

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

1 Purpose of Application

1.1 The submission requested Section 100 – Efficient Funding of Chemotherapy – listing for brentuximab vedotin for patients with relapsed or refractory Hodgkin lymphoma following at least two prior therapies when autologous stem cell transplant (ASCT) or multi-agent chemotherapy is not a treatment option.

2 Requested listing

2.1 The Pre-Sub-Committee Response (PSCR) (p.1) 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 not be in the patients’ best interest. Furthermore, CD30+ status does not change over the course of the disease. The ESC agreed with the PSCR.

2.2 The ESC noted that the average duration of treatment with brentuximab vedotin from the studies presented in the submission was 4.57 cycles (Table 9), and that this was inconsistent with the initial treatment criterion “Patient must not receive more than 4 cycles of treatment under this restriction”.

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	Nº. 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:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	<i>Relapsed or Refractory</i>
Condition:	<i>Hodgkin lymphoma</i>
PBS Indication:	<i>Relapsed or Refractory Hodgkin lymphoma</i>

Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>The Patient must be naïve for autologous stem cell transplant (ASCT) AND The Patient must have received at least two prior therapies for the treatment of Hodgkin lymphoma, including front line treatment and at least one line of subsequent treatment following relapse or refractoriness to chemotherapy. AND <i>Patient must have experienced a relapsed CD30+ Hodgkin lymphoma following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option; OR</i> <i>Patient must have experienced a refractory CD30+ Hodgkin lymphoma following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option;</i> AND <i>Patient must not receive more than 4 cycles of treatment under this restriction</i> AND The patient must be unable to receive further multi-agent chemotherapy.</p>
Prescriber Instructions	<p>Applications for authorisation of initial treatment must be in writing and must include:</p> <p>(a) a completed authority prescription form; and (b) a completed Hodgkin lymphoma brentuximab vedotin-PBS Authority Application -</p> <p>Supporting Information Form which includes the following:</p> <ol style="list-style-type: none"> I. A histology report including evidence of the tumour's CD30 positivity from a biopsy at time of diagnosis treatment with radiation, chemotherapy, biologics, immunotherapy or other agents; II. The date of initial diagnosis of Hodgkin lymphoma; III. Dates of commencement and completion of front-line curative intent chemotherapy and all lines of subsequent salvage chemotherapy; IV. A declaration of whether the disease is classified as relapsed or refractory subsequent to the most recently delivered prior therapy V. A declaration that the patient: <ol style="list-style-type: none"> a) has not received a prior ASCT, and the reason why, such as refractory disease, OR b) is unsuitable for further multi-agent chemotherapy, and the reason/s such as age, or comorbidities

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Administrative Advice	<p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p>
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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:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	<i>Relapsed or Refractory</i>
Condition:	<i>Hodgkin Lymphoma</i>
PBS Indication:	<i>Relapsed or Refractory Hodgkin lymphoma</i>
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must not have progressive disease AND Patient must have previously been issued with an authority prescription for this drug AND <i>Patient must not receive more than 12 cycles of treatment under this restriction</i>

Prescriber Instructions	<p>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).</p> <p>The treatment must not exceed a lifetime total of 16 cycles.</p> <p>Patients should be assessed for response after 4 cycles of brentuximab vedotin treatment.</p> <p>Patients should not be continued on brentuximab vedotin treatment if they are in a progressive disease state after the first assessment of response.</p> <p>The following information is to be provided at time of request for continuation of treatment:</p> <p>The date of initial treatment with brentuximab vedotin;</p> <p>The date and means by which the patient's disease was assessed as being responsive or not to brentuximab vedotin treatment;</p> <p>A declaration of the patient's response to initial treatment (categorised by type of response), and</p> <p>A declaration of whether the patient has had, or is planned to have, a transplant.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised</p>

- 2.3 The submission presented a cost-per-responder analysis compared with salvage chemotherapy (represented by gemcitabine + vinorelbine).

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

3 Background

- 3.1 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.

The sponsor's Pre-PBAC response (p.1) noted that the basis of the TGA's registration for the use of brentuximab vedotin in the ASCT naïve group of patients was not a clinical trial, unlike the post-ASCT population (Study 0003, item 7.03, November 2016 PBAC meeting). Rather, registration for this group of patients with high unmet clinical need was based on a report compiled by the sponsor on the efficacy and safety of brentuximab vedotin in 59 ASCT Naïve patients, comprising data from a number of sources, including the sponsor's Named Patient Program (NPP).

- 3.2 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.
- 3.3 Brentuximab vedotin was previously considered at the March 2015 PBAC meeting for the treatment of patients with relapsed or refractory Hodgkin lymphoma post ASCT.

A resubmission in this indication was also submitted for consideration at the November 2016 PBAC meeting (see item 7.03).

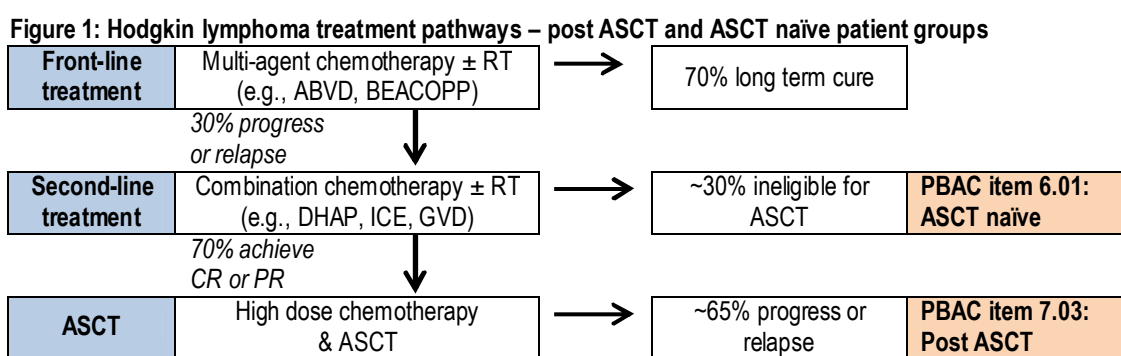
For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Clinical place for the proposed therapy

4.1 Hodgkin lymphoma is a neoplasm characterised by the presence of clonal malignant Reed-Sternberg cells. Brentuximab vedotin is an antibody-drug conjugate that targets the cell membrane protein CD30 which is expressed on the surface of such cells.

