7.01 BRENTUXIMAB VEDOTIN, Powder for I.V. infusion 50 mg, Adcetris®, TAKEDA PHARMACEUTICALS AUSTRALIA PTY. LTD.

1 Purpose of submission

1.1 The standard re-entry submission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required (Written) listing for the first-line treatment of advanced Hodgkin lymphoma in combination with chemotherapy.

1.2 The resubmission claimed that there is an unmet clinical need for first-line treatments of advanced Hodgkin lymphoma that improve survival compared to current standard of care whilst reducing long-term toxicities such as lung toxicity, secondary malignancies and fertility; as well as safe and effective treatments in patients aged 60 years and above.

1.3 Listing was requested on the basis of a cost-effectiveness analysis versus ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) as a proxy for positron emission tomography (PET)-adapted ABVD. PET-adapted ABVD consists of ABVD for the first 2 cycles with options to de-escalate to AVD (doxorubicin, vinblastine and dacarbazine) for a further 4 cycles in PET-negative patients or escalate to eBEACOPP (escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) for a further 4 cycles in PET-positive patients.

Table 1: Key components of the clinical issue addressed in the resubmission

Component	Description
Population	Adult patients with previously untreated CD30+ advanced (stage III or IV) Hodgkin lymphoma
Intervention	Brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine (A+AVD), for 6 × 28-day cycles
Comparator	Main comparator: PET-adapted ABVD regimen consisting of ABVD for the first 2 × 28-day cycles followed by: • AVD for a further 4 × 28-day cycles in iPET2-negative patients, or • eBEACOPP for a further 4 × 21-day cycles in iPET2-positive patients ~~Supplementary comparator:~~ ~~PET-adapted eBEACOPP regimen consisting of eBEACOPP for the first 2 × 21-day cycles followed by:~~ ~~• eBEACOPP for a further 2 × 21-day cycles or ABVD for 4 × 28-day cycles in iPET2-negative patients, or~~ ~~• eBEACOPP for a further 4 × 21-days cycles in iPET2-positive patients~~
Outcomes	Improved modified progression-free survival, overall survival, and health-related quality of life
Clinical claim	A+AVD is superior in terms of efficacy but inferior in terms of safety compared to PET-adapted ABVD ~~No clinical claim was made in terms of efficacy for A+AVD versus PET-adapted eBEACOPP~~ ~~A+AVD is superior in terms of safety compared to PET-adapted eBEACOPP~~

Source: Table 1.1, p4 of the resubmission
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; AVD, doxorubicin, vinblastine and dacarbazine; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; iPET2, interim positron emission tomography after 2 cycles of chemotherapy; PET, positron emission tomography
Note 1: Key changes compared to the March 2024 submission are marked using ~~strikethrough~~
Note 2: Australian guidelines (Cochrane 2021) note that trial definitions of response based on the iPET2 may differ. The cut-off for negative iPET2 is based on a Deauville Score (5-point scale) of either ≤2 or ≤3.

2 Background

Registration status

2.1 The TGA approved brentuximab vedotin in May 2024 for the treatment of adult patients with previously untreated CD30+ advanced Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine (AVD).

2.2 Brentuximab vedotin is also TGA-approved for the following indications:

- Hodgkin lymphoma
  - Treatment of adult patients with CD30+ Hodgkin lymphoma at higher risk of relapse or progression following ASCT.
  - Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma following ASCT; or following at least 2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
- Peripheral T-cell lymphoma
  - Treatment of adult patients with previously untreated CD30+ peripheral T-cell lymphoma in combination with cyclophosphamide, doxorubicin and prednisone.
  - Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma.
- Cutaneous T-cell lymphoma

- Treatment of adult patients with CD30+ cutaneous T-cell lymphoma after at least 1 prior systemic therapy.

2.3 Brentuximab vedotin is currently under TGA evaluation for the treatment of adult patients with previously untreated CD30+ Stage IIb with risk factors, Stage III or Stage IV Hodgkin lymphoma in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD). The TGA Delegate's overview is expected in November 2025 and an Advisory Committee on Medicines (ACM) meeting if needed in December 2025.

Previous PBAC consideration

2.4 The sponsor