6.02 Brentuximab vedotin
Powder for I.V. infusion 50 mg, Adcetris®, Takeda Pharmaceuticals Australia Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy) listing for brentuximab vedotin for the treatment of relapsed or refractory CD30 positive cutaneous T-cell lymphoma (CTCL) in patients who have previously used systemic therapy. This was the first brentuximab vedotin submission for this indication.

1.2 The requested listing was based on cost-effectiveness analyses and a cost-utility analysis comparing brentuximab vedotin to its main comparator, vorinostat, and to its supplementary comparator, methotrexate.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Relapsed or refractory CD30+ cutaneous T-cell lymphoma (CTCL)
Intervention	Brentuximab vedotin
Comparator	Vorinostat (primary comparator). Methotrexate (supplementary comparator)
Outcomes	Objective response rate, ORR4, complete response, progression-free survival and adverse events
Clinical claim	In patients with relapsed or refractory CD30+CTCL, brentuximab vedotin is more effective than vorinostat or methotrexate at improving clinical response (higher objective response rate) and has a longer progression-free survival. Brentuximab vedotin has a different, non-inferior safety profile to both vorinostat and methotrexate that is considered tolerable and manageable.

Source: 1.1-1, p21 of the submission
CTCL = cutaneous T-cell lymphoma; ORR4 = objective global response lasting 4 months

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Amt.	№.of Rpts	Dispensed Price Max. Amt.	Proprietary Name and Manufacturer
BRENTUXIMAB VEDOTIN 50 mg injection, 1vial	200 mg	Initial: 3 Continuing: 11	Effective Private $[redacted] Public $[redacted] Published Private $21,427.47 Public $ 21,283.83	Adcetris Takeda Pharmaceuticals Australia Pty Ltd

Category/Program:	Section 100 – Efficient Funding for Chemotherapy
PBS indication:	CD30 positive cutaneous T-cell lymphoma
Treatment phase:	Initial and continuing
Restriction:	Authority Required (In Writing – Initial) (Telephone – Continuing)

Clinical criteria:	Initial: Patient must have histologically confirmed CD30 positive disease, AND Patient must have had prior systemic treatment, AND Patient must demonstrate relapsed or refractory disease, AND Patient must not receive more than 4 cycles of treatment under this restriction. Continuing: 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 for this condition, AND Patient must not receive more than 12 cycles of treatment under this restriction.
Prescriber Instructions:	Initial: Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed cutaneous T-cell lymphoma (CTCL) brentuximab vedotin PBS Authority Application Continuing: The treatment must not exceed a lifetime total of 16 cycles.

2.1 The submission requested a special pricing arrangement (SPA) where the current published ex-manufacturer price of $5,300 per vial is maintained, resulting in published dispensed prices for maximum amount of $21,283.83 (public) and $21,427.47 (private). The proposed effective approved ex-manufacturer price (AEMP) is $[redacted] per vial. The pre-PBAC response offered a [redacted]% price reduction on the proposed price of $[redacted] for the MF, SS and pcALCL subtypes, while for the LyP subtype a price consistent with the current ASCT naive RR HL indication was proposed (i.e. $[redacted]). The pre-PBAC response stated that, assuming a proportional split of MF [redacted]%, SS [redacted]%, pcALCL [redacted]% and LyP [redacted]%, the price reduction resulted in a weighted average price of $[redacted] per vial.

2.2 The proposed restriction was consistent with the TGA indication.

2.3 Consistent with the current PBS listings of brentuximab vedotin the proposed listing did not include an explicit definition of CD30 positivity. The definition and reporting of CD30 status may be inconsistent across Australian pathology practice. The key ALCANZA trial only recruited patients whose biopsy had 10% or more target cells with CD30 staining. The Pre-Sub-Committee Response (PSCR) highlighted that in the ALCANZA trial, response to brentuximab vedotin was seen across a range of baseline CD30 expression from 3% to 100% and there was no correlation between CD30 expression and objective global response lasting 4 months (ORR4). The PSCR supported a CTCL authority application requiring provision of a histology report showing evidence of CD30 positivity as per the current brentuximab vedotin authority application for systemic anaplastic large cell lymphoma (sALCL) if required.

The PBAC considered that the proposed restriction should include a requirement for the provision of a histology report showing evidence of CD30 positivity. The PBAC noted that no explicit definition of CD30 positivity in CTCL was included in the restriction and considered that a clear definition was desirable to minimise the potential for inconsistency across Australian pathology practice to reduce access that is not cost-effective.

2.4 The PBAC considered that the listing for continuing treatment should include a requirement for the patient to have achieved a response to therapy. The PBAC considered that further advice is required on how response assessment can be pragmatically included as part of a restriction that is amenable to use in clinical practice.

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

3 Background

Registration status

3.1 The submission was lodged under the TGA/PBAC Parallel Process. On 23 May 2018 the delegate's overview and approval of registration of brentuximab vedotin in the new indication for CTCL was received. The registered indications are now:

- Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
- Treatment of adult patients with CD30+ HL at higher risk of relapse or progression following ASCT; and
- Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).
- Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

Previous PBAC consideration

3.2 This is the first submission to PBAC requesting listing of brentuximab vedotin for the treatment of relapsed or refractory CD30 positive CTCL.

3.3 Vorinostat was listed on the PBS on 1 July 2017 for the treatment of CTCL that was relapsed or refractory after systemic treatment with chemotherapy. The March 2017 PBAC recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of vorinostat would be acceptable (paragraph 5.2, March 2017 Public Summary Document (PSD)). The cost effectiveness analysis that was considered at the March 2017 PBAC meeting was a cost per responder

analysis, in which response was defined as a ≥ 25% decrease in the modified Severity-Weighted Assessment Tool (mSWAT).

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

4 Population and disease

4.1 CTCLs are a group of non-Hodgkin lymphomas (NHLs) in which malignant T-cell clones accumulate in the skin. The symptoms and prognosis of CTCL are highly varied and depend on the subtype and stage of disease. CTCL may cause skin lesions, tumours, pruritus and erythroderma and may affect the blood and visceral organs. Patients with advanced disease may have extensive skin disease that is disfiguring. The ESC acknowledged that there is a need for additional/alternative therapies for patients with advanced CTCL who have failed prior systemic therapies but also considered that with vorinostat listed, the unmet need addressed by brentuximab vedotin is somewhat reduced. The pre-PBAC response disputed that the unmet need is reduced, citing clinician feedback that current treatments are characterised by low response rates and short durations of response. The PBAC agreed with the ESC that vorinostat has provided an additional treatment option for patients with CTCL and also agreed with the sponsor that there remains a substantial unmet clinical need for effective treatments that provide a lasting response for these patients. The PBAC noted the impact of pruritus, chronic inflammation and ulceration and frequent infections on quality of life for patients with CTCL.

4.2 Mycosis fungoides (MF) is the most common form of CTCL. It results in plaques and patches on the skin, in addition to lesions and tumours in the more advanced stages. Patients diagnosed with advanced stage disease (stages IIB, III and IVA) or visceral involvement (other organs affected, stage IVB) have median overall survivals (OS) of five years and 2.5 years, respectively. Sézary syndrome (SS) is a leukemic form of CTCL that affects the blood and causes erythroderma. It has a poor prognosis with a median OS of five years. The PBAC noted that in a large cohort study of MF and SS patients with clinical stage IIB or higher disease[1] only 23% had CD30 positivity of more than 10%. Hence, the PBAC considered only a minority of stage IIB - IVB patients would have been eligible for the ALCANZA trial. The PBAC considered that this was a major issue when considering how to perform fair comparisons with alternative therapies which have not been evaluated in CTCL selected on the basis of CD30 positivity, and also when considering the restriction and any measures required to address the potential for use outside of the restriction.

4.3 Primary cutaneous anaplastic large cell lymphoma (pcALCL) is an indolent lymphoma that causes raised red skin lesions, nodules or tumours. Ten-year survival with

[1] Scarisbrick et al J Clin Oncol 2015; 33: 3766–3773

pcALCL is approximately 77% (Liu (2003)). The ESC considered that, although it is a cancer, pcALCL generally doesn't require systemic therapy. Lymphomatoid papulosis (LyP) is a benign, chronic skin condition that causes skin lesions that can self-resolve. It does not affect life expectancy (Liu (2003)). LyP is not consistently considered to be a cancer. The PSCR noted that although LyP is not considered to be as severe as other CD30 positive CTCL subtypes and survival is unaffected, patients with LyP require treatment as they are at risk for second cutaneous or nodal lymphoid malignancies, including MF, pcALCL, and Hodgkin lymphoma (HL) (Willemze et al, 2005; Prince et al, 2016). However, the ESC noted the submission did not present evidence suggesting that brentuximab vedotin treatment would affect the likelihood of developing a LyP-associated malignancy. The ESC considered that given the potential toxicity of brentuximab vedotin it may not be appropriate to use in patients with LyP. The pre-PBAC response noted that the Australian Cutaneous Lymphoma Network (ACLN) database showed [redacted] of patients with a confirmed CD30 positive LyP diagnosis were repeatedly treated with various systemic therapies, and argued this suggests that a proportion of these patients do require systemic treatment.