4.2 The submission proposed that the place in therapy was for the treatment of patients with relapsed or refractory Hodgkin lymphoma following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

Figure 1 presents treatment pathways for ASCT naïve and post ASCT patient groups.



Source: Figure ES-1, pi of the submission

ABVD = the combination of doxorubicin (Adriamycin) + bleomycin + vinblastine + dacarbazine; ASCT = autologous stem cell transplant; BEACOPP = the combination of bleomycin + etoposide + doxorubicin + cyclophosphamide + vincristine + procarbazine + prednisone; DHAP = the combination of cisplatin + cytarabine + dexamethasone; GVD = the combination of gemcitabine + vinorelbine + doxorubicin; ICE = the combination of ifosfamide + carboplatin + etoposide; RT = Radiotherapy.

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

5 Comparator

5.1 The submission did not nominate a single main comparator as it argued that there was large variety of salvage treatment options for this population. The evidence provided in the submission to support the clinical effectiveness and safety of salvage chemotherapy was mainly from studies evaluating gemcitabine-based regimens.

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 transplant' for younger patients while providing palliative benefit to the older ASCT naïve HL population, 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 to different patient populations with relapsed HL.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (4), health professionals (2) 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 particular benefit as a bridging agent to stem cell transplant.
- 6.3 The PBAC noted advice from the Leukaemia Foundation that brentuximab vedotin is well tolerated and provides an improved quality of life to patients with Hodgkin lymphoma. The PBAC specifically noted a comment from Lymphoma Australia emphasizing the benefit of brentuximab vedotin, especially in younger patients with refractory disease where it can serve as a bridge to transplant. The PBAC also noted Rare Cancer Australia's support for PBS listing of brentuximab vedotin. The PBAC considered that this advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.4 The submission was based on a naïve comparison of brentuximab vedotin versus salvage chemotherapy using the following evidence:

Brentuximab vedotin (7 studies; N=375)

- One *post-hoc* analysis of a case series (the Millennium Report) which included data from Phase I studies (SG035-0001, SG035-0002, SGN35-007, TB-BC010088) as well as data from the Global Named Patient Program.
- Six retrospective observational studies (Bröckelmann 2016; Zinzani 2015; Sasse 2013; Viviani 2015; Onishi 2015; Gibb 2013).

The submission also presented the baseline patient characteristics of the ongoing Phase 4 single-arm study, C25007 (n=60). The results of Study C25007 were provided during evaluation and were incorporated into the analysis where possible.

Salvage chemotherapy (5 studies; N=155):

- Four prospective single-arm Phase II studies of gemcitabine as a single agent or in combination with other chemotherapies (Santoro 2000; Venkatesh 2004; Oki 2008; Zinzani 2000); and
- One retrospective observational study of gemcitabine as a single agent (Validire 2008).

- 6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: List of studies presented in the submission

Study	Protocol title/ Publication title	Publication citation
Brentuximab vedotin		
Millennium report 2012	Case series report: brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma who have not received prior autologous stem cell transplantation.	Millennium Pharmaceuticals November 2012
Bröckelmann 2016	Bröckelmann PJ, Zagadailov EA, Coman S et al. Brentuximab vedotin (BV) in patients who are ineligible for autologous stem cell transplant (ASCT) with relapsed or refractory Hodgkin lymphoma (RRHL): a UK and Germany retrospective study.	Poster presented at European Hematology Association 21st Congress, Copenhagen, Denmark 9-12 June 2016.
Gibb 2013	Gibb A, Jones C, Bloor A, et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Program at a single UK centre.	<i>Haematol</i> 2013;98(4):611–614
Onishi 2015	Onishi M, Solomon G, Holmberg L et al. Brentuximab vedotin administered to platinum refractory transplant naïve hodgkin lymphoma patients can increase the proportion achieving FDG PET negative status.	<i>Hematol Oncol</i> 2015; 33(4): 187-191
Sasse 2013	Sasse S, Rothe A, Goergen H, et al. Brentuximab Vedotin (SGN-35) in patients with transplant-naïve relapsed/refractory Hodgkin Lymphoma.	<i>Leuk Lymphoma</i> 2013; 54 (10):2144–148.
Viviani 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 Conference: 20th Congress of the European Hematology Association Vienna Austria Conference Start: 20150611 Conference End: 20150614 Conference Publication: (var pagings) 2015; 100(pp 455-456): 22
Zinzani 2015	Zinzani PL, Pellegrini C, Cantonetti M et al. Brentuximab vedotin in transplant naïve relapsed/refractory Hodgkin lymphoma: experience in 30 patients.	<i>The Oncologist</i> 2015; 20 (12): 1413-1416.
C25007	Clinical study protocol C25007. A single-arm study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma who are not suitable for stem cell transplantation or multiagent chemotherapy.	Millennium Pharmaceuticals July 2013.
Salvage chemotherapy		
Oki 2008	Oki Y, Pro B, Fayad LE et al. Phase 2 study of gemcitabine in combination with rituximab in patients with recurrent or refractory Hodgkin lymphoma.	<i>Cancer</i> 2008; 112 (4): 831-836.
Santoro 2000	Santoro A, Bredenfeld H, Devizzi L et al. Gemcitabine in the treatment of refractory Hodgkin's disease: results of a multicenter phase II study.	<i>Journal of Clinical Oncology</i> 2000; 18 (13): 2615-2619.
Validire 2008	Validire P, Ferme C, Brice P et al. A multicentre study of gemcitabine-containing regimen in relapsed or refractory Hodgkin's lymphoma patients.	<i>Anti-Cancer Drugs</i> 2008; 18: 309-315
Venkatesh 2004	Venkatesh H, Di Bella N, Flynn TP et al. Results of a phase II multicenter trial of single-agent gemcitabine in patients with relapsed or chemotherapy-refractory Hodgkin's Lymphoma.	<i>Clinical Lymphoma</i> 2004; 5 (2): 110-115.

Study	Protocol title/ Publication title	Publication citation
Zinzani 2000	Zinzani PL, Bendandi M, Stefoni V et al. Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients.	Haematologica 2000; 85: 926-929.

Source: Table B.2.3, pp30-33 of the submission

ASCT = Autologous stem cell transplant; FDG = fludeoxyglucose; PET = positron emission tomography

- 6.6 The key features of the evidence used in the naïve comparison are summarised in Table 2.

Table 2: Key features of the included evidence – naïve comparison

Study	N	Design/ median follow-up or study period	Risk of bias	Patient population	Outcomes	Use in economic evaluation
Brentuximab vedotin						
Millennium Report 2012	59	Post-hoc case series, single-arm, MC, NR	High	R/R HL with no prior ASCT	ORR, CR, PR, patients proceeding to SCT	Subgroup (n=41)
Brocklemann 2016	136	Retro, observational, MC, 38.5 mths	High	R/R HL with no prior ASCT	PFS, OS, RR	Used
Zinzani 2015	30	Retro, observational, MC, 18 mths	High	R/R HL with no prior ASCT	PFS, OS, RR, patients proceeding to SCT	Used
Sasse 2013	14	Retro, observational, SC, NR	High	R/R HL with no prior ASCT	ORR, patients proceeding to SCT, PFS, OS	Used
Viviani 2015	45	Retro, observational, MC, 14 mths	High	R/R HL with no prior ASCT	Patients proceeding to SCT PFS, OS	Subgroup (n=20)
Onishi 2015	16	Retro, observational, MC, 17 mths	High	R/R HL with no prior ASCT	PFS, OS, RR, patients proceeding to SCT	Subgroup (n=15)
Gibb 2013	75	Retro, observational, SC, 13 mths	High	R/R HL with no prior ASCT	PFS, CR, PR, patients proceeding to SCT	Subgroup (n=12)
C25007	60	Prospective, single-arm, MC, NA	High	R/R HL with no prior ASCT	ORR, CR, PFS, OS, patients proceeding to SCT	n=56 ^a
Salvage chemotherapy						
Santoro 2000	23	Prospective, single-arm, MC, NR	High	R/R HL with no prior ASCT	PFS, OS, ORR	Used
Venkatesh 2004	29	Prospective, single-arm, MC, 12 mths	High	R/R HL with/without ASCT	RR, duration of response, time to progression	Subgroup (n=11)
Oki 2008	34	Prospective, single-arm, SC, NR	High	R/R HL with/without ASCT	ORR, failure-free survival, response duration	Subgroup (n=15)
Zinzani 2000	14	Prospective, single-arm, SC, NR	High	R/R HL with/without ASCT	RR	Subgroup (n=12)
Validire 2008	55	Retro, observational, MC, 14 mths	High	R/R HL with/without ASCT	OS, RR	Subgroup (n=21)

Source: compiled during evaluation

ASCT = autologous stem cell transplant; CR = complete response; HL = Hodgkin lymphoma; MC = multi-centre; mths = months; retro = retrospective; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PR = partial response; R/R = relapsed/refractory; RR = response rate; SC = single-centre; SCT = any stem cell transplant.

^a Ongoing study, results were provided during evaluation

- 6.7 The salvage chemotherapy reported in the included studies were gemcitabine-based regimens with single agent gemcitabine (Santoro 2000, Venkatesh 2004 and Zinzani 2000), gemcitabine alone or in combination with other chemotherapy (Validire 2008), and gemcitabine with rituximab (Oki 2008).

- 6.8 Clinical response comprising complete response, partial response, and overall response (complete or partial response) was the primary outcome, whereas survival, duration of response and toxicity were secondary outcomes.
- 6.9 The majority of the included studies used the International Working Group Criteria (Cheson 2007, Cheson 1999 and Cheson 1992) to assess clinical response; however, the older versions of the International Working Group Criteria (before Cheson 2007) were used in the salvage chemotherapy studies in the era before positron emission tomography (PET). PET scan results, as interpreted using the Deauville scores, were incorporated in the updated assessment criteria in Cheson 2007 which was used to assess response in brentuximab vedotin studies. PET scan, as described in Cheson 2007, is a more powerful imaging tool than the conventional computerised tomography (CT) that would eliminate the 'Complete Response Uncertain' category from the older response assessment criteria resulting in a higher reporting of clinical response. This would favour brentuximab vedotin. The ESC considered that these differences in techniques employed to measure clinical response made the comparative effectiveness data difficult to interpret. The sponsor's Pre-PBAC Response (p.3) argued that the differences in imaging techniques would have little impact on the patient relevant outcomes, i.e. rates of ORR (which captured both CR and PR), or the number of patients proceeding to ASCT. The PBAC considered that this was reasonable.

Comparative effectiveness

Benefits

- 6.10 Table 3 summarises the results for overall survival and progression free survival as reported in the included studies.

Table 3: Results of clinically relevant outcomes (OS and PFS) for the included studies

Study	Brentuximab vedotin				Salvage chemotherapy	
	Bröckelmann 2016	Sasse 2013	Viviani 2015	Study C25007	Santoro 2000	Oki 2008
N	125	14	20	56	23	15
Median follow-up, months	38.5 (10.4, 94.4) ^a	NR	14 (1,36)	NR	NR	NR
Median PFS, months (95%CI)	15.1 (8.9, 22.0)	9 (NR)	NR	5 (NR)	NR	2.3 (NR) ^b
Median OS, months (95%CI)	17.8 (13.7-33.5)	Not reached	Not reached	Not reached	10.7 (4-34.7)	NR
OS at 1 year, % (95% CI)	68.2% (59.2, 77.1)	69% (39-100)	NR	■% (■-■)	NR	NR
OS at 2 years, % (95% CI)	NR	NR	70%	■% (■-■)	NR	NR

Table B.6.5, p71 of the submission and the Addendum document Brentuximab vedotin_ASCT Naive_Addendum 1_Study C25007 results.docx

CI = confidence interval; NR = not reported; OS = overall survival; PFS = progression free survival

^a Hodgkin lymphoma diagnosis, not from start of brentuximab vedotin

^b Reported as failure-free survival

- 6.11 The submission noted that the median overall survival with brentuximab was 17.8 months in Bröckelmann 2016 study and 10.7 months with salvage chemotherapy in Santoro 2000. Median progression-free survival with brentuximab was 15 months in

the Bröckelmann 2016 study and 2.3 months with salvage chemotherapy in the subgroup of patients in Oki 2008.

- 6.12 The submission acknowledged the limitations in the available survival data and presented response as the key outcome to support the clinical claim.
- 6.13 Table 4 summarises the overall response rates (i.e. complete or partial response) for brentuximab vedotin and salvage chemotherapy studies.

Table 4: Overall response rates for brentuximab vedotin and salvage chemotherapy

	Brentuximab vedotin	Salvage chemotherapy	RR (95% CI)	RD (95% CI)	NNT (95% CI)
Millennium Report	22/41 (54%)	-	-	-	-
Bröckelmann (2016)	101/136 (74%)	-	-	-	-
Zinzani (2015)	12/30 (40%)	-	-	-	-
Sasse (2013)	10/14 (71%)	-	-	-	-
Viviani (2015)	15/20 (75%)	-	-	-	-
Onishi (2015)	NR	-	-	-	-
Gibb (2012)	7/12 (58%)	-	-	-	-
Study C25007 ^a	30/56 (54%)	-	-	-	-
Santoro (2000)	-	9/23 (39%)	-	-	-
Venkatesh (2004)	-	1/11 (9%)	-	-	-
Oki (2008)	-	5/15 (33%)	-	-	-
Zinzani (2000)	-	4/12 (33%)	-	-	-
Validire (2008)	-	5/21 (24%)	-	-	-
Naïve pooled comparison without Study C25007	167/253 (66.0%)	24/82 (29.3%)	2.3 (1.6,3.2)	36.7% (25.3, 48.2)	3 (2.0, 4.0)
Naïve pooled comparison including Study C25007	197/309 (63.8%)	24/82 (29.3%)	2.2 (1.5,3.1)	34.5% (23.3,45.7)	3 (2.0,4.0)

Source: Tables B.6.1, B.6.2 and B.6.3, pp67-68 of the submission and Response rate pooled analysis - Section B (C25007 update).xlsx

CI = confidence interval; NNT = number needed to treat; NR = not reported; RD = risk difference; RR = relative risk; **bold** = statistically significant

^a Study results (per independent review) provided during evaluation

- 6.14 Table 5 summarises the complete response rates for brentuximab vedotin and salvage chemotherapy studies.

Table 5: Complete response rates for brentuximab vedotin and salvage chemotherapy

	Brentuximab vedotin	Salvage chemotherapy	RR (95% CI)	RD (95% CI)	NNT (95% CI)
Millennium Report	9/41 (22%)	-	-	-	-
Bröckelmann (2016)	47/136 (35%)	-	-	-	-
Zinzani (2015)	9/30 (30%)	-	-	-	-
Sasse (2013)	5/14 (36%)	-	-	-	-
Viviani (2015)	8/20 (40%)	-	-	-	-
Onishi (2015)	8/15 (53%)	-	-	-	-
Gibb (2012)	2/12 (17%)	-	-	-	-
Study C25007 ^a	7/56 (13%)	-	-	-	-
Santoro (2000)	-	2/23 (9%)	-	-	-
Venkatesh (2004)	-	0/11 (0)	-	-	-
Oki (2008)	-	NR	-	-	-
Zinzani (2000)	-	1/12 (8%)	-	-	-
Validire (2008)	-	NR	-	-	-

	Brentuximab vedotin	Salvage chemotherapy	RR (95% CI)	RD (95% CI)	NNT (95% CI)
Naïve pooled comparison without Study C25007	88/268 (32.8%)	3/46 (6.5%)	5.03 (1.7, 15.2)	26.3% (17.2, 35.4)	4 (3.0, 6.0)
Naïve pooled comparison including Study C25007	95/324 (29.3%)	3/46 (6.5%)	4.5 (1.5, 13.6)	22.8% (14.1, 31.5)	5.95 (1.8, 19.6)

Source: Tables B.6.1, B.6.2 and B.6.3, pp67-68 of the submission and Response rate pooled analysis - Section B (C25007 update).xlsx

CI = confidence interval; NNT = number needed to treat; NR = not reported; RD = risk difference; RR = relative risk; **bold** = statistically significant

^a Study results (per independent review) provided during evaluation

- 6.15 Table 6 summarises the proportion of patients proceeding to stem cell transplant after treatment with brentuximab vedotin and salvage chemotherapy.

Table 6: Stem cell transplant outcomes for brentuximab vedotin and salvage chemotherapy

	Brentuximab vedotin	Salvage chemotherapy	RR (95% CI)	RD (95% CI)	NNT (95% CI)
Millennium Report	8/41 (19%)	-	-	-	-
Bröckelmann (2016)	NR	-	-	-	-
Zinzani (2015)	14/30 (47%)	-	-	-	-
Sasse (2013)	5/14 (36%)	-	-	-	-
Viviani (2015)	7/20 (35%)	-	-	-	-
Onishi (2015)	12/15 (80%)	-	-	-	-
Gibb (2012)	1/12 (8%)	-	-	-	-
Study C25007 ^a	28/49 (57%)				
Santoro (2000)	-	0	-	-	-
Venkatesh (2004)	-	NR	-	-	-
Oki (2008)	-	NR	-	-	-
Zinzani (2000)	-	NR	-	-	-
Validire (2008)	-	NR	-	-	-
Naïve pooled comparison without Study C25007	47/132 (35.6%)	-	-	-	-
Naïve pooled comparison including Study C25007	75/181 (41.4%)	-	-	-	-

Source: Tables B.6.1, B.6.2 and B.6.3, pp67-68 of the submission and Response rate pooled analysis - Section B (C25007 update).xlsx

CI = confidence interval; NNT = number needed to treat; NR = not reported; RD = risk difference; RR = relative risk

^a Study results (per independent review) provided during evaluation

- 6.16 It appeared that brentuximab vedotin had a substantial incremental improvement compared with salvage chemotherapy in overall response rate with a risk difference of 37% (95% confidence interval (CI): 25% to 48%) and complete response rate with a risk difference of 26% (95% (CI): 17% to 35%). Further, the criteria to assess clinical response varied across studies; the assessment of response in brentuximab vedotin studies incorporated PET scans which might result in an increase in the reported response rates compared with salvage chemotherapy studies, which used older response assessment criteria. The inclusion of the results from Study C25007 in the pooled analyses of brentuximab vedotin resulted in a slight reduction in both overall response rate (from 66% to 64%) and complete response rate (from 33% to 29%).
- 6.17 The PBAC had previously considered that brentuximab vedotin is not a cure, but could serve as a bridge to ASCT; therefore, a comparative assessment of how many

patients proceeded to have transplant is crucial (paragraph 7.5, March 2015 PBAC Public Summary Document (PSD)). The proportion of patients proceeding to stem cell transplant with brentuximab vedotin was 36% without Study C25007 and 41% after the inclusion of that study. ASCT rate was not reported in the majority of salvage chemotherapy studies, except in Santoro 2000 where none of the patients proceeded to stem cell transplant.

- 6.18 As acknowledged by the PSCR (p.2), the ESC noted the limited nature of the survival data. While the PSCR argued that clinical response was a measure of effectiveness in this context, the ESC maintained that clinical response was difficult to interpret given that the criteria to assess clinical response varied across studies (PET vs CT).

Comparative harms

Safety (harms)

- 6.19 Safety outcomes for brentuximab vedotin were available from the Millennium Report and other non-randomised studies, whereas, the only salvage chemotherapy study to report safety data in ASCT naïve patients was Santoro 2000.
- 6.20 Table 7 summarises the safety outcomes for brentuximab vedotin and salvage chemotherapy represented by gemcitabine single agent.

Table 7: Safety outcomes for brentuximab vedotin and salvage chemotherapy in the non-randomised studies

Study	Brentuximab vedotin		Salvage chemotherapy
	Millennium Report 2012	Onishi 2015	Santoro 2000 ^a
N		15	23
Alopecia	-	-	-
Allergic	-	-	-
Anaemia	1 (10%)	-	2 (10%) ^b
Cardiac function ¹	-	-	1 (5%)
Cutaneous	-	-	-
Diarrhoea	1 (10%)	-	-
Fatigue	1 (10%)	-	-
Fever	1 (10%)	-	0
Haemorrhage	-	-	1 (4%)
Infection	-	-	2 (9%)
Leukopenia	-	-	6 (30%) ^b
Nausea/vomiting	1 (10%)	-	2 (9%)
Neutropenia	1 (10%)	-	6 (30%) ^b
Pain	-	-	-
Peripheral neuropathy	1 (10%)	1 (7%)	-
Peripheral neurotoxicity	-	-	-
Pulmonary	-	-	1 (4%)
Thrombocytopenia	1 (10%)	-	4 (20%) ^b

Source: Tables B.6.6 and Table B.6.7, pp 74-75 in the submission

^a Gemcitabine single agent

^b Twenty assessable patients

- 6.21 The most common brentuximab vedotin related adverse events reported in non-randomised studies were neutropenia and peripheral neuropathy. The most

commonly reported adverse events for salvage chemotherapy were thrombocytopenia, anaemia and neutropenia. The safety of brentuximab vedotin and salvage chemotherapy could not be directly compared as there was no common comparator. Further, there were no details from Santoro 2000 on baseline characteristics and prognostic factors (e.g. disease stage).

Benefits/harms

- 6.22 A summary of the comparative benefits and harms from the naïve comparison of brentuximab vedotin versus salvage chemotherapy is presented in Table 8.

Table 8: Summary of naïve comparison of benefits for brentuximab vedotin and salvage chemotherapy

Outcome	BV ^a	SC	RR (95% CI)	Event rate/100 patients ^b		RD (95% CI)
				BV	SC	
Pooled ORR	197/309	24/82	2.2 (1.5,3.1)	63.8	29.3	0.35 (0.23,0.46)
Pooled CR	95/324	3/46	5.03 (1.7,15.2)	29.3	6.5	0.23 (0.14,0.32)
Pooled Proceed to SCT	75/181	NR	-	35.6	NR	-

Source: compiled during evaluation

BV = brentuximab vedotin; CI = confidence interval; CR = complete response; NR = not reported; ORR = overall response rate; RD = risk difference; RR = relative risk, SC = salvage chemotherapy; SCT = stem cell transplant; **bold** = statistically significant;

^a All brentuximab vedotin studies including Study C25007

^b Median follow-up ranged from 13 to 18 months for brentuximab vedotin and from 12 to 14 for salvage chemotherapy studies

- 6.23 The submission did not present comparative survival or comparative harm analysis
- 6.24 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.

Clinical claim

- 6.25 The submission 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:
- a naïve indirect comparison was presented using poor quality evidence with a high risk of bias. Further, the included studies on salvage chemotherapy had small sample sizes and limited event data reported;
 - there was high heterogeneity in patient characteristics and prognostic factors across the included studies and variation in the years in which patient data were collected. Further, data for some prognostic factors and confounders were not available particularly for the salvage chemotherapy studies;
 - limited data were available for overall survival and progression free survival. The majority of the data for efficacy was for the assessment of clinical response, which is important for subsequent patient management (e.g. suitability for stem cell transplant), but the value for clinical response in patients not eligible for stem cell transplant (e.g. due to age of comorbidities) was not sufficiently established; and
 - the criteria to assess clinical response varied across studies; the assessment of response in brentuximab vedotin incorporated PET scan findings which might result in an increase in the reported response rates compared with salvage chemotherapy studies where old imaging techniques were used.

- 6.26 The PSCR (p.2) acknowledged the low quality of the evidence presented especially for salvage chemotherapy, arguing that without controlled data or a common comparator, a naïve comparison was the only possible approach. However, the PSCR contended that the value of achieving a better clinical response with brentuximab vedotin is improved quality of life and survival for those patients in whom ASCT is not a subsequent treatment option, citing Study0003 (Chen 2015) which showed improved overall survival with complete and partial response compared with stable disease, as evidence. The ESC noted that Study0003 was on brentuximab vedotin in the post-ASCT population and not ASCT naïve patients. Further, the main clinical outcome in the post-ASCT submission was overall survival and not clinical response.
- 6.27 Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable, although the magnitude of benefit remained unclear from the data presented in the submission. The PBAC considered that the claim of non-inferior comparative safety was conservative. 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

- 6.28 The submission presented a cost-per-responder analysis based on the naïve comparison of non-randomised studies. The ESC noted that no formal assessment of the studies and their applicability to the Australian population was reported in the submission.
- 6.29 The submission estimated the incremental cost and incremental response for patients receiving brentuximab vedotin versus salvage chemotherapy using the following definitions of response:
1. Overall response rate: a complete or partial response to treatment
 2. Complete response rate: a complete response to treatment
 3. Proportion of patients progressing to stem cell transplant: receiving an allogenic or autologous transplant
- 6.30 The submission considered that the cost-per-responder analysis was in line with the primary aim of therapy of providing a bridge to a potentially curative stem cell transplant. This approach has the following limitations:
- the economic evaluation based on cost-per-responder analysis is unlikely to have captured all benefits and costs of brentuximab vedotin compared with salvage chemotherapy; and
 - not all patients are eligible for curative stem cell transplant due to age or comorbidities, the aim of treatment in this group is palliative to prolong survival and improve health-related quality of life.
- 6.31 Table 9 summarises the main elements of the economic evaluation

6.32 Table 9: Summary of the economic evaluation and rationale as per the submission

Time horizon	Treatment course with BV (4.57 cycles) or salvage chemotherapy (3.76 cycles)
Outcomes	ORR, RR, proportion progressing to SCT
Methods used to generate results	Pooled clinical response rates from the included studies (<i>without Study C25007</i>) compared with total treatment costs (drug, administration, monitoring and co-medications costs)
Cycle length	21 days for BV and 28 days for salvage chemotherapy
Discount rate	Not applied because treatment duration is less than one year
Software package	Excel 2010

Source: constructed during the evaluation

BV = brentuximab vedotin; ORR = overall response rate; RR = response rate; SCT = stem cell transplant

6.33 Table 10 presents the key drivers of the economic evaluation.

Table 10: Key drivers of the economic evaluation

Description	Method/Value	Impact
Response rate to brentuximab vedotin and salvage chemotherapy	Pooled response rates from the included studies were used in the naïve comparison. The response rates for salvage chemotherapy appeared to be underestimated due to: <ul style="list-style-type: none"> - the majority of salvage chemotherapy studies included gemcitabine single agent which might be less effective than chemotherapy combination. - clinical response was assessed using old criteria that did not incorporate PET scans; PET scans are more sensitive in detecting response than the old imaging methods used in salvage chemotherapy studies. 	High, favoured brentuximab vedotin
Number of cycles of brentuximab vedotin course	The submission calculated 4.57 cycles per course based on the number of treatment cycles of brentuximab vedotin in the clinical studies with patients of median age <60 years (i.e. excluding Bröckelmann 2016). This underestimated the number of cycles for brentuximab vedotin as when Bröckelmann 2016 was included the number of overall treatment cycles per course became 6.64. Further, including both Bröckelmann 2016 and Study C25007 would result in an overall 6.81 cycles per course.	High, favoured brentuximab vedotin

Source: compiled during the evaluation

PET = positron emission tomography

6.34 The PSCR (p.3) acknowledged that it would have been more appropriate to consider the overall treatment cycles (i.e. before and beyond response assessment) of brentuximab vedotin in the economic evaluation. The PSCR updated the overall number of brentuximab vedotin cycles (including study C25007 and Bröckelmann 2016) to be 6.81 cycles in the calculations of cost per responder. However, for the cost-per patient proceeding to ASCT, the PSCR argued that in the estimation of the number of brentuximab vedotin cycles, Bröckelmann 2016 should be excluded as 73.5% and 56.6% of patients in that study were not eligible for ASCT due to co-morbidities or advanced age, respectively. Thus, the number of cycles without Bröckelmann 2016 would be 5.93. The ESC considered that this was reasonable.

6.35 The PSCR presented a revised economic evaluation using an updated response rates and number of overall treatment cycles after including study C25007. Table 11 summarises the revised economic evaluation presented in the PSCR.

6.36 Table 11: Results of the revised economic evaluation in the PSCR compared with the results in the submission

Outcome	Analysis in the submission			Revised analysis in PSCR		
	BV	SC	Incremental	BV	SC	Incremental
Overall response rate						
Cost per cycle	\$ [redacted]	\$ [redacted]	-	\$ [redacted]	\$ [redacted]	-
Cycles per patient	4.57	3.76	-	6.81	3.76	-
Cost per patient	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Response rate	67.1%	29.3%	37.8%	64.6%	29.3%	35.3%
Cost-per-responder	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Complete response rate						
Cost per cycle	\$ [redacted]	\$ [redacted]	-	\$ [redacted]	\$ [redacted]	-
Cycles per patient	4.57	3.76	-	6.81	3.76	-
Cost per patient	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Response rate	33.7%	6.5%	27.2%	30.0%	6.5%	23.4%
Cost-per-responder	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Progression to any SCT						
Cost per cycle	\$ [redacted]	\$ [redacted]	-	\$ [redacted]	\$ [redacted]	-
Cycles per patient	5.16	3.76	-	5.93	3.76	-
Cost per patient	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Response rate	37.6%	0.0%	37.6%	43.1%	0.0%	43.1%
Cost-per-responder	\$ [redacted]	-	\$ [redacted]	\$ [redacted]	-	\$ [redacted]

Source: 2016-0921_PSCR_BV_revised ASCT Naive Cost Analysis_Takeda.xlsm and Section_D_brentuximab vedotin_ASCTNaive Section D_PBAC Nov2016.xlsm.

BV = brentuximab vedotin; PSCR = Pre-Sub-Committee Response; SC = salvage chemotherapy; SCT = stem cell transplant

The redacted table above shows that cost per responder for:

- Overall and complete response is more than \$200,000 per responder; and
- Progression to SCT is in the range of \$105,000 - \$200,000 per responder.

6.37 The ESC noted that the ICER increased due to lower response rate and longer duration of treatment (brentuximab vedotin cycles) in the revised analysis. Despite the increase in the number of brentuximab vedotin cycles, the ICER increased slightly for the proportion of patients proceeding to stem cell transplant, due to the increase in stem cell transplant rate with brentuximab vedotin from 37.6% to 43.1% with the inclusion of Study C25007.

6.38 The ESC considered that the submission underestimated the proportion of patients proceeding to ASCT with salvage chemotherapy (0%, based on the results of a single study Santoro 2000) as the remaining studies on salvage chemotherapy did not report this outcome. Assuming 0% rate of progression to ASCT transplant with salvage chemotherapy is unlikely given that 29.3% of patients in the pooled analysis achieved overall response which would make them eligible for ASCT if their age and performance status were suitable. Therefore, the ESC advised that the incremental cost per additional patient proceeding to ASCT is likely underestimated.

6.39 A revised price of \$ [redacted] / vial (formerly \$ [redacted] / vial, an approximate [redacted]% price reduction) was offered in the sponsor's Pre-PBAC response (p.1). Accounting for the changes to the economic evaluation presented in the PSCR and using the proposed revised price of \$ [redacted], the re-specified base case was \$105,000 - \$200,000 per responder in the group of patients likely to proceed to ASCT. The PBAC considered

that the cost per additional patient progressing to ASCT presented in the Pre-PBAC response remained inappropriately high and was not cost-effective.

- 6.40 The results of the sensitivity analyses indicated that the results of the economic evaluation were most sensitive to the number of treatment cycles and response rates.

Drug cost/patient/course: \$ [REDACTED]

- 6.41 The drug cost per patient per cycle was \$ [REDACTED] in the Private Hospital setting, and \$ [REDACTED] in the Public Hospital setting based on three vials per cycle and an AEMP of \$ [REDACTED] per vial (based on the revised price offered in the Pre-PBAC response). The public to private hospital ratio was assumed to be 32:68. The submission calculated an average of 4.57 cycles for the course of treatment with brentuximab.

Estimated PBS usage & financial implications

- 6.42 This submission was not considered by DUSC.
- 6.43 The submission 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.
- 6.44 Table 12 presents the estimated use and financial implications of listing brentuximab vedotin for the treatment of ASCT naïve Hodgkin lymphoma patients.

Table 12: Estimated use and financial implications of brentuximab vedotin

	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]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Tables E.2.1 to E.2.4, pp127-129 of the submission.

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

- 6.45 The submission estimated a total net cost of \$30 – 60 million to the PBS/RPBS and MBS over the first five years of listing. This was updated to \$30 - \$60 million during the evaluation. There was a potential for the net cost/year for the PBS to be greater or less than the estimate in the submission due to:
- Uncertainty in the number of patients eligible for brentuximab vedotin (i.e., refractory or relapsed who are ASCT naïve) due to uncertainty in the number of patients undergoing initial ASCT;
 - Underestimated number of brentuximab vedotin treatment cycles and associated total treatment cost; and
 - Overestimated savings from listing brentuximab vedotin due to overestimated

cost of salvage chemotherapy and concomitant medications.

- 6.46 PBS costs could be higher if brentuximab vedotin was used outside the proposed restriction in earlier lines of treatment (e.g. as first line salvage treatment) or post ASCT, if the concurrent submission for the post-ASCT population was not recommended for listing. While acknowledging the potential for brentuximab vedotin to be used outside the requested listing in patients with relapsed or refractory Hodgkin lymphoma following only one line of prior therapy, or post ASCT, the PSCR (p.4-5) emphasised that a written Authority for the initiation of brentuximab vedotin would restrict this scenario. The PSCR further noted that the post-ASCT restriction is also via a written Authority and this required the date of the ASCT to be provided, making utilisation of an ASCT naïve script for a post-ASCT patient extremely unlikely. The ESC considered that this was reasonable.

Financial Management – Risk Sharing Arrangements

- 6.47 A Risk-Sharing Arrangement was proposed including two subsidisation caps with rebates beyond each cap. Specifically, the first rebate of [REDACTED] between the first and second subsidisation cap was calculated by the sponsor to produce an effective price per vial of \$ [REDACTED].
- 6.48 Beyond the second subsidisation cap, a rebate of [REDACTED]% was calculated by the sponsor to align the price of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma who were ASCT naïve to the current price of ifosfamide, carboplatin and etoposide combination therapy for the treatment of patients with Systemic Anaplastic Large Cell Lymphoma (brentuximab vedotin's current PBS indication). This was intended to produce an effective vial price of \$ [REDACTED].

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

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 patients who were ASCT naïve. 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 providing a 'bridge to transplant', its tolerability and its benefits in improving quality of life in patients for whom ASCT was not a treatment option due to age and/or comorbidities.
- 7.3 The PBAC noted that the submission requested listing for brentuximab vedotin in two distinct ASCT naïve patient populations, in whom the goal of treatment is different;
- Palliative group - patients who are transplant-ineligible due to age or comorbidities (i.e. intent of treatment is palliative, potentially resulting in quality of life improvements), and

- Salvage group - patients who are not currently eligible for ASCT due to substantial disease burden, but for whom treatment with brentuximab vedotin may achieve minimal residual disease in order to proceed to ASCT.
- 7.4 The PBAC noted that although two submissions for brentuximab vedotin were considered at the November 2016 PBAC meeting, the possibility of patients 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 agreed with ESC that the data presented in the submission were of poor quality with a high risk of bias. The submission was based on naive comparisons using pooled estimates from non-randomised studies with small sample sizes and sparse event data.
- 7.7 The PBAC noted that there was high heterogeneity in patient characteristics and prognostic factors across the included studies, and variation in the years in which patient data were collected. Specifically, the criteria to assess clinical response varied across studies; while the assessment of response to brentuximab vedotin incorporated PET scan findings, older CT-based imaging techniques were used in the salvage chemotherapy studies. However, the PBAC considered that the argument in the Pre-PBAC Response (p.3) stating that the differences in imaging techniques would have little impact on the patient relevant outcomes, i.e. rates of ORR (which captured both CR and PR), or the number of patients proceeding to ASCT, was reasonable.
- 7.8 The PBAC considered that the clinical claim of superior efficacy over salvage chemotherapy was reasonable, although the nature of the comparison presented in the submission made it difficult to estimate the magnitude of benefit of brentuximab vedotin over salvage chemotherapy.
- 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 limited data were available for overall survival and progression free survival, and that the majority of the data for efficacy was for the assessment of clinical response and was mostly in the salvage patient group. The PBAC considered that data on survival and/or potential quality of life impacts of the palliative group of patients would have been useful in estimating the benefit of brentuximab vedotin in this population.
- 7.11 The PBAC considered that the intent of brentuximab vedotin therapy in the palliative group was similar to that of patients with relapsed disease post-ASCT (item 7.03, November 2016 PBAC meeting) from a clinical perspective. The data presented for this group (Brocklemann study) was also similar to that presented for the post-ASCT population (Study 003). Therefore, the PBAC considered that there was no reason to

treat these two populations differently in terms of treatment intent, number of cycles administered and cost of treatment. On this basis, the PBAC considered that it was reasonable to assume that the cost-effectiveness of treating the palliative care group would be consistent with the cost-effectiveness of treating the post-ASCT patients.

- 7.12 The PBAC noted that the Pre-PBAC Response (p.1) offered a revised price of \$█████ per vial (formerly \$█████ per vial), and considered that brentuximab vedotin was cost-effective in the palliative group of patients at this price, similar to the post ASCT group of patients, November 2016 PBAC meeting), where the ICER was in the range of \$45,000 to \$75,000/QALY.
- 7.13 The PBAC noted that accounting for the changes to the economic evaluation presented in the PSCR and using the proposed revised price of \$█████, the re-specified base case was \$105,000 - \$200,000 per additional patient proceeding to ASCT, i.e. the salvage group of patients. The PBAC considered that this was unacceptably high and had a high degree of uncertainty, and a price reduction of approximately ███% would be appropriate to achieve cost-effectiveness in this group of patients. Furthermore, the PBAC considered that the maximum number of treatment cycles in the salvage population should be capped at 4 cycles. This was supported by evidence presented in the submission (average number of cycles per course was calculated to be 4.57) and in the sponsor hearing for this item.
- 7.14 Given that it is not always possible to identify patients who will be salvage patients (compared to palliative) at treatment initiation, the PBAC considered that the overall price should be weighted to reflect the requirement for a lower price to achieve cost-effectiveness in the salvage population. The PBAC noted that the information in the submission did not provide a strong basis for determining the proportional split between the salvage and palliative groups and therefore proposed a 50/50 split of patients across the two populations. The same 50/50 split should also be applied to the subsidisation caps in terms of the maximum number of treatment cycles.
- 7.15 The PBAC noted that the sponsor had proposed a Risk-Share Arrangement with two subsidisation caps, and advised that the caps should be reduced to reflect:
- the revised price per vial, weighted 50/50 across the price presented in the Pre-PBAC response for the palliative population and the PBAC's recommended price reduction of ███% to achieve cost-effectiveness in the salvage population
 - and the PBAC's recommendation of a maximum of 4 treatment cycles in the salvage and 16 in the palliative populations.
- 7.16 The PBAC considered that there was some uncertainty in utilisation numbers particularly in the light of patients potentially accessing brentuximab vedotin in more than one line of therapy, and noted the sponsor's willingness to negotiate with the Department on the proposed Risk-Share Arrangement. However, the Committee noted that the per vial cost of brentuximab beyond each Cap as presented in the submission would need to be further reduced, in order to appropriately manage these uncertainties for the Commonwealth.
- 7.17 The PBAC recommended that brentuximab vedotin should not be treated as interchangeable with any other drugs.

- 7.18 The PBAC advised that brentuximab vedotin was not suitable for prescribing by nurse practitioners.
- 7.19 The PBAC noted that the Early Supply Rule does not currently apply to Section 100 (Efficient Funding of Chemotherapy) listings.
- 7.20 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	No. 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:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Relapsed or Refractory
Condition:	Hodgkin lymphoma
PBS Indication:	Relapsed or Refractory Hodgkin lymphoma
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

<p>Clinical criteria:</p>	<p>Patient must have never undergone an autologous stem cell transplant (ASCT) for this condition AND Patient must be unsuitable for ASCT for this condition; OR Patient must be unsuitable for treatment with multi-agent chemotherapy for this condition AND Patient must have experienced a relapsed CD30+ Hodgkin lymphoma following at least two prior therapies for this condition; OR Patient must have experienced a refractory CD30+ Hodgkin lymphoma following at least two prior therapies for this condition AND Patient must not receive more than 4 cycles of treatment under this restriction</p>
<p>Prescriber Instructions</p>	<p>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:</p> <ol style="list-style-type: none"> I. A histology report including evidence of the tumour's CD30 positivity from a biopsy at time of diagnosis; II. The date of diagnosis of Hodgkin lymphoma; III. Dates of commencement and completion of front-line curative intent chemotherapy and all lines of subsequent salvage chemotherapy; IV. A declaration of whether the disease is classified as relapsed or refractory subsequent to the most recently delivered prior therapy V. A declaration that the patient is unsuitable for ASCT
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p>

Name, Restriction, Manner of administration and form	Max. Amount	No. 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:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Relapsed or Refractory
Condition:	Hodgkin lymphoma
PBS Indication:	Relapsed or Refractory Hodgkin lymphoma
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition. AND Patient must 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 who are ASCT naïve. Takeda Australia also acknowledges and thanks the clinical community and the patients / carers who contributed to this outcome via their input to the PBAC.