to address concerns about the uncertainty of the incremental benefit. The new or updated key evidence were:

- Updated data from the final-planned follow-up of Study 0003 (62 months versus 37 months in the previous submission);
- Two cohorts of patients from the long-term follow-up of the placebo group of the AETHERA trial who received either brentuximab vedotin or salvage chemotherapy after relapse. This appeared to be unblinded, prospective, post hoc data in which clinicians and patients could choose the treatment. The ESC noted that healthier patients may have been more likely to choose brentuximab vedotin in the AETHERA trial, especially if they were from a region where it was not reimbursed;
- Twenty additional patients were included from the British Columbia registry as the comparator was expanded to include single-agent chemotherapy and steroid

regimens. The ESC noted that survival data in this registry was measured from the time of relapse, rather than the time of the onset of treatment.

This new data increased the number of patients in the comparison to 249, compared with 164 in the previous submission.

Table 3: Details of the studies presented in the resubmission are provided in the table below.

Study ID	Protocol title/ Publication title	Publication citation
Key evidence: Brentuximab vedotin		
Study 0003	A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin lymphoma. Clinical study report Addendum 1. Key publication Younes A, Gopal AK, Smith SE, *et al*. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma.	20 December 2010. 30 November 2011. *Journal of Clinical Oncology* 2012; 30(18): 2183-2189.
AETHERA	Key publication Moskowitz CH, Nademanee A, Masszi T et al., Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial.	*Lancet.* 2015 ; 9; 385 (9980): 1853–62.
Key evidence: Salvage chemotherapy		
Kaloyannidis 2012 (Greek Registry)	Kaloyannidis P, Voutiadou G, Baltadakis I, *et al*. Outcomes of Hodgkin's lymphoma patients with relapse or progression following autologous hematopoietic cell transplantation.	*Biol Blood Marrow Transplant.* March 2012; 18(3): 451-457.
Connors 2013 (British Columbia Registry)	Connors JM, MD. Clinical Director, BC Cancer Agency Centre for Lymphoid Cancer Acting Head, Division of Medical Oncology, University of British Columbia. "Clinical Characteristics and Outcome for Patients with Relapse of Hodgkin Lymphoma after High Dose Chemotherapy and Autologous Hematopoietic Stem Cell Transplantation (ASCT) in British Columbia"	Unpublished report dated 5 February 2014.
Supplementary evidence – brentuximab vedotin		
Zagadailov *et al* 2016	Zagadailov EA, Corman S, Hagan M, *et al.* Real-world effectiveness of brentuximab vedotin (BV) vs. other treatments in patients with relapsed/refractory hodgkin lymphoma (rrhl) post autologous stem-cell transplantation (ASCT).	Poster presentation at the European Haematology Association meeting, Copenhagen, Denmark, 10th June 2016.
Garciaz *et al*, 2013	Garciaz S, Coso D, Peyrade F, *et al*. Brentuximab vedotin followed by allogeneic transplantation as salvage regimen in patients with relapsed and/or refractory Hodgkin's lymphoma.	*Hematol Oncol*. 2013; 32(4): 187-191.
Salihoglu *et al,* 2015	Salihoglu A, Elverdi T, Karadogan I, *et al*. Brentuximab vedotin for relapsed or refractory Hodgkin lymphoma: experience in Turkey.	*Ann Hematol*. March 2015; 94(3):415-20.
Yang *et al,* 2014	Yang QM, Hong JY, Ko YH, *et al*. Brentuximab vedotin for relapsed or refractory CD30+ Hodgkin lymphoma: a multicenter analysis from Asia.	*Onco Targets Ther.* 2014; 7:1717-1722.
Viviani *et al,* 2015	Viviani S, Guidetti A, Dalto S, *et al*. Brentuximab vedotin (BV) an effective treatment for transplant ineligible patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL).	*Haematologica.* 2015; 100:455-456. (abstract only).
Supportive evidence – salvage therapy		
Bartlett *et al*, 2007	Bartlett NL, Niedzwiecki D, Johnson J, *et al*. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin lymphoma: CALGB 59804.	*Ann of Oncology.* 2007; 18(6):1071-1079.

Study ID	Protocol title/ Publication title	Publication citation
Czyz *et al*, 2013	Czyz A, Romejko-Jarosinska J, Knopinska-Posluszny W *et al.* Treatment strategy based on gemcitabine-containing salvage chemotherapy used with intent to proceed to second stem cell transplant for patients with Hodgkin lymphoma relapsing after a prior autologous transplant.	*Leukemia and Lymphoma.* 2013; 54(5):973-978.
Czyz *et al,* 2014	Czyz A, Romejko-Jarosinka J, Manko J, *et al*. Treatment Of Patients With Hodgkin Lymphoma Relapsing After Autologous Haematopoietic Stem Cell Transplantation- A Polish Lymphoma Research Group (Plrg) Multicenter Retrospective Analysis Of Prognostic Factors And Long-Term Outcome.	*Supplement Bone Marrow Transplantation.* 2014; (Poster abstract only):_PH-P166.

Source: Table B.2-2, pp 42-45 in the resubmission

6.6 The key features of the evidence used in the naïve comparison are summarised in Table 4. Details on the supplementary evidence were not presented in the executive summary because they were not used in the key efficacy assessment or the economic evaluation.

Table 4: Key features of the included evidence – naïve comparison

Study	n used (ITT)	Design/ median follow-up or study period	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Brentuximab vedotin						
Study 0003	45 (102)	Prospective single-arm cohort; MC 62 months [a]	High	Relapsed HL post-ASCT, any line (ITT)	OS, PFS,ORR	Sub-group who received BV in 1st line post ASCT (n=45)
AETHERA	[redacted] (329)	Prospective, randomised, double-blind, placebo-controlled, MC 21 months [a]	High	HL with high risk for relapse or progression post ASCT	OS, PFS [b], ORR	Cohort of patients from the long term follow-up of the placebo arm who received BV post progression (n=[redacted])
Salvage chemotherapy						
Kaloyannidis dataset	87	IPD; R; MC 17 months	High	Relapsed HL post-ASCT, 1st-line	OS; PFS	Used
British Columbia	42	IPD; R 13 months [a]	High	Relapsed HL post-ASCT, 1st line	OS; PFS	Used
AETHERA	[redacted] (329)	As above, 18 months [a]				Cohort of patients from the long term follow-up of the placebo arm who received chemotherapy post progression (n=[redacted])

Source: compiled during the evaluation

ASCT = autologous stem cell transplant; BV = brentuximab vedotin; HL = Hodgkin lymphoma; IPD = individual patient data; ITT = intention-to-treat; MC=multi-centre; ORR = overall response rate; OS=overall survival; PFS=progression-free survival; R = retrospective.

[a] Follow-up was calculated during evaluation based on Individual Patient Data

[b] Progression free survival data were not available for the AETHERA follow-up cohorts

6.7 The PSCR (p1-2) acknowledged the limitations in the evidence presented; however, it argued that in the absence of any controlled comparative data, a naïve indirect comparison was the only possible approach to assessing the comparative effectiveness of brentuximab vedotin versus salvage chemotherapy. The PSCR also contended that "the addition of the AETHERA data is important because not only does it provide additional efficacy data (particularly for BV), but these recent data demonstrating BV's efficacy (which align with BV's benefit seen in the controlled trial

environment) are informative to the PBAC's consideration of BV's use and effectiveness in the real word".

6.8 The ESC noted that the AETHERA study included patients who were older and more heavily pre-treated but with less refractory disease than patients in the other studies. Thus, the ESC considered that including AETHERA in the naïve comparison introduced additional heterogeneity. The overall impact of this was difficult to determine, particularly as AETHERA contributed significantly more patients to the brentuximab vedotin group than the salvage chemotherapy group for the naïve comparison ([redacted]% of all patients in the brentuximab vedotin group versus [redacted]% for salvage chemotherapy). The ESC considered that this can potentially increase the PBAC's previous concerns about the high risk of bias, although the direction of the bias is unclear.

6.9 The ESC noted that the resubmission did not discuss the applicability of the AETHERA follow-up data to the proposed PBS population.

Comparative effectiveness

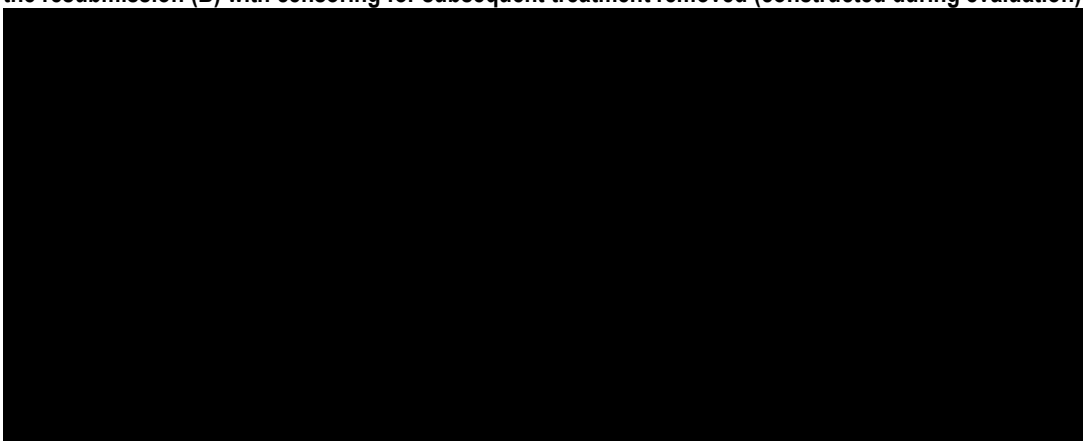
Overall-survival

6.10 The resubmission presented overall survival outcomes from the combined cohorts for brentuximab vedotin (Study 0003 first-line post ASCT subgroup + AETHERA follow-up cohort) versus salvage chemotherapy (British Columbia + Kaloyannidis + AETHERA follow-up cohort). The resubmission's methods for conducting the survival analyses were inappropriate because:

- In the overall survival analysis, some patients were censored when they commenced a subsequent treatment deemed "experimental". However, this was not a valid reason to censor overall survival data. Patients commence subsequent therapies as their condition worsens, so this was informative censoring. Further, use of subsequent therapies would reflect use in Australian clinical practice. The rates of censoring were significantly higher in the brentuximab vedotin group ([redacted]% versus [redacted]% in the chemotherapy studies).
- In the progression free survival analysis, patients with missing data in the Kaloyannidis study (salvage chemotherapy) were assumed to have 15 days of progression free survival. This affected 74% of patients in this study, many of whom had stable disease or a complete or partial response. This significantly underestimated progression free survival in the salvage chemotherapy arm. The PSCR (p3) notes that "…the date of relapse was located for an additional 25 patients, meaning the total number of patients with 15 days of PFS is 40 out of 87 patients, or 46%, not 74% as stated in the evaluation." The additional PFS data were incorporated into the revised economic analysis presented in the PSCR.

Figure 1 shows the Kaplan-Meier curve for overall survival, as presented in the resubmission (A) and without censoring for subsequent therapies as constructed during evaluation (B). Table 5 presents a comparison of the overall survival results as presented in the previous submission, the resubmission and without censoring for subsequent therapies.

Figure 1: Overall survival curves for brentuximab vedotin and salvage chemotherapy (A) as presented in the resubmission (B) with censoring for subsequent treatment removed (constructed during evaluation)



Source: Figure B.6-4, p106 of the resubmission; *and constructed during evaluation: using Spreadsheets 12.B - 2. Censoring", and "12C - 3. Survival Analyses".*

Table 5: Overall survival results from the key evidence versus the previous submission: with and without censoring for subsequent therapies

	Previous submission		Resubmission			
			As presented		Remove censoring for subsequent therapies	
	BV	Salvage Chemo	BV	Salvage chemo	BV	Salvage chemo
N						
Median follow-up, months (95% CI)		[a]	[b]	[b]	[b]	[b]
Number of events *						
Patients censored, n (%) - subsequent therapies* - alive*						
Median OS, m				[d]	*	*
Hazard ratio (95% CI)		[c]			[d]*	

Source: compiled during evaluation based on Table B(ii).6.2, p.6.02.COM.31 of the previous submission;
*calculated during evaluation using method described under Figure B(ii).6.2.
BV = brentuximab vedotin; CI = confidence interval; OS = overall survival; NA = not available; NR = not reached; **bold** = statistically significant
[a] 17 months for Kaloyannidis and 36 months for the British Columbia registry
[b] Based on time from 'start date (first exposure to BV)' until 'last long-term follow-up date' in spreadsheet "12B - 2. Censoring"
[c] Calculated in the previous Commentary
[d] Calculated with STATA 13.0, using Cox regression (Breslow method)

6.11 Median overall survival for salvage chemotherapy was lower than that presented previously. This was likely due to the inclusion of patients on single agent therapies from the British Columbia registry, while in the previous submission only patients on gemcitabine-vinorelbine were included.

6.12 In the survival analysis presented in the resubmission, median overall survival was not reached for the brentuximab vedotin. However due to censoring of patients who moved on to further lines of treatment, only (%) deaths were included for brentuximab vedotin versus (%) deaths when censoring for subsequent therapies was removed. Median overall survival was not estimable (95% confidence

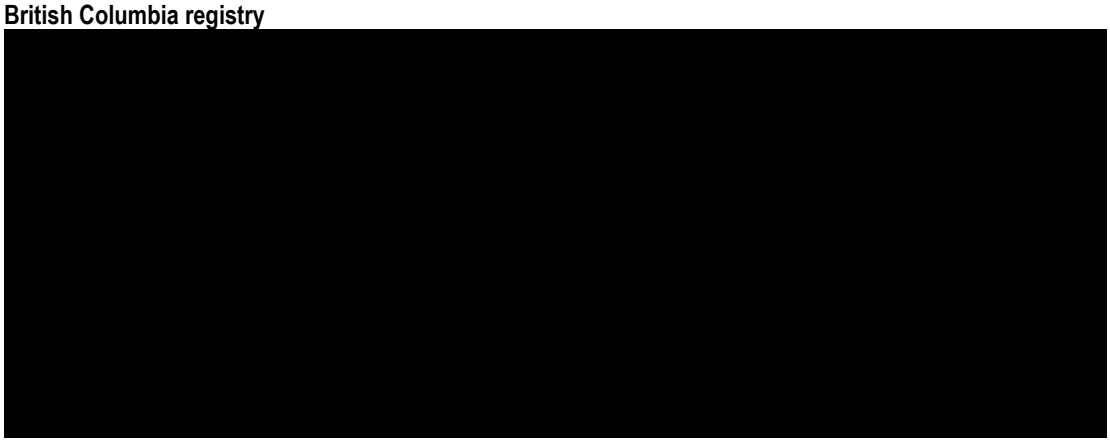
interval (CI): 41.0 months to not estimable) with appropriate censoring. For the salvage chemotherapy arm, censoring made little difference to median overall survival, which was approximately [redacted] months in both analyses.

6.13 With censoring adjusted during the evaluation of the resubmission, there continued to be improved survival with brentuximab vedotin compared to salvage chemotherapy; albeit the effect size was reduced (hazard ratio [redacted]; [redacted]% confidence interval: [redacted] to [redacted]). The results from this analysis should be interpreted with caution due to the low quality of evidence and heterogeneity between the studies included in the analysis.

Progression free survival

6.14 Progression free survival presented in the resubmission was based on Study 0003, Kaloyannidis and the British Columbia registry, as results were not available from the AETHERA follow-up data. Figure 2 presents the Kaplan-Meier curve as used in the resubmission's economic model (A) and only using data from the British Columbia registry (i.e. without Kaloyannidis data) (B).

Figure 2: Progression free survival for brentuximab vedotin and salvage chemotherapy (A) per the resubmission (based on Kaloy + British Columbia registry) (B) salvage chemotherapy based only on British Columbia registry

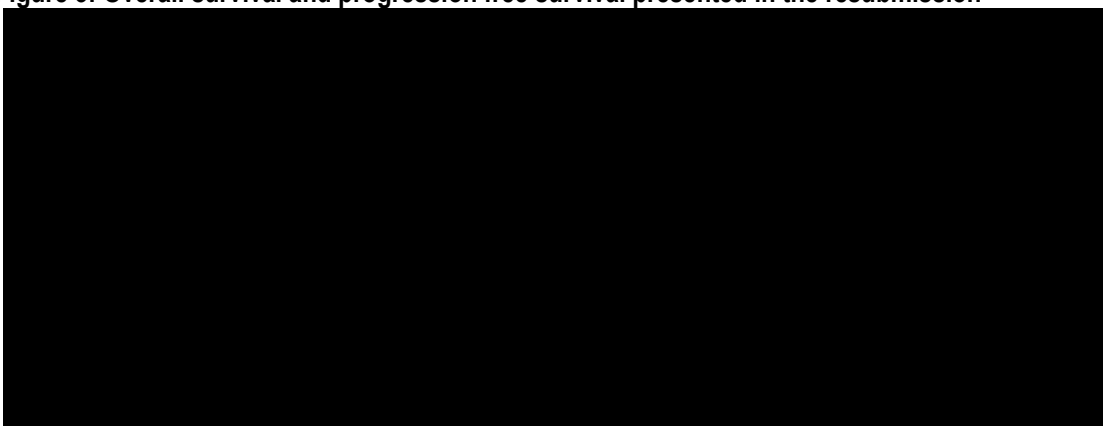


Source: Spreadsheet "12C -3. survival analyses" worksheet "KM Charts (with at risk)"
BC = British Columbia; BV = brentuximab vedotin; Kaloy = Kaloyannidis; PFS = progression free survival

6.15 As shown in Figure 2(A), over half of patients in the salvage chemotherapy group progressed after 15 days. Thus median progression free survival was 15 days, due to the assumption that patients in the Kaloyannidis study with missing data had progression free survival of 15 days only. This significantly underestimated progression free survival in the salvage chemotherapy group. The PSCR (p2) that progression free survival was biased against brentuximab vedotin because of the different definition of progression free survival in the British Columbia registry and the expansion of the comparator to include single-agent chemotherapy and disease-directed steroid regimens. The ESC disagreed, and considered that the differences in the time taken to relapse in the two datasets reduced the perceived bias against brentuximab vedotin. The ESC noted that using only the British Columbia registry data, progression free survival for salvage chemotherapy increased from [redacted] months to [redacted] months although half these patients received steroid regimens or single-agent

chemotherapy (due to the changed comparator definition). Thus, the British Columbia data might also underestimate progression free survival for salvage chemotherapy.

Figure 3: Overall survival and progression free survival presented in the resubmission



Source: Section D_BV_Adcetris_RR HL Post ASCT.xlsm
BV = brentuximab vedotin; PSCR = pre-Sub-Committee Response; SC = salvage chemotherapy

Revised OS and PFS as presented in the PSCR

6.16 The PSCR (p5) presented revised overall survival and progression free survival analyses. Overall survival was revised by removing the censoring for patients who started subsequent therapies. For progression free survival, the revised analysis was based on British Columbia patients plus the full revised Kaloyannidis datasets (i.e. including the 25 patients whose dates of relapsed were identified in the PSCR).

Comparative harms

6.17 Compared with the data considered by the PBAC previously, the resubmission presented some limited additional information on the comparative safety of brentuximab vedotin and salvage chemotherapy. The PBAC previously considered that brentuximab vedotin was "less toxic than salvage chemotherapy". The new safety data presented in the resubmission were consistent with the PBAC's previous conclusions.

Benefits/harms

6.18 Table 6 summarises the comparative benefits of brentuximab vedotin versus salvage chemotherapy as calculated during evaluation. The PBAC had previously accepted the claim of superior safety for brentuximab vedotin compared with salvage chemotherapy.

Table 6: Summary of comparative benefits for brentuximab vedotin and salvage chemotherapy

Benefits				
	BV	Salvage chemo	Absolute Difference	HR (95% CI)
PFS – excluding Kaloyannidis study [a]				
Progressed	[redacted]	[redacted]	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]
OS – remove censoring for subsequent therapies [a]				
Died	[redacted]	[redacted]	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]

Source: calculated during evaluation using method described under Figure B(ii).6.2.
BV = brentuximab vedotin; chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression free survival;
[a] Calculated during evaluation using STATA 13.0

6.19 The ESC considered that it was difficult to make a reliable estimate of the incremental benefit and harms on the basis of the naïve indirect comparison presented in the submission.

6.20 The sponsor's pre-PBAC response (p1) highlighted the key differences between brentuximab vedotin and salvage chemotherapy, with respect to its selective mechanism of action, and superior safety and tolerability profile. Further, brentuximab vedotin had a simple and short administration protocol, requiring a 30-minute i.v. infusion once in three weeks without concomitant medication, contrary to standard salvage chemotherapy that involves multiple infusions in every cycle of treatment with additional medication to manage side effects.

Clinical claim

6.21 The resubmission described brentuximab vedotin as superior in terms of comparative efficacy and non-inferior in terms of comparative safety over salvage chemotherapy. Key concerns with the claim of superior efficacy were:

- The resubmission censored overall survival when patients commenced certain subsequent therapies, except in the Kaloyannidis study. This was inappropriate and meant that overall survival in the brentuximab vedotin group was based on only five events. Patients commenced subsequent therapies as their condition worsened, so this was informative censoring. The ESC considered that removal of censoring for subsequent therapies provided a more reliable estimate of comparative overall survival.
- For progression free survival, the resubmission assumed that 50% of patients on salvage chemotherapy progressed after 15 days.
- Inclusion of the new data from the AETHERA trial (for overall survival) *possibly* increased the heterogeneity within the comparison in terms of both patient characteristics and time when the studies were conducted. In addition, limited information was provided about the patients and methods of the post hoc analysis. Overall, this would increase PBAC's previous concerns about the high risk of bias.

6.22 Overall, the PBAC considered that the claim of superior comparative efficacy over salvage chemotherapy was reasonable, although the magnitude of the comparative benefit was difficult to determine from the data provided in the resubmission. The claim of non-inferior comparative safety was consistent with the PBAC's previous consideration that brentuximab vedotin was less toxic than salvage chemotherapy in

the post ASCT setting (paragraph 7.10, brentuximab vedotin Public Summary Document, March 2015 PBAC meeting).

Economic analysis

6.23 The resubmission presented an updated modelled economic evaluation.

Table 7: Comparison of the economic evaluation in the current resubmission and the previous submission

	Previous submission			**This resubmission**		
Time horizon	13 years			13 years. The PBAC previously requested a model with an eight year time horizon.		
Source of clinical evidence	BV: Study 0003 (n = 45) Salvage Chemotherapy: Kaloyannidis and British Columbia registry (pooled n = 109)			BV: Study 0003, AETHRA follow-up cohort on BV (pooled n = [redacted]) Salvage Chemotherapy: Kaloyannidis and British Columbia registry, AETHERA follow-up cohort on chemotherapy (pooled n = [redacted])		
Rates of second stem cell transplant	30% in each arm in the base case.			[redacted]% for BV; [redacted]% for salvage chemotherapy based on the naïve comparison studies. This appeared reasonable.		
Extrapolation	Applied the same rate of decline in salvage chemotherapy to BV until 13 years			- Used KM curve until the end of follow-up (BV OS: 6 yrs vs median follow-up of 2 yrs); then - applied the same rate of decline in salvage chemotherapy to BV until 11 years (for OS only); then - Survival declined linearly until it was 0% at 13 years		
Post progression disease mngt	BV: $[redacted] Salvage chemotherapy: $[redacted]			BV: $[redacted] Salvage chemotherapy: $[redacted]		
Adverse event costs	BV: $[redacted]/course Salvage chemotherapy: $[redacted]/course			BV: $[redacted]/course Salvage chemotherapy: $[redacted]/course		
Adverse event Disutilities	BV: -0.0025/course Salvage chemotherapy: -0.0033/course			BV: -0.098/course Salvage chemotherapy: -0.018/course		
	BV	**Salvage chemotherapy**	**Δ**	**BV**	**Salvage chemotherapy**	**Δ**
Cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
LY	5.03	3.40	1.64	7.79	3.36	4.43
QALYs	2.85	1.85	1.00	4.05	1.40	2.65
ICER/QALY			$[redacted]	**Resubmission base case**: $[redacted]		
				Revised base case presented in PSCR $[redacted]		

Source: compiled during the evaluation, *updated analyses provided in PSCR*

BV= brentuximab vedotin; LY = life year; ICER = incremental cost-effectiveness ratio; mngt = management; QALY = quality-adjusted life year; yrs = years

6.24 The resubmission used a three-health state model, comprising the following health states: stable disease; progressive disease; and death. The structure was unchanged from the previous submission. The ESC noted that the structure of the model was unchanged from the previous submission, and agreed that the use of a three health state model was reasonable.

6.25 A summary of the key drivers of the model is presented in the table below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Time horizon	Assumed 13 years	High, favoured brentuximab vedotin
OS and PFS analyses	OS: Censored patients who started subsequent therapy, except for patients from the Kaloyannidis study PFS: assumed patients in the Kaloyannidis study had 15-day PFS when data on progression was missing	OS : does not impact the ICER PFS: High , favoured brentuximab vedotin
Extrapolation	3 phases for OS: - Use of full KM curve until end of follow-up (6 yrs for BV); - for BV, the rate of survival decline was assumed to be the same as with salvage chemotherapy until 11 years; - beyond 11 yrs OS in both groups declined linearly to 0% at 13 yrs. For PFS, beyond 6.5 yrs, survival in both groups declined linearly to 0% at 13 yrs.	High, favoured brentuximab vedotin (however only the linear survival decline could be tested in sensitivity analyses)

Source: compiled during the evaluation

BV = brentuximab vedotin; chemo = chemotherapy; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; yrs = years

6.26 On the extrapolation of overall survival beyond the study period, the PSCR (p2-3) argued that the approach in the resubmission was conservative, as it would be unlikely that risk of death after the end of study follow-up would be the same for both brentuximab vedotin and salvage chemotherapy. The ESC noted that although the rate of decline was assumed to be the same between the two groups, the starting point in the brentuximab vedotin arm was higher. As the ESC had previously noted, this implied that there is some continued benefit from brentuximab vedotin beyond the study duration, although the survival curves do eventually merge (paragraph 6.26, March 2015 Public Summary Document).

6.27 The PSCR (p4) contended that 13 years was the appropriate time horizon, presenting survival data from Martinez 2013 and Arai 2013 as supportive evidence. The PSCR also presented additional sensitivity analyses to test the effect of reducing the time horizon from 13 to 8 years and varying the cost of post progression disease management. The ESC noted these arguments but considered that the issue remained unresolved.

6.28 Table 9 presents the results of the stepped economic evaluation.

Table 9: Results of the stepped economic evaluation

Step and component	Brentuximab vedotin	Salvage chemotherapy	Increment
Step 1: trial-based costs and outcomes			
Costs	$	$	$
Life year gained	3.89	2.53	1.35
Incremental cost/extra life year gained			**$**
Step 2: Modelled economic evaluation including extrapolation to time horizon			
Costs	$	$	$
Life year gained	5.68	3.27	2.41
Incremental cost/extra life year gained			**$**
Step 3: Modelled economic evaluation including all healthcare resource utilisation			
Costs	$	$	$
Life year gained	5.68	3.27	2.41
Incremental cost/extra life year gained			**$**
Step 4: Modelled economic evaluation including utilities			
Costs	$	$	$
QALY	3.16	1.60	1.56
ICER/QALY			**$**

Source: BV Post ASCT Economic Evaluation Censoring Revised Sept 2016.xlsm
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years

6.29 The PSCR (p4) presented an updated base case to account for the revised censoring of overall survival, the additional 25 patients from the Kaloyannidis dataset for whom PFS data was located, updated costs, and corrected disutilities associated with adverse events (AEs). In the revised base case, the ICER increased to $75,000/QALY - $105,000/QALY. The updated base case and sensitivity analyses are presented in Table 10.

Table 10: Base case and revised ICERs as presented in the PSCR

	Δ costs	Δ QALY	ICER
Base case in re-submission	$	2.65	$
Revised base case: adjusted for censoring of OS; 25 additional patients with PFS data from Kaloyannidis dataset; correction implementation of utility values	**$**	**1.56**	**$**
Univariate analyses (around revised base case)			
8-year time horizon instead of 13 years	$	1.38	$
Cost of PPDM: Same for both brentuximab vedotin and salvage chemotherapy	$	1.56	$
Cost of PPDM: $ for both brentuximab vedotin and salvage chemotherapy	$	1.56	$
Multivariate analyses			
Revised base case, 8-year time horizon, cost of PPDM: $ for both BV and salvage chemotherapy.	$	1.38	$
Adjusted for censoring of OS; PFS data from BC only; correction implementation of utility values, 8-year time horizon, cost of PPDM: $ for both brentuximab vedotin and salvage chemotherapy	$	1.24	$

Source: Table 1, p5 of the PSCR and BV Post ASCT Economic Evaluation Censoring Revised Sept 2016.xlsm
BC = British Columbia; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression free survival; PPDM = post progression disease management; QALY = quality adjusted life years

6.30 As acknowledged by the PSCR (p3-4), the ESC noted that the costs used for salvage chemotherapy were based on each patient receiving gemcitabine plus vinorelbine.

However, in the resubmission, the comparator included single-agent chemotherapy and anti-tumour steroid regimens (which would have lower costs for drug acquisition, concomitant medicines and monitoring). As such, the ESC advised that costs in the salvage chemotherapy arm were likely overestimated in the resubmission.

6.31 Table 10 presents key sensitivity analyses presented in the resubmission and conducted during evaluation. The below table shows a base case ICER in the range of $45,000/QALY - $75,000/QALY.

Table 10: Results of key univariate sensitivity analyses (around submission base case)

	Δ costs	Δ QALY	ICER
Base case	**$**	**2.65**	**$**
Univariate analyses			
Time horizon 8 years (base case = 13 year)	$	2.16	$
No linear extrapolation after 11 years for OS and 6.5 years for PFS [a]	$	2.32	$
OS survival without censoring for further therapies (base case OS censored for subsequent therapies)	$	2.01	$
PFS from BC only (in base case: PFS missing data in Kaloyannidis assumed to be 15 days before progression)	$	2.29	$
Multivariate analyses			
OS without censoring for further therapies + PFS only (base case: OS censored for subsequent therapies, PFS analyses from Kaloyannidis and the BC dataset)	$	1.65	$
OS without censoring + time horizon 8 year	$	1.65	$
OS without censoring + PFS from BC only + time horizon 8 year	$	1.32	$

Source: Table D.6-1; p208 in the resubmission; Section_D_brentuximab vedotin_Adcetris_RR HL post ASCT_CE Model_Nov216 PBAC.xlsm

AE = adverse event; BC = British Columbia; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression free survival; PD = progressive disease; PPDM = post progression disease management; QALY = quality adjusted life years; SCT = stem cell transplant

[a] Note this only adjusts extrapolation beyond 11 years (i.e. the BV data was still extrapolated until the end of the follow-up for chemotherapy, which was around 11 years for OS and 6.8 years for PFS)

6.32 The ICER was most sensitive to progression free survival, the time horizon and the extrapolation of overall survival with brentuximab vedotin. However, it was not possible to test the first phase of the extrapolation method for overall survival, from 6 years to 11 years, which assumed a treatment benefit for brentuximab vedotin beyond the trial duration (only the linear extrapolation beyond 11 years for overall survival and 6.5 years for progression free survival could be tested during evaluation).

6.33 A revised price of $ / vial (formerly $ / vial) was offered in the sponsor's Pre-PBAC response (p1). Accounting for the revised price reduced the ICER from $75,000 - $105,000/QALY to $45,000 - $75,000/QALY.

Drug cost/patient/course: $

6.34 The drug cost per patient per course was based on three 50 mg vials per patient per cycle (based the revised price presented in the Pre- PBAC response, and assuming an average body weight of 73.8 kg) and 10.3 cycles per treatment course (based on mean dose in Study 0003) and an average vial cost of $ (based on 32% of patients being treated in public hospital).

Estimated PBS usage & financial implications

6.35 This resubmission was not considered by DUSC.

6.36 Like the previous submission, the resubmission used an epidemiological approach and forecasted the number of eligible patients using the number of ASCTs conducted in Australia for Hodgkin lymphoma. The uptake rate was increased from [redacted]% to [redacted]% to address the PBAC's concerns that uptake was underestimated in the previous submission.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vials [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Hospital impact (additional allo-SCT)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Tables E.4-3, p235; E.4-4, p235; of the resubmission

allo-SCT = allogenic stem cell transplant; MBS = Medical Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation;

[a] Assuming 3 vials per cycle and 10 cycles per treatment course as estimated by the resubmission

6.37 The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 per year. The resubmission estimated that the cost to the PBS/RPBS and MBS would be $20 - $30 million in the first five years of listing (compared with $10 - $20 million in the previous submission). There was potential for the net PBS cost/year to be less than estimated due to the likely overestimated number of eligible patients. This was because:

- the number of ASCTs was overestimated because it was based on an increasing trend forecast; and
- the number of patients who were assumed to relapse post ASCT was higher than estimated from the Australasian Bone Marrow Transplant Recipient Registry Report or other literature.

The PSCR (p5) argued that the number of ASCT procedures was not overestimated but rather held constant from the second year of listing. The ESC noted that the rate of ASCT procedures may increase with the potential future listing of brentuximab vedotin, in ASCT naïve patients.

6.38 PBS costs could be substantially higher if brentuximab vedotin was used outside the proposed restriction in earlier lines of treatment particularly if the concurrent submission for ASCT-naïve population was not listed. The PBAC noted that a Risk Sharing Arrangement would be appropriate to reduce this risk.

7 PBAC Outcome

7.1 The PBAC recommended a written Authority Required Section 100 (Efficient Funding of Chemotherapy) listing of brentuximab vedotin for the treatment of relapsed Hodgkin Lymphoma post ASCT. The PBAC was satisfied that brentuximab vedotin is well tolerated, and provides, for some patients, an improvement in efficacy over best supportive care.

7.2 The PBAC welcomed the input received from individuals, clinicians and professional organisations in support of the submission, including the sponsor hearing. The comments highlighted brentuximab vedotin's effectiveness in HL patients post ASCT failure, its tolerability, and its efficacy in serving as a 'bridge' to a potentially curative allogeneic transplant in some patients.

7.3 The PBAC considered that the proposed restriction was consistent with its previous advice (paragraph 7.6, brentuximab vedotin Public Summary Document, March 2015 PBAC meeting).

7.4 The PBAC noted that although two submissions for brentuximab vedotin were considered at the November 2016 PBAC meeting (this item 7.03 and item 6.01), the impact of patients potentially accessing brentuximab vedotin more than once (for instance, before ASCT and then again after) was not considered in the proposed restriction for either submission, and neither was the potential financial impact considered. The PBAC noted that the Product Information for brentuximab vedotin allowed for a lifetime maximum of 16 treatment cycles, and considered that the restriction should be consistent with this.

7.5 The PBAC agreed that salvage chemotherapy, represented by gemcitabine and vinorelbine, was an appropriate comparator.

7.6 The PBAC noted that the PSCR (p5) presented revised overall survival and progression free survival analyses. Overall survival was revised by removing the censoring for patients who started subsequent therapies, while the revised analysis for progression free survival was based on British Columbia patients plus the full revised Kaloyannidis datasets (i.e. including the 25 patients whose dates of relapsed were identified in the PSCR). The PBAC considered that this was reasonable.

7.7 The PBAC noted that compared to the previous submission, additional data were provided from the long-term follow-up of the placebo group of the AETHERA trial who received either brentuximab vedotin or salvage chemotherapy after relapse. This appeared to be unblinded, prospective, post hoc data in which clinicians and patients could choose the treatment. The PBAC acknowledged the statement in the PSCR (p1) regarding the value of the AETHERA data in providing additional efficacy data for the comparison, but also considered that:

- the AETHERA study included patients who were older and more heavily pre-treated but with less refractory disease than patients in the other studies. Thus, including AETHERA in the naïve comparison introduced additional heterogeneity. The overall impact of this was difficult to determine, particularly as AETHERA contributed significantly more patients to the brentuximab vedotin group than the salvage chemotherapy group in the naïve comparison ([redacted]% of all patients in the brentuximab vedotin group versus [redacted]% for salvage chemotherapy).

- the resubmission did not discuss the applicability of the AETHERA follow-up data to the proposed PBS population context.

7.8 The PBAC considered that brentuximab vedotin was an effective treatment in the post-ASCT population, and its claim of superior efficacy over salvage chemotherapy was reasonable. However, the magnitude of the comparative benefit was difficult to determine from the data provided in the resubmission.

7.9 The PBAC considered that brentuximab vedotin is less toxic than salvage chemotherapy, but noted that neurotoxicity can develop after longer exposure.

7.10 The PBAC noted that a 13-year time horizon was used in the economic model in the resubmission, contrary to the PBAC's previous request for a model with an eight-year time horizon (paragraph 7.14, brentuximab vedotin Public Summary Document, March 2015 PBAC meeting). The PBAC noted the arguments provided in the PSCR (p4) around the time horizon of the model, and considered that the difference in the time horizon did not impact the ICER significantly.

7.11 The PBAC noted that the Pre-PBAC Response (p1) offered a revised price of $[redacted] per vial (formerly $[redacted] per vial).

7.12 The PBAC noted that the PSCR (p4) presented an updated base case to account for the revised censoring of overall survival, the additional 25 patients from the Kaloyannidis dataset for whom PFS data was located, updated costs, and corrected disutilities associated with adverse events (AEs). The PBAC further noted that the revised price presented in the sponsor's Pre-PBAC response (p1) reduced the ICER to $45,000 – 75,000/QALY. This was consistent with the PBAC's previous advice, where it considered that an ICER in the range of $50,000 to $60,000/QALY would be acceptably cost-effective (paragraph 7.14, brentuximab vedotin Public Summary Document, March 2015 PBAC meeting). The PBAC considered that brentuximab vedotin was therefore cost-effective at the proposed price, for the treatment of HL patients with relapsed disease post ASCT.

7.13 The PBAC recommended a Risk Share Arrangement with a subsidisation cap, and advised that the caps should be based on recalculated financial estimates to reflect the Committee's recommendation and the revised price per vial proposed in the sponsor's Pre-PBAC response. The Committee also noted that the cost of brentuximab beyond each cap should be reduced further in order to appropriately manage the risk to the Commonwealth.

7.14 The PBAC noted that the resubmission used an epidemiological approach to forecast the number of eligible patients by using the number of ASCTs conducted in Australia for Hodgkin lymphoma. The PBAC further noted that the uptake rate of brentuximab vedotin was updated from 80% to 90%, following its previous advice (paragraph 7.13, brentuximab vedotin Public Summary Document, March 2015 PBAC meeting).The PBAC considered that while this approach was reasonable, the utilisation of brentuximab vedotin in the proposed line of therapy could be affected by uncertainties in the number of future ASCTs, particularly with more effective earlier line therapies including brentuximab vedotin, in the ASCT naïve setting.

7.15 The PBAC recommended that brentuximab vedotin should not be treated as

interchangeable with any other drugs.

7.16 The PBAC advised that brentuximab vedotin was not suitable for prescribing by nurse practitioners.

7.17 The PBAC noted that the Early Supply Rule does not currently apply to Section 100 (Efficient Funding of Chemotherapy) listings.

7.18 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer
BRENTUXIMAB VEDOTIN 50 mg vial for IV infusion, 1	200 mg	3	Adcetris® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	Relapsed or Refractory
Condition:	Hodgkin lymphoma
PBS Indication:	Relapsed or Refractory Hodgkin lymphoma
Treatment phase:	Initial treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined

Clinical criteria:	Patient must have undergone a primary autologous stem cell transplant (ASCT) AND Patient must have experienced a relapsed CD30+ Hodgkin lymphoma post ASCT; OR Patient must have experienced a refractory CD30+ Hodgkin lymphoma post ASCT AND Patient must not receive more than 4 cycles of treatment under this restriction
Prescriber Instructions	Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed Hodgkin lymphoma Brentuximab PBS Authority Application - Supporting Information Form which includes the following: I. A histology report including evidence of the tumour's CD30 positivity from a biopsy at time of diagnosis; II. The date of the primary ASCT performed III. A declaration of whether the disease is classified as relapsed or refractory post ASCT IV. A declaration of whether the patient is planned to have an allogeneic SCT.
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. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer	
BRENTUXIMAB VEDOTIN 50 mg vial for IV infusion, 1	200 mg	11	Adcetris®	Takeda Pharmaceuticals Australia Pty Ltd

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐ Optometrists ☐Midwives
Severity:	Relapsed or Refractory
Condition:	Hodgkin lymphoma
PBS Indication:	Relapsed or Refractory Hodgkin lymphoma
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug AND Patient must not receive more than 12 cycles of treatment under this restriction
Prescriber Instructions	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The treatment must not exceed a total of 16 cycles in a lifetime.
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

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Takeda Pharmaceuticals Australia welcomes the PBAC's positive recommendation for the listing of its innovative medicine brentuximab vedotin for patients with relapsed or refractory Hodgkin lymphoma post ASCT. Takeda Australia also acknowledges and thanks the clinical community and the patients / carers who contributed to this outcome via their input to the PBAC.