4.4 Early stage CTCL is managed using skin-directed therapies. This includes topical corticosteroids, phototherapy and total skin electron beam (TSEB) therapy. Systemic therapy is used by patients who do not respond to, or are refractory to, initial skin-directed therapies. Systemic therapies include low dose methotrexate, interferon-alpha, retinoids, histone deacetylase (HDAC) inhibitors, chemotherapy and extracorporeal photopheresis (ECP), where available. Radiotherapy is also used for pcALCL. For LyP, methotrexate may be used chronically or episodically (Newland (2015)). The PBAC noted that there is no clearly defined standard of care for CTCL. The approach to treatment is based on CTCL subtype, disease severity and prior treatments. Previously used therapies may be re-used for subsequent lines of therapy.

4.5 The submission proposed that brentuximab vedotin would be used after first-line systemic therapy and will displace current treatment options, such as vorinostat. The clinical management algorithm appropriately reflected the use of several sequential lines of systemic therapy.

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

5 Comparator

5.1 The submission nominated vorinostat as the main comparator. The ESC considered this to be appropriate for the MF and SS subtypes of CTCL. However, it may not have been appropriate for the pcALCL and LyP subtypes as the clinical evidence presented for vorinostat was based on the treatment of MF and SS only. It was unclear whether vorinostat is used to treat pcALCL and LyP in Australian clinical practice, although the

ESC noted that the vorinostat PBS listing also allows use in patients with pcALCL and LyP. The pre-PBAC response argued that there is evidence of a benefit in these patients, though it is from a limited evidence base, and that the decision to use a specific treatment for a CTCL sub-type should be for the specialist clinicians who manage these patients. The PBAC considered that the evidence for brentuximab vedotin in MF and SS should form the basis for decision-making as evidence in pcALCL and LyP is limited. However, the PBAC considered the use of vorinostat as a comparator in this submission was limited by the fact that, unlike brentuximab vedotin, its use was not restricted to CD30 positive CTCL.

5.2 The submission nominated low dose methotrexate as a supplementary comparator. The evaluators considered a basket of comparators may have been more appropriate. Data from the ACLN database, from 2010 to prior to the July 2017 PBS-listing of vorinostat, demonstrated that TSEB was the most commonly used second line therapy ([redacted]%), followed by methotrexate ([redacted]%) and interferon ([redacted]%). The PSCR argued that psoralen plus ultraviolet A radiation (PUVA) and TSEB are not considered systemic treatments based on the sponsor's advisory board minutes. However, the ESC noted that TSEB was commonly used as a second line treatment after first line systemic therapy. This makes TSEB a potential comparator, irrespective of its classification as a systemic or topical therapy. The ESC considered that methotrexate is not standard of care for relapsed or refractory CTCL, and agreed with the evaluation that a basket of therapies would be an appropriate comparator, particularly for pcALCL and LyP subtypes. The pre-PBAC response disagreed that methotrexate is not standard of care, arguing that methotrexate is used extensively in multiple lines of treatment, particularly in patients with advanced stage disease.

5.3 The PBAC noted that there was no defined standard of care for relapsed or refractory CTCL. As such, the PBAC considered that the use of a basket of therapies as a supplementary comparator had significant limitations as the relative weighting of each therapy would carry substantial uncertainty. In addition, the PBAC considered that such a comparison would also be limited by the fact that, unlike brentuximab vedotin, the use of these therapies is not restricted to CD30 positive CTCL. The PBAC noted that the best comparative evidence available in this submission is for patients treated with methotrexate, which is one of the standard therapies in Australia for this rare condition.

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. The clinician presented clinical case studies and discussed the natural history of the disease, how brentuximab vedotin

would be used in practice, 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 treating this uncommon disease. The PBAC also considered it provided additional information, not all readily verifiable, regarding the proportion of patients with CD30 positive disease, the treatment implications of levels of CD30 positivity and the CD30 status of patients with CTCL.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (8), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with brentuximab vedotin including the ability to return to normal daily activities, relief from rash, constant itch, peeling skin, frequent skin and ear infections, total body hair loss, hand nail deterioration and loss. Individuals noted the limited treatment options for patients with CTCL and the expense associated with brentuximab treatment currently. Patients noted a willingness to endure potential side effects associated with treatment as they valued the benefits provided by the treatment.

6.3 The PBAC noted the support for brentuximab vedotin from Rare Cancers Australia, stating that brentuximab vedotin would be of benefit to patients as an additional treatment option to vorinostat. The PBAC specifically noted the information provided regarding the patient experience of CTCL, particularly the physical impact on the skin of the disease and the side effects of the older chemotherapy and radiation treatments.

Clinical trials

6.4 The submission's primary comparison was a naïve comparison of the brentuximab vedotin arm of the Phase III, open-label ALCANZA randomised controlled trial (RCT) (n=131) with the vorinostat arm of the Phase III, open-label MAVORIC RCT (n=372). The submission also presented two single-arm studies of brentuximab vedotin: Duvic (2015) (N=48) and Kim (2015) (N=32); and two single-arm studies of vorinostat: P001 (n=74) and P005 (n=33). Studies P001 and P005 were the basis of November 2016 vorinostat submission (paragraph 6.7 November 2016 PSD).

6.5 The submission's supplementary comparison with methotrexate was based on one head-to-head randomised trial (ALCANZA) that compared brentuximab vedotin with methotrexate or bexarotene (physician's choice) (N = 131).The submission compared the brentuximab vedotin arm of the study with the methotrexate subgroup of the physician's choice arm (n = 26). An additional single-arm, retrospective, Australian study (Newland 2015) of methotrexate in the CTCL subtype LyP was included during the evaluation. This was because the submission did not include evidence comparing brentuximab vedotin to either of the comparators in LyP patients and as an

Australian study, it was considered reflective of Australian treatment practices. The PSCR contended that Newland (2015) should not be relied upon as a base from which to draw effectiveness and safety conclusions as it was a 'letter to the editor' and lacked detail on outcome assessment, survival and duration of response data. The ESC considered that although there are limitations to the Newland study it was unreasonable to exclude as it added to the limited evidence available on the use of methotrexate in patients with LyP. The PBAC agreed with the ESC that it was unreasonable to exclude Newland (2015) but also considered that this study was of limited relevance to the submission overall given the indolent nature of LyP, the common watch & wait approach used in its management, and the ability to use other therapies such as topical steroids or oral retinoids in patients with this subtype of CTCL.

6.6 Details of the studies presented in the submission and included during the evaluation are provided in the table below.

Table 2: Trials and associated reports presented in the submission and included during the evaluation

Trial ID	Protocol title/Publication title	Publication citation
Brentuximab vedotin randomised trial		
ALCANZA	A randomised, open-label, phase 3 Trial of brentuximab vedotin (SGN-35) versus physician's choice (methotrexate or bexarotene) in patients with CD30-positive cutaneous T-cell lymphoma.	CSR (February 2017)
	Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial.	The Lancet 2017; 390(10094):555-66
Brentuximab vedotin: non-randomised studies		
Duvic (2015)	Duvic M, Tetzlaff MT, Gangar P, et al. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis.	J Clin Oncol. 2015; 33(32):3759-65
	Lewis DJ, Talpur R, Huen AO, et al. Brentuximab Vedotin for Patients With Refractory Lymphomatoid Papulosis: An Analysis of Phase 2 Results.	JAMA Dermatology 2017; 153(12):1302-1306
Kim (2015)	Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: A multi-institution collaborative project.	J Clin Oncol. 2015 Nov 10;33(32):3750-8
Vorinostat randomised trial		
MAVORIC	Kim YH, Bagot M, Pinter-Brown L, et al. Anti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients with Previously Treated Cutaneous T-Cell Lymphoma (CTCL): Results from the Phase III MAVORIC Study (abstract)	American Society of Hematology conference
Vorinostat non-randomised studies		
P001	Olsen EA, Kim YH, Kuzel TM, et al. Phase IIB multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous t-cell lymphoma.	J Clin Oncol. 2007; 25(21):3109-15
	Duvic M, Olsen E, Breneman D, Pacheco T, Parker S, Vonderheid E, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma.	Clinical Lymphoma and Myeloma 2009; 9(6):412-6.
P005	Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL).	Blood 2007; 109(1):31-9.
Methotrexate non-randomised study		
Newland (2015)	Newland KM, McCormack CJ, Twigger R, et al. The efficacy of methotrexate for lymphomatoid papulosis.	J Am Acad Dermatol. 2015 Jun;72(6):1088-90.

Source: Table 2.2-1, p59 of the submission

6.7 The key features of the included evidence are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Brentuximab vedotin vs. vorinostat						
ALCANZA (brentuximab)	131	R, OL 22.9 months [a]	High	CD30 + MF or pcALCL ≥ 1 prior therapy [b]	ORR, ORR4, CR, PR, PFS, mSWAT, EQ-5D-3L, AEs	PFS, EQ-5D-3L
Duvic (2015) (brentuximab)	48	Single-arm, OL 27 months [a]	High	CD30+ MF, pcALCL or LyP [c] ≥ 1 prior therapy	ORR, CR, PR, PFS, mSWAT, AEs	Not used
Kim (2015) (brentuximab)	32	Single-arm, OL 71.7 weeks [a]	High	MF or SS ≥ 1 prior therapy	ORR, CR, PR, mSWAT, PFS , AEs	Not used
MAVORIC (vorinostat)	372	R, OL ≈ 7.7 months [d]	High	MF or SS ≥ 1 prior therapy	ORR, PFS, AEs	PFS
P001 (vorinostat)	74	Single-arm, OL 14.7 months	High	MF or SS ≥ 2 prior therapies	ORR, CR, PR, mSWAT, AEs	Not used
P005 (vorinostat)	33	OL 40 months	High	CTCL Refractory to tx	ORR, CR, PR, TTP, AEs	TTP
Brentuximab vedotin vs. methotrexate						
ALCANZA	131	R, OL 22.9 months [a]	High	CD30 + MF or pcALCL ≥ 1 prior therapy	ORR, ORR4, CR, PR, PFS, AEs	PFS
Newland (2015)	53	Single-arm, OL, Retro Duration not stated	High	LyP MTX or topical tx	ORR, CR, PR	Not used

Source: Tables 2.2-1 to 2.6-2, pp59 – 127 of the submission and compiled during evaluation

AE = adverse event; CR = complete response; CTCL = cutaneous T-cell lymphoma; EQ-5D-3L = euroQol-5 dimension-3 levels; LyP = lymphomatoid papulosis; MF = mycosis fungoides; mSWAT = modified severity weighted assessment tool; MTX = methotrexate; ORR = objective response rate; ORR4 = objective global response lasting 4 months; PFS = progression-free survival; OL=open label; pcALCL = primary cutaneous anaplastic large cell lymphoma; PFS=progression-free survival; SS = Sézary syndrome; R=randomised; retro = retrospective; TTP = time to progression; tx = treatments

Source: Table 2.4-5, p81;

[a] Median follow-up

[b] Systemic therapy for MF, systemic therapy or radiotherapy for pcALCL

[c] Systemic therapy for MF and pcALCL. For LyP, more than 10 lesions, scarring, or active lesions on the face, hands, or feet requiring systemic treatment

[d] Median follow-up not reported in abstract publication. Median PFS for vorinostat was 7.7 months.

6.8 The main comparison in the submission (brentuximab vedotin vs. vorinostat) was considered by the ESC to have a high risk of bias because it was based on a naïve comparison of studies with poor transitivity that may have confounded the observed clinical outcomes. The transitivity issues included: more patients with the more severe subtypes of CTCL in the vorinostat studies compared to the brentuximab vedotin studies (more patients with SS, no patients with pcALCL or LyP); differences in CTCL stage; potential differences in treatment practices due to studies being conducted over 12 years apart; and differences in the use of prior therapies, performance status, age, and CD30 positivity. The PBAC agreed with the ESC and considered that differences in CD30 positivity between patients included in the trials was a major transitivity issue because the efficacy of vorinostat in a CD30 positive subset of CTCL, especially MF, is unknown.

6.9 The key studies for brentuximab vedotin (ALCANZA trial, Duvic (2015), Kim (2015)) and vorinostat (MAVORIC trial) assessed response outcomes and PFS in accordance with the International Society for Cutaneous Lymphomas (ISCL), the US Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) 2011 consensus guidelines (ISCL/EORTC CTCL guidelines for brevity). These studies, excluding the MAVORIC trial, also used the mSWAT to assess skin disease. Study P001 (vorinostat) used mSWAT to assess skin response and appeared consistent with the ISCL/EORTC CTCL guidelines for skin response. Response outcomes from Study P005 (vorinostat) were not fully comparable with the other studies because P005 used Physician's Global Assessment rather than mSWAT. In P005, response was defined as a 50% or greater clearance of skin surface area or erythroderma skin score and reduction in lymph or blood disease. The PSCR considered that comparison of the ALCANZA trial (brentuximab vedotin) with the MAVORIC trial (vorinostat) would address some of the transitivity issues, such as differences in outcome assessments because both trials assessed outcomes in accordance with the 2011 ISCL/EORTC CTCL guidelines (Olsen et al 2011). The ESC considered that mSWAT is also an appropriate measure of efficacy as adopted previously by PBAC. The committee considered that mSWAT may give a better indication of skin involvement and better reflect patient quality of life and the requirement for hospitalisation. The pre-PBAC response argued that mSWAT is a subjectively assessed measure whose use has now been replaced with the ISCL system. The PBAC considered that mSWAT may be less relevant for patients with more severe CTCL, who are the group with greatest clinical need. The PBAC considered that it was appropriate to take into account all outcomes that were common across the included studies.

6.10 The submission's supplementary comparison (brentuximab vedotin vs. methotrexate) was based on a subgroup analysis of the open-label ALCANZA trial. The comparison was considered by the ESC to have a high risk of bias because selection of physician's choice treatment (methotrexate or bexarotene), and assessment of skin response (mSWAT) were performed by an unblinded investigator. The PSCR contended that Newland (2015) also had a high risk of bias – likely in favour of methotrexate. The PSCR noted that patients in Newland (2015) were younger at diagnosis (median age 39 years for treated and untreated patients) compared with [redacted] years for the ACLN database patients. The ESC noted that no reliable data are available for methotrexate in CTCL. The PBAC agreed with the sponsor that there may be bias in favour of methotrexate in Newland (2015) and with the ESC that overall data on methotrexate is suboptimal in robustness. However, the PBAC noted the ALCANZA trial did provide data on the efficacy of methotrexate, although underpowered, in a CD30 positive subset of CTCL.

Comparative effectiveness

6.11 The key effectiveness outcomes were response, either objective response rate (ORR) or ≥ 25% improvement in mSWAT, and PFS. A ≥ 25% improvement in mSWAT was the basis of the vorinostat cost per responder analysis considered by the PBAC in March 2017 (paragraph 4.5, March 2017 PSD).

Brentuximab vedotin vs. vorinostat

Table 4: Results of response outcomes (brentuximab vedotin vs. vorinostat naïve comparison)

Outcome	Brentuximab vedotin			Vorinostat			
	ALCANZA	Duvic (2015)	Kim (2015)	MAVORIC	P001	P005 (all patients)	P005 (PI dose)
ORR	43/64 (67%) [a] (95% CI: [redacted], [redacted])	35/48 (73%) [b]	21/30 (70%) [b]	9/186 (4.8%) [a]	22/74 (30%) (95% CI: 20, 42)	8/33 (24%) [b,c] (95% CI: 11, 42)	4/13 (31%) [b,c] (95% CI: 9, 61)
CR	10/64 (16%) [a] (95% CI: [redacted], [redacted])	17/48 (35%) [b]	1/30 (3%) [b]	NR	1/74 (1%) [b,c]	0/33 (0%) [b,c]	0/13 (0%) [b,c]
PR	[redacted]/[redacted] ([redacted]%) [a] (95% CI: [redacted], [redacted])	18/48 (38%) [b]	20/30 (67%) [b]	NR	21/74 (28%) [b,c]	8/33 (24%) [b,c] (95% CI: 11, 42)	4/13 (31%) [b,c] (95% CI: 9, 61)
≥ 25% mSWAT decrease [d]	[redacted]% [b]	NR	NR	NR	49% [d]		NR

Source: Table 2-6-1, p126 of the submission

CI = confidence interval; CR = complete response; EORTC = European Organisation for Research and Treatment of Cancer; ISCL = International Society for Cutaneous Lymphomas; n = number of participants with event; N = total participants in group; ORR = objective response rate; PR = partial response; PSD = public summary document

[a] IRF assessment

[b] Investigator assessment

[c] Response not assessed according to 2011 ISCL/EORTC definitions

[d] Outcome used in the March 2017 vorinostat consideration when it was recommended for listing (Vorinostat PSD March 2017)

6.12 The ORR in the brentuximab vedotin studies ranged from 67% to 73%. The ESC noted this was higher than the ORR in vorinostat studies, which ranged from 4.8% to 31%. The vorinostat ORR in the MAVORIC trial was substantially lower than the ORR in studies P001 and P005. P001 and P005 were the basis of the March 2017 PBAC recommendation for vorinostat listing on the PBS. The submission inferred that the lower ORR in the MAVORIC study was due to the "more stringent" 2011 ISCL/EORTC guideline definitions of response. However, this did not fully explain the difference in response rates. The MAVORIC trial reported that 15.6% of patients had a skin response, higher than the ORR of 4.8%. Study P001 did not appear to assess lymph nodes, blood or visceral disease. This suggested that assessment of lymph nodes, blood and visceral disease may have detected a lack of global response. The PBAC considered that the difference in response rates is likely to be due to the different mix of subtypes and disease stages included in the studies. However, the PBAC also considered the disparity observed may be due to differences in response rates between CD30 positive and CD30 negative CTCL patients.

6.13 Table 5 presents the results of PFS for the brentuximab vedotin and vorinostat studies.

Table 5: Results of PFS across the studies (brentuximab vedotin vs. vorinostat)

Outcome	Brentuximab vedotin				Vorinostat	
	ALCANZA (IRF)[a]	ALCANZA (Investigator)[b]	Duvic (2015)[b]	Kim (2015)	MAVORIC (Investigator)	MAVORIC (IRF)
N	64	64	48	30	186	186
Median follow-up	17.5 months	20.6 months	23-27 months [c]	16.5 months [d]	NR	NR
Patients with events Progression Death	36/64 (56%) 30/64 (47%) 6/64 (9%)	40/64 (63%) 35/64 (55%) 5/64 (8%)	NR	NR	NR	NR
Censored	28/64 (44%)	24/64 (38%)	NR	NR	NR	NR
Median PFS (95% CI)	16.7 months (14.9, 22.8)	[redacted] months ([redacted], [redacted])	13.2 months (10.8, 16.8)	Not reached	3.1 months (2.9, 4.1)	3.8 months (NR, NR)
KM estimate for PFS (95% CI)						
6 months	82% (70, 90) [n=48]	79% (66, 87) [n=48]	NR	NR	NR	NR
12 months	68% (54, 78) [n=29]	63% (50, 74) [n=30]	NR	NR	NR	NR
18 months	40% (26, 55) [n=13]	31% (19, 46) [n=12]	NR	NR	NR	NR

Source: Table 2.5-4, p106; Table 2.6-2, p127 of the submission; Table 11n, p96; Table 11p, p101 of the ALCANZA CSR;
CI = confidence interval; IRF = independent review facility; KM= Kaplan-Meier; N = total participants in group; NR = not reported; PFS = progression-free survival;
[a] Independent review
[b] Investigator
[c] 23 months for LyP and pcALCL, 27 months for MF
[d] 71.7 weeks converted to months by dividing by 0.23

6.14 The brentuximab vedotin studies reported a median PFS ranging from 13.2 months to 16.7 months. This was substantially longer than the 3.1 months to 3.8 months reported in the vorinostat (MAVORIC) trial. Patients who are defined as progression-free do not necessarily have a response to treatment as patients can be considered progression-free with: a small increase in skin disease (< 25% increase); no improvement (stable disease); a minor skin response (< 50% clearance required for partial response); partial response; or complete response. The ESC considered that PFS appeared to be improved for patients treated with brentuximab vedotin but most data were in the MF subtype and the extent of PFS improvement was difficult to determine. The pre-PBAC response contended that PFS is the most appropriate measure of efficacy to inform decision-making in this context as it is objectively assessed and captured both response and duration of response. The PBAC considered that PFS was difficult to interpret and compare across the trials due to differences in the patient populations and outcome measurement. The PBAC also considered that time to next treatment (TTNT), adjusted for the time therapy ceased, may be a more appropriate outcome for considering the duration of treatment response.

6.15 Brentuximab vedotin appeared to provide a substantial improvement in response and PFS compared with vorinostat. However, the PBAC considered that the extent of the incremental benefit was difficult to determine because the comparison was based on a naïve comparison of treatment groups with poor transitivity. This was due to more patients with CTCL subtypes with worse prognosis (more SS, no pcALCL and LyP) in the vorinostat studies; more patients with Stage III or IV CTCL in the vorinostat studies; fewer prior systemic therapies used by patients in the brentuximab vedotin studies; differences in outcome assessment; and potential changes in CTCL treatment due to some of the vorinostat studies being conducted 12 years earlier than the brentuximab vedotin studies. These factors mostly favoured brentuximab vedotin. In addition, the PBAC considered that a major concern with the naïve comparison presented was the fact that, unlike brentuximab vedotin, vorinostat use was not restricted to patients with CD30 positive CTCL.

Brentuximab vedotin vs. methotrexate

6.16 Table 6 presents the response outcomes from the ALCANZA trial that compared brentuximab vedotin with physician's choice of methotrexate or bexarotene.

Table 6: Results of response outcomes from the ALCANZA trial (brentuximab vedotin vs. methotrexate)

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

Source: Table 2.5-1 to Table 2.5-3, pp100-104 of the submission.

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

6.17 The PBAC noted that patients in the brentuximab vedotin arm had higher ORR, ORR4 (objective response rate lasting at least 4 months) and complete response rates than patients in the methotrexate arm. No formal statistical analyses were presented for the comparison between brentuximab vedotin and the methotrexate subgroup. The differences in ORR, ORR4, and investigator-assessed complete response were statistically significantly higher in the brentuximab vedotin arm than the physician's choice arm (methotrexate or bexarotene).

6.18 Table 7 presents the PFS outcomes from the ALCANZA trial.

Table 7: Results of PFS from the ALCANZA trial

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

Source: Table 2.5-4, pp106-7 of the submission; Figure 2.5-2, p105 of the submission; Table 14.3.1.5A, p640-643 of Appendix 11B; and calculated during the evaluation

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

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

6.19 The PBAC noted that patients treated with brentuximab vedotin had a median PFS of 16.7 months, which was significantly longer than the median 2.3 months PFS experienced by patients treated with methotrexate. Brentuximab vedotin appeared to provide a meaningful improvement in PFS compared to methotrexate. However, the extent of the incremental benefit was uncertain due to a high risk of bias from the lack of blinding in the open-label trial and non-random allocation of physician's choice treatments (methotrexate or bexarotene) which likely favoured brentuximab vedotin, and transitivity issues from differences in baseline patient characteristics with an unclear direction of bias. The key differences in baseline characteristics included differences in CTCL subtype, differences in CTCL stage and extent (blood and visceral disease), and Eastern Cooperative Oncology Group (ECOG) performance status.

<u>Outcomes by CTCL subtype</u>

6.20 The PBAC noted that the ORR was the only measure of outcome for which some comparison of effects by sub-type was possible. Table 8 presents ORR outcomes by CTCL subtype.

Table 8: Results of ORR across the studies by CTCL subtype

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

Source: Complied during the evaluation from Table 14.3.1.4E of Appendix 11B, pp635-637; Table 2.5-7, p112 of the submission; Table 2 p 2111 of Olsen (2007) (P001) Table 1 p 3 of Kim (2017); Table 4 p 34 of Duvic (2007) and Newland (2015)
CTCL = cutaneous T-cell lymphoma; LyP = lymphomatoid papulosis; MF = mycosis fungoides; ORR = objective response; pcALCL = primary cutaneous anaplastic large cell lymphoma; SS = Sézary syndrome

6.21 The ESC noted that there is no information comparing brentuximab vedotin to vorinostat in patients with pcALCL and LyP subtypes. The number of patients treated with brentuximab vedotin for both subtypes was also very low. The ESC considered that the results may indicate that there are very small numbers of patients with pcALCL and LyP who need second line systemic therapy. In addition, the ESC considered that patients with these subtypes do appear to respond to brentuximab vedotin, but no reliable information is available to clarify the differential response to either vorinostat or methotrexate.

6.22 The ORR in MF patients treated with brentuximab vedotin was 54% to 77% compared to 67% to 73% for the broader study populations. The ORR for MF patients treated with methotrexate in the ALCANZA trial ([redacted]%) was [redacted]% for all methotrexate-treated patients. The PBAC noted that the evidence base to support the comparative effectiveness of brentuximab vedotin over vorinostat and methotrexate in patients with SS was very limited because the data were based on three patients. Patients with pcALCL and LyP had higher ORRs for both brentuximab vedotin and methotrexate.

6.23 Newland (2015), a retrospective Australian study included during the evaluation, reported a very high response rate of 88% (22/25) for LyP patients treated with methotrexate.

6.24 As described above, in the naïve comparisons of brentuximab vedotin and vorinostat, there are more patients with CTCL subtypes with worse prognosis (more SS, no pcALCL and LyP) in the vorinostat studies. The ESC considered that in order to compare outcomes across populations with differing distributions of subtypes crude weighted ORRs may be informative. The crude weighted ORR for brentuximab vedotin and vorinostat/methotrexate are shown in Table 9.

Table 9: Crude weighted ORRs for brentuximab vedotin and its comparators by CTCL subtype

CTCL subtype	Brentuximab vedotin ORR	Comparator ORR	Weighting (Section 4 eligible population)
MF	65% [a]	7% [b] (vorinostat)	43%
SS	50% [c]	2% [b] (vorinostat)	6%
pcALCL	75% [a]	[redacted]% [a] (methotrexate)	51% [f]
LyP	92% [d]	88% [e] (methotrexate)	
Weighted ORR	**73%**	**38%**	-

Source: Table 14.3.1.4E of Appendix 11B, pp635-637; Table 2.5-7, p112 of the submission; Table 1 p 3 of Kim (2017); Table 4 p 34 of Duvic (2007), Newland (2015) and Table 3, p5 of the PSCR

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

[a] ALCANZA trial

[b] MAVORIC trial

[c] Duvic (2015) and Kim (2015) combined, Table 3, p5 of the PSCR

[d] Duvic (2015), Table 3, p5 of the PSCR. The Pre-PBAC response identified an error in the SS comparator ORR and calculations are corrected in Table 8 above.

[e] Newland (2015)

[f] Based on Year 1 eligible population. PcALCL and LyP are not reported separately. It was assumed each subtype comprised 50% of the subpopulation.

6.25 The ESC noted that the weighted difference in ORR may be overestimated due to the following factors that are likely to favour brentuximab vedotin: CTCL stage; differences in treatment practice due to inclusion of studies conducted over 12 years apart; number and type of prior therapies; performance status; patient age; and CD30 positivity. The ESC considered that these differences in baseline characteristics may account for some or all of the difference in the estimated weighted ORR, making it uncertain that brentuximab vedotin has superior efficacy compared with vorinostat. The ESC considered that if superior efficacy has not been adequately demonstrated that a cost-minimisation approach may be more appropriate.

Comparative harms

6.26 Table 10 presents the summary of key adverse events (AEs) from the included studies.

Table 10: Summary of key adverse events in the studies

Trial ID	Brentuximab (ALCANZA) n/N (%)	Vorinostat (P005) n/N (%)	Vorinostat (P001) n/N (%)	Methotrexate (ALCANZA) n/N (%)
Any AE	63/66 (95%)	NR	NR	23/25 (92%)
Drug-related AE	57/66 (86%)	NR	NR	14/25 (56%)
Drug-related Grade ≥ 3 AE	19/66 (29%)	NR	21/74 (28%)	[redacted]/25 (12%)
Drug-related serious AE	9/66 (14%)	NR	8/74 (11%)	[redacted]25 (8%)
AE resulting in discontinuation	16/66 (24%) [a,b]	7/37 (19%)	7/74 (9%)	1/25 (4%)
On-treatment deaths	4/66 (6%) [c]	2 /37(5%) [e]	3/74 (4%) [d]	[redacted]/25 (0%)
Any dose modification	48/66 (73%)	NR	11/74 (15%)	13/25 (52%)
Peripheral sensory neuropathy	30/66 (45%)	NR		1/25 (4%)
Grade ≥3 neutropenia	3/66 (5%)	NR		0/25 (0%)
Grade ≥3 fatigue	3/66 (5%)	2/86 (2%) [f]		1/25 (4%)
Grade ≥3 diarrhoea	2/66 (3%)	0/86 (0%) [f]		0/25 (0%)
Grade ≥3 thrombocytopenia	1/66 (2%)	5/86 (6%) [f]		0/25 (0%)
Grade ≥3 anaemia	0/66 (0%)	2/86 (2%) [f]		0/25 (0%)
Grade ≥3 pulmonary embolism	1/66 (2%)	2/37 (5%)	4/74 (5%)	[redacted]

Source: Constructed during the evaluation from Table 2.5-12 to 2.6-3, pp120-130 of the submission; Olsen (2007) (P001) and Duvic (2007) (P005)

AE = adverse event; MTX = methotrexate; n = number of participants reporting data; N = total participants in group; NR = not reported;

[a] One patient discontinued due to a fatal treatment-emergent AE of lymphoma progression, and the recorded action was "discontinued from the study"

[b] 9 patients discontinued due to peripheral sensory neuropathy

[c] Deaths within 30 days after the last dose of study drug. Three of four deaths no considered to be due to brentuximab vedotin. One death due to multiple organ dysfunction syndrome was considered related to brentuximab vedotin and underlying disease in a patient who did not meet eligibility criteria. The three other deaths, were due to lymphoma (related to disease under study), pulmonary embolism (not related to disease or drug), and skin sepsis (not related to drug or disease).

[d] One death secondary to disease progression, one death secondary to ischemic stroke, and one of unexplained cause on day 2 without confirmation of having taken vorinostat

[e] One patient died from disease progression and untreated sepsis that was considered unrelated to vorinostat.

[f] Based on patients who received a dose of 400 mg once daily (N=86) from the Zolinza (vorinostat) Product Information

6.27 Patients treated with brentuximab vedotin appeared to report a similar number of AEs and Grade 3 or higher drug-related AEs to patients treated with vorinostat. Brentuximab vedotin had more instances of peripheral sensory neuropathy, Grade 3 or higher neutropenia, more AEs resulting in discontinuation, and more dose modifications than vorinostat. Vorinostat had more instances of pulmonary embolism than brentuximab vedotin. When considering vorinostat in November 2016, the ESC noted that the frequency of pulmonary embolism would have significant implications for patients that were likely to go onto treatments with agents that induce thrombocytopenia (paragraph 6.15, November 2016 PSD). Overall, brentuximab vedotin appeared to have different but non-inferior safety profile to vorinostat.

6.28 The submission noted that the AE data from the ALCANZA trial did not appear to favour brentuximab vedotin when compared to methotrexate. The submission considered this to be due to the longer treatment exposure compared to methotrexate (or bexarotene). Brentuximab vedotin had more drug related Grade 3 or higher AEs, serious AEs, AEs resulting in dose modification or treatment

discontinuation, and more on-treatment deaths. The PBAC considered that brentuximab vedotin appeared to have an inferior safety profile compared with methotrexate.

Benefits/harms

6.29 The naïve comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of brentuximab vedotin and vorinostat. Accordingly, a benefits/harms table has not been presented. The PBAC considered that brentuximab vedotin may provide greater benefits than vorinostat in some CTCL subtypes and with a different toxicity profile. However, overall, the PBAC considered it is uncertain that brentuximab vedotin has superior efficacy compared with vorinostat. The PBAC considered that benefit/harm considerations would differ depending on the CTCL subtype and that treatment with brentuximab vedotin may not be in the patient's best interest in the more benign subtypes (LyP and pcALCL). A summary of the comparative benefits and harms for brentuximab vedotin versus methotrexate is presented in the table below. The PBAC considered that the majority of evidence for the benefits and harms shown in Table 11 are in the MF subtype as the majority of patients in the ALCANZA trial had MF.

Table 11: Summary of comparative benefits and harms for brentuximab vedotin and methotrexate

Trial	Brentuximab n/N	Methotrexate n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Brentuximab	Methotrexate	
Benefits						
Objective response (IRF)						
ALCANZA	43/64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS: ALCANZA trial						
	Brentuximab	**Methotrexate**	**Absolute difference**		**HR (95% CI)**	
Progressed/Died* n/N (%)	40/64 (63%)	22/26 (85%)	-22%		0.17 (0.09, 0.31)	
Median (months)	16.7 (14.9, 22.8)	2.3 (1.2, 3.5)	14.4 months		-	
Harms						
	Brentuximab n/N	**Methotrexate n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Brentuximab n	**Methotrexate n**	
Drug-related severe adverse event (Grade 3 or higher)						
ALCANZA	19/66	3/25	3.36 (1.07, 10.57)	29	12	0.20 (0.06, 0.35)
Peripheral sensory neuropathy						
ALCANZA	30/66	1/25	15.91 (2.26, 111.8)	45	4	0.43 (0.29, 0.56)
Neutropenia (Grade 3 or 4)						
ALCANZA	3/66	0/25	NE	5	0	0.05 (-0.01, 0.10)

Source: Table 2.6-3, pp129-130; Table 2.5-14, p122; Table 2.5-4, pp106-7 of the submission; Table 14.4.1.2A, pp886-929, Table 14.4.1.4A, pp944-1096; Table 14.4.1.5A, p1097; Table 14.3.1.5A, pp640-643 of Appendix 11B; and calculated during the evaluation.
HR = hazard ratio; NE = not estimable; PFS = progression-free survival; RD = risk difference; RR = relative risk
* Median duration of follow-up in the ALCANZA trial was 22.9 months.

6.30 On the basis of direct evidence presented by the submission, noting that the majority of evidence for benefits and harms is in patients with the MF subtype, for

every 100 patients treated with brentuximab vedotin in comparison to methotrexate and over a median 23 month duration of follow-up:

- Approximately 55 additional patients would have an objective response. An objective response is an improvement of at least 50% in CTCL-affected skin, lymph nodes, blood, or other organs (visceral disease);
- Approximately 22 more patients would remain progression-free over a median duration of follow-up of 23 months;
- Approximately 17 more patients would have a severe adverse event; and
- Approximately 41 additional patients would have peripheral sensory neuropathy (numbness and tingling of the hands and feet).

Clinical claim

6.31 The submission described brentuximab vedotin as superior in terms of effectiveness compared with the primary comparator, vorinostat. The ESC considered this was not fully supported because the clinical comparison presented was unreliable. The studies presented in the naïve comparison had a high risk of bias and poor transitivity, especially in relation to the vorinostat studies including patients with CTCL subtypes which had worse prognoses (more SS, no pcALCL and LyP) and, the PBAC noted different distributions of CD30 positivity. The PBAC considered that the comparison across different disease subtypes and stages, along with different distributions of CD30 positivity meant that the comparison provided in the submission was flawed and difficult to interpret.

6.32 Brentuximab vedotin appeared to have superior effectiveness compared with vorinostat for the treatment of MF, however the PBAC considered that this was uncertain due to poor transitivity between the trials. It was difficult to make a conclusion on the comparative effectiveness of brentuximab vedotin in the SS subtype because only three SS patients received brentuximab vedotin. The submission presented no evidence for the comparative effectiveness of brentuximab vedotin with vorinostat in pcALCL or LyP.

6.33 The submission considered brentuximab vedotin to be non-inferior in terms of safety compared to the primary comparator, vorinostat. The PBAC noted that there were differences in the toxicity profile, including major drug-specific adverse effects.

6.34 The submission described brentuximab vedotin as superior in terms of effectiveness compared with the supplementary comparator, methotrexate. The PBAC considered this was adequately supported by the evidence presented in the submission for the MF subtype. However, the extent of benefit of brentuximab vedotin was uncertain due to a high risk of bias in the ALCANZA trial, transitivity issues (differences in baseline characteristics), and methotrexate effectiveness being inferred from a subgroup of the Physician's choice arm. Nevertheless, the PBAC considered that the

best available evidence for brentuximab vedotin in this submission was the comparison with methotrexate in patients with MF from the ALCANZA trial.

6.35 The ESC considered the submission's claim that brentuximab vedotin had superior effectiveness compared with methotrexate was not supported for the other subtypes of CTCL as the submission only presented data for methotrexate for four patients with pcALCL and no data was available for patients with SS. However, the PBAC considered that on balance it was reasonable to concede that the submission's claim was reasonable for pcALCL. The PBAC considered that the naïve comparison with an Australian study of methotrexate in patients with LyP demonstrated that brentuximab vedotin was not superior in terms of comparative effectiveness compared with methotrexate.

6.36 The submission described brentuximab vedotin as non-inferior in terms of safety compared with methotrexate. The PBAC considered this was not supported by the evidence presented in the submission. Patients treated with brentuximab vedotin had more drug related Grade 3 or higher AEs, serious AEs, AEs resulting in dose modification or treatment discontinuation, and more on-treatment deaths than patients treated with methotrexate in the ALCANZA trial. The PBAC considered brentuximab vedotin may have an inferior safety profile compared with methotrexate, although the PBAC acknowledged the longer treatment exposure with brentuximab vedotin compared to methotrexate.

Economic analysis

6.37 The submission presented several modelled economic evaluations of brentuximab vedotin which were all based on the one economic model structure. The cost per responder (ORR) was presented as the base case and the cost utility analysis and cost per ≥ 25% mSWAT responder as secondary base cases. A cost per ≥ 25% mSWAT responder was presented in the March 2017 vorinostat consideration (paragraphs 4.5 and 4.6, March 2017 PSD). Table 12 presents an overview of the three key economic evaluations. The ESC considered the economic evaluations presented in the submission were based on a clinical comparison with vorinostat that was unreliable due to transitivity issues already outlined. The PBAC agreed with the ESC that the economic analyses presented were unreliable due to uncertainty in the clinical comparisons.

Table 12: Summary of model structure and rationale

Component	Economic evaluation		
	Cost per responder (ORR)	**Cost per responder (≥ 25% mSWAT)**	**Cost-utility analysis**
Type of analysis	CEA	CEA	CUA
Outcome	ORR	≥ 25% mSWAT	QALYs
Comparators	Vorinostat Methotrexate No treatment	Vorinostat Methotrexate No treatment	Vorinostat Methotrexate
Time horizon	2.71 years	2.71 years	2.71 years
Cycle length	21 days	21 days	21 days
Post-progression costs	Yes (Vorinostat and methotrexate only)	Yes (Vorinostat and methotrexate only)	Yes (Vorinostat and methotrexate only)
Discounting (5%)	Outcomes: No Costs: Yes	Outcomes: No Costs: Yes	Outcomes: Yes Costs: Yes
Computational method	Δ Costs/Δ response rate. PSM for drug costs (during PFS) and PD costs (after PFS) (discounted).[a] Reponses not discounted.	Δ Costs/Δ response rate. PSM for drug costs (during PFS) and PD costs (after PFS) (discounted)[a]. Reponses not discounted.	Δ Costs/Δ QALY. Costs/PFS LYG. PSM for costs and outcomes (discounted).
Transition probabilities	Response rates from studies. PFS KM for drug and PD costs.	Response rates from studies. PFS KM for drug and PD costs.	PFS KM from included studies
Software package	Excel 2016 (single model structure for all analyses)		

Source: Table 3.1-2, p153 of the submission

Δ = change in; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; KM = Kaplan-Meier; LYG = life year gained; mSWAT = modified severity-weighted assessment tool; ORR = objective response rate; PFS = progression-free survival; PD = progressive disease; PSM = partitioned survival model QALY = quality-adjusted life year;

[a] PD monitoring costs were attributed to the proportion of comparator patients with "excess" progressive disease (i.e. comparator progressive disease % - brentuximab vedotin progressive disease %).

6.38 The cost per responder (ORR) analyses used study-based response outcomes from the ALCANZA trial (brentuximab vedotin and methotrexate subgroup) and the MAVORIC trial (vorinostat) to determine the additional responders with brentuximab vedotin. The cost per responder (mSWAT) analyses used study-based response outcomes (≥ 25% mSWAT improvement) from the ALCANZA trial (brentuximab vedotin and methotrexate subgroup) and the P001/P005 trials (vorinostat) to determine the additional responders with brentuximab vedotin.

6.39 The cost utility analysis used a partitioned survival model (PSM) with two health states, progression-free and progressive disease. Patients received treatment while they were in the progression-free state and only incurred monitoring costs in the post-progression state. Both the cost per responder analyses and cost utility analysis used the treatment and monitoring costs from the PSM. This did not reflect the clinical management algorithm, in which patients received several lines of therapy. Although treatment costs from the PFS-based partitioned survival model were applied to the cost per responder analyses, patients who were progression-free were not all responders. Patients with stable disease but insufficient response to be considered a responder (either ≥ 25% mSWAT improvement or 50% improvement for ORR) were considered to be progression-free. Additionally, the cost per responder analyses did not account for the potentially longer duration of response

associated with brentuximab vedotin.

6.40 The ESC noted that TTNT was considered by an Australian clinician to be closely related to PFS in CTCL. For the brentuximab vedotin arm, treatment was assumed to last 15 months, at which point 68% patients remained progression-free.

6.41 The key drivers of the economic evaluations were ORR and PFS inputs. This may have favoured brentuximab vedotin for the reasons outlined in paragraphs 6.12 and 6.15.

6.42 The utility values used in the cost-utility analysis were derived from EQ-5D-3L data mapped to Australian preference weights from all observations in the ALCANZA trial based on progression status. These data may not be applicable to the proposed PBS population because the utility of patients with CTCL would be expected to differ greatly with the extent of disease, CTCL subtype and the extent of response. Patients classified as progression free included patients with stable disease and no CTCL improvement. The PSCR noted that the aim of CTCL treatment was broader than skin response and more aligned with PFS because treatment is aimed at "maximising patients' quality of life and ameliorating their symptoms, while minimising the toxicities of treatments. Inducing and maintaining remission are therefore major therapeutic goals" (Hughes et al 2016). The ESC considered that skin response is likely to be important to most of the eligible PBS population. Hughes et al 2015 reported that the majority of Australian MF and SS patients requiring systemic therapy did not have nodal, visceral or blood involvement (70%, 97% and 69% respectively). The utility values may not have been applicable to patients with SS (more severe disease) or LyP (a less severe, remitting disease) as only 3 patients with SS and no patients with LyP were included in the ALCANZA trial.

6.43 The economic model did not include disutility for peripheral neuropathy nor costs for managing other AEs. This was inappropriate and favoured brentuximab vedotin. The utility study by Swinburn (2015) showed respondents considered having peripheral sensory neuropathy to have a worse health state than complete response without peripheral sensory neuropathy and similar to a partial response. The PSCR considered that the application of a disutility in a sensitivity analysis performed during the evaluation significantly overestimated the disutility of peripheral sensory neuropathy. The PSCR suggested that if the costs for treating severe neutropenia were included for brentuximab vedotin, the costs of treating pulmonary embolism should be included for vorinostat and argued that inclusion of disutility for these AEs would be unlikely to affect the ICER. The PBAC considered that the inclusion of AE treatment costs would be appropriate due to the differing AE profiles for brentuximab vedotin, vorinostat and methotrexate.

6.44 The results of the economic evaluation are presented in Table 13.

Table 13: Results of the economic evaluations

Component	Brentuximab	Vorinostat	Methotrexate	Brentuximab vs. Vorinostat	Brentuximab vs. Methotrexate
ORR					
Costs	$	$	$	$	$
Responders	67.2%	4.8%	%	62.3%	%
Incremental cost/responder				**$**	**$**
≥ 25% mSWAT improvement					
Costs	$	$	$	$	$
Responders	88.9%	49.0%	%	39.9%	%
Incremental cost/≥ 25% mSWAT responder				**$**	**$**
Cost-utility analysis					
Costs	$	$	$	$	$
QALYs	0.928	0.842		0.086	
Incremental cost/extra QALY gained				**$**	**$**

Source: Complied during the evaluation from Table 3.8-1 to 3.8-2, p183; Table 3.10-1 to 3.10-2, p189 of the submission, and Section 3 spreadsheet

mSWAT = modified severity-weighted assessment tool; ORR = objective response rate; QALY = quality-adjusted life year

6.45 The incremental benefit of brentuximab vedotin over vorinostat could not be reliably estimated because it was informed by a naïve comparison of studies which had a high risk of bias and transitivity issues. This was mainly due to the vorinostat studies including patients with subtypes of CTCL with worse prognoses and the different distributions of CD30 positivity.

6.46 The comparison with methotrexate was considered more reliable as it was based on the results of a RCT. However, there were differences in baseline characteristics across the treatment groups. The comparison with methotrexate was not applicable to patients with the SS or LyP subtypes, as the trial did not include any patients with SS or LyP subtypes. Newland (2015) demonstrated that Australian patients with LyP and treated with methotrexate had a high rate of response.

6.47 The submission claimed that brentuximab vedotin was at least as cost-effective as vorinostat for the treatment of CTCL. This was implicitly based on a comparison with "no active therapy" (i.e. zero cost and effectiveness) resulting in brentuximab vedotin having a cost per responder (ORR) of $105,000 - $200,000 compared with more than $200,000 for vorinostat. The vorinostat ICER in this application was derived from the MAVORIC trial which had a lower ORR than studies P001 and P005 (the basis of the vorinostat recommendation) (4.8% in MAVORIC vs. 29.5% in P001, 31% in P005 patients using Product Information dosing). The PSCR presented a new cost per responder analysis (brentuximab vedotin vs methotrexate) where a responder was a patient with an objective response lasting four months (ORR4) – the primary outcome of the ALCANZA trial. The PSCR reported an ICER of $105,000/responder - $200,000/responder, however ESC could not replicate this ICER.

6.48 Application of the crude weighted ORRs and a weighted cost for vorinostat and methotrexate (49% and 51% respectively) in the economic model resulted in a cost per responder of $105,000 - $200,000.

6.49 During the November 2016 vorinostat consideration, the PBAC noted the ESC's concerns regarding "no active therapy" being the nominated comparator. The PBAC considered that if recommended for PBS listing, vorinostat would be used to displace, rather than replace, currently available treatments, which vary widely in nature and applicability to individual cases. As such, the PBAC viewed that "no active therapy" could reasonably be considered a comparator (paragraph 7.3, November 2016 PSD). Due to the cycling of treatments in CTCL, patients may receive again a previous treatment as supportive care, which may result a response for some patients. Thus, the assumed 0% ORR for no active therapy would be inappropriate. It would also be inappropriate for LyP, which self-resolves.

6.50 The cost per responder analysis, in which a ≥ 25% improvement in mSWAT was the response outcome, was similar to the analysis presented in the March 2017 PBAC consideration of vorinostat. A ≥ 25% improvement in mSWAT is a less stringent outcome than ORR which requires ≥ 50% improvement in skin and other disease assessments. The cost per ≥ 25% mSWAT improvement may not capture all patient relevant benefits, including more brentuximab vedotin patients achieving complete or near-complete responses.

6.51 The submission presented an ICER for brentuximab vedotin of more than $200,000/QALY and more than $200,000/QALY compared with vorinostat and methotrexate, respectively. The PBAC considered that the ICERs presented were unacceptably high based on previous PBAC decisions, even in the context of difficult to treat and relatively rare diseases and that, in addition, the ICER for the comparison with vorinostat was highly uncertain.

6.52 The PBAC noted that in the pre-PBAC response the sponsor offered a reduced price of $[redacted] per vial. The PBAC considered that the revised ICER with the reduced price remained very high and uncertain.

Drug cost/patient/course = $[redacted]

6.53 The cost of brentuximab vedotin was $[redacted] (undiscounted) consisting of $[redacted] in brentuximab vedotin costs and $[redacted] in IV infusion costs. This was based on a dose of approximately [redacted] mg and [redacted] cycles of brentuximab vedotin ([redacted]% compliance). The pre-PBAC response proposed a reduced price of $[redacted] per vial. The cost of vorinostat was $31,202 (undiscounted) based on 100% compliance and treatment until disease progression using PFS from the MAVORIC trial, with an average treatment duration of 30 weeks. The modelled cost of methotrexate was $45.93 (undiscounted) based on an average dose of 21.67 mg for an average treatment duration of approximately 21 weeks.

Estimated PBS usage & financial implications

6.54 This submission was not considered by DUSC.

6.55 The submission appropriately used an epidemiological approach to estimate the utilisation and financial impact of listing brentuximab vedotin. The submission estimated the prevalent and incident CTCL population using Australian Institute of Health and Welfare cancer and mortality data. The proportion of CD30 positive CTCL patients requiring systemic treatment was estimated from the ACLN database. The estimated use and financial implications are presented in Table 14. The PBAC noted that the approach taken did not apply the definition of CD30 positivity used in the pivotal trial and considered that it made significant assumptions in the extrapolations from the ACLN database.

Table 14: Estimated use and financial implications

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

Source: Table 4.5-1, p202 of the submission, and corrected during the evaluation.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

[a] 10.3 prescriptions per patient per course.
[b] Brentuximab vedotin estimated to require 10 additional IV infusions, 5 additional specialist consultations, and 10 additional blood tests (full blood count and biochemistry).

6.56 The eligible population may be smaller or larger than estimated because:

- the use of 15 year CTCL prevalence data may have overestimated the eligible population;
- LyP diagnoses may not be reported to cancer registries;
- there was uncertainty surrounding the proportion of patients with CD30 positive CTCL (no standard definition of CD30 positivity); and
- mortality may have been underestimated as some deaths may be due to CTCL but not recorded as such, e.g. recorded as infection.

6.57 The submission estimated that less than 10,000 patients would be treated in Year 1, decreasing to less than 10,000 patients in Year 6. This resulted in 90% of eligible patients being treated with brentuximab vedotin by Year 6. The overall net cost to government was less than $10 million in Year 1, decreasing to less than $10 million in Year 6, resulting in a net cost of $20 - $30 million for the Australian Government health budget over the first six years of listing. The PBAC noted that with the reduced proposed price the overall net cost to the government reported in the pre-PBAC response was less than $10 million in Year 1, decreasing to less than $10 million in Year 5.

6.58 The financial estimates were most sensitive to the use of a larger number of treatment cycles (increased cost), a larger eligible population with CD30 positive CTCL who required systemic therapy (increased cost) and the inclusion of vorinostat cost offsets (decreased net cost).

6.59 The PBAC considered that there was a substantial risk of use of brentuximab vedotin outside the restriction. This included use as a first line systemic therapy, retreatment of patients and in combination treatment with other CTCL therapies.

Quality Use of Medicines

6.60 The submission stated the sponsor operates in full accordance with the current TGA guidelines for pharmacovigilance responsibilities of sponsors and has an appropriate system of pharmacovigilance in place.

Financial Management – Risk Sharing Arrangements

6.61 The submission requested revision to the subsidisation caps in any current Risk Sharing Arrangements (RSA) for CTCL because brentuximab vedotin provides a substantial survival benefit and is intended to be an additional line of therapy. The

submission suggested a two tier arrangement consistent with some existing brentuximab vedotin listings as the percentage of patients requiring systemic treatment for CTCL may fluctuate from year to year. The pre-PBAC response proposed an RSA with a rebate above an upper expenditure cap for this indication; similar to the RSAs that are in place for the two relapsed or refractory Hodgkin lymphoma indications.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of brentuximab vedotin in relapsed or refractory CD30 positive CTCL in patients who have previously used systemic therapy, due to major reservations regarding the naïve comparison with vorinostat, which meant that cost-effectiveness against vorinostat was unable to be assessed. The PBAC also considered that brentuximab vedotin was not cost-effective compared with methotrexate at the proposed price. The PBAC noted that the ICER presented was unacceptably high based on previous PBAC decisions, even in the context of difficult to treat and relatively rare diseases.

7.2 The PBAC welcomed the input from individuals, health care professionals and organisations which highlighted the limited treatment options available for patients with CTCL.

7.3 The PBAC acknowledged that there is a need for additional therapies for patients with CTCL who have failed prior systemic therapies as current treatments are characterised by low response rates and short durations of response. The PBAC considered that although vorinostat has provided an additional treatment option for patients with CTCL, there remains a substantial unmet clinical need for effective treatments that provide a lasting response for these patients.

7.4 The PBAC noted that no explicit definition of CD30 positivity in CTCL was included in the proposed restriction and considered that a clear definition was desirable. The PBAC considered that the proposed restrictions should include a requirement for the provision of a histology report showing evidence of CD30 positivity (Initial) and for patients to have achieved an appropriate response to therapy (Continuing).

7.5 The submission nominated vorinostat as the main comparator. The PBAC agreed with the ESC that this was appropriate for the MF and SS subtypes of CTCL only as patients with pcALCL and LyP were not included in the vorinostat trial. The PBAC considered that it was unclear whether vorinostat is used to treat pcALCL and LyP in Australian clinical practice although the vorinostat PBS listing also allows use in these subtypes. The PBAC also considered that the use of vorinostat as a comparator in this submission was limited by the fact that, unlike brentuximab vedotin, its use was not restricted to CD30 positive CTCL.

7.6 The PBAC noted that there was no defined standard of care for relapsed or refractory CTCL. As such, the PBAC considered that the use of a basket of therapies as a supplementary comparator had significant limitations as the relative weighting of each therapy would carry substantial uncertainty. In addition, the PBAC considered that such a comparison would be limited by fact that, unlike brentuximab vedotin, the use of these therapies is not restricted to CD30 positive CTCL. The PBAC considered that the best comparative evidence available in this submission was for patients treated with methotrexate, which the PBAC accepted as one of the standard therapies in Australia for this rare condition.

7.7 The submission's primary comparison was a naïve comparison of the brentuximab vedotin arm of the Phase III, open-label ALCANZA RCT (n=131) with the vorinostat arm of the Phase III, open-label MAVORIC RCT (n=372). The PBAC agreed with the ESC that the comparison had a high risk of bias because it was based on a naïve comparison of studies with poor transitivity that may have confounded the observed clinical outcomes. The PBAC considered the comparison was flawed with the major transitivity issues being the different mix of disease subtypes/stages and the difference in CD30 positive selection between the two trials. The PBAC considered that due to differences in CD30 positivity between patients included in the trials the efficacy of vorinostat in a CD30 positive subset of CTCL patients was unknown. The PBAC considered that because of these differences this comparison could not currently be accepted as the basis for decision-making regarding the cost-effectiveness of brentuximab vedotin.

7.8 The PBAC considered that the claim of superior comparative effectiveness to vorinostat was not adequately supported by the data. The PBAC considered that the claim of non-inferior comparative safety to vorinostat was reasonable.

7.9 The submission's supplementary comparison with methotrexate compared the brentuximab vedotin arm of the ALCANZA trial with the methotrexate subgroup (n=26) of the physician's choice arm of the trial. The PBAC noted that the ALCANZA trial included patients with MF and pcALCL only, with the majority of patients having MF. The PBAC noted the Newland (2015) study provided information on the use of methotrexate in patients with LyP but considered it was of limited relevance to the submission overall given the indolent nature of LyP, the common watch and wait approach used in its management, and the ability to use other therapies such as topical steroids or oral retinoids in this condition. The PBAC agreed with the ESC that overall data on methotrexate was suboptimal in robustness. However, the PBAC noted that the ALCANZA trial did provide data on the efficacy of methotrexate, although underpowered, in a CD30 positive subset of CTCL.

7.10 The PBAC noted that the results of the ALCANZA trial indicated that patients in the brentuximab vedotin arm had higher ORR, ORR4 and complete response than patients in the methotrexate arm. The PBAC also noted that patients treated with

brentuximab vedotin had a median PFS of 16.7 months, which was significantly longer than the median 2.3 months PFS experienced by patients treated with methotrexate. Acknowledging the limitations of the data, the PBAC considered that brentuximab vedotin appears to be effective over an extended duration in patients with proven CD30 positive CTCL and more effective than methotrexate in patients with MF.

7.11 The PBAC considered that the claim of superior comparative effectiveness to methotrexate was reasonable for the MF and pcALCL subtypes only and was not adequately supported by the data in LyP and SS subtypes.

7.12 The PBAC considered that the claim of non-inferior comparative safety to methotrexate was not adequately supported by the data. The PBAC considered brentuximab vedotin may have an inferior safety profile compared with methotrexate, although the PBAC acknowledged the longer treatment exposure with brentuximab vedotin compared to methotrexate.

7.13 The submission presented several modelled economic evaluations of brentuximab vedotin based on the cost per responder (ORR), cost per ≥ 25% mSWAT responder, and a cost utility analysis based on PFS. The PBAC noted that the cost per ≥25% mSWAT responder was presented in the March 2017 vorinostat consideration (paragraphs 4.5 and 4.6, March 2017 PSD). The PBAC noted that the cost per ≥25% mSWAT responder is a less stringent outcome than overall response.

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

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

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

considered that the revised ICER with the reduced price remained very high and uncertain.

7.16 The PBAC considered that overall the estimated budget impact was relatively low, due to the small number of patients eligible for treatment. However, the PBAC considered the estimates to be uncertain as there was a substantial risk of use of brentuximab vedotin outside the restriction particularly for use as a first line therapy.

7.17 The PBAC noted the RSA proposed by the sponsor in the pre-PBAC response. The PBAC considered that a RSA with a substantial rebate above an upper expenditure cap would be required to manage the risks associated with potential use outside the restriction, a decrease in the threshold to commence systemic therapy, and an unclear definition of CD30 positivity.

7.18 The PBAC acknowledged the rarity of CTCL and the difficulty of conducting phase III trials in the heterogeneous subgroups of CTCL but considered that the naïve comparison of brentuximab vedotin and vorinostat did not provide good evidence for the cost-effectiveness of brentuximab vedotin compared with vorinostat. The PBAC noted that the comparison with methotrexate was based on more robust data but based on this comparison brentuximab vedotin had an unacceptably high ICER. Nevertheless, in this uncommon and incurable disease where there is a high unmet need and significant impacts on patient quality of life, the PBAC considered that brentuximab vedotin appears effective for some time in patients with proven CD30 positive disease and more effective than methotrexate in patients with MF. As such, and consistent with the approach taken with vorinostat, the PBAC considered a cost per responder assessment of cost-effectiveness may be appropriate in any future submission. The PBAC noted that a considerable price reduction would be required in order to show that brentuximab vedotin is cost-effective compared with methotrexate.

7.19 Alternatively, for a comparison with vorinostat, the PBAC proposed that any future resubmission would need to provide additional data to address several of the major concerns raised by the PBAC that made the naïve comparison with vorinostat problematic. The data required include, but are not necessarily limited to:

- response and duration of response (or TTNT) in CD30 positive MF or SS with vorinostat;
- relatively contemporary Australian data on vorinostat in MF or SS; and
- duration of response data for brentuximab vedotin in the MF subgroup of the ALCANZA trial.

The PBAC considered that isolating the comparison to MF, resolving issues around whether CD30 positivity is a response-modifier for vorinostat, and focussing on duration of response (rather than simply PFS) may increase robustness sufficiently to enable assessment of cost-effectiveness in this rare disease with major chronic

morbidity.

7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

Although disappointed by the PBAC's rejection, Takeda is committed to working with the PBAC and the Department of Health to resolve the Committee's concerns so that patients with this very rare and debilitating cancer can get timely access to brentuximab vedotin on the PBS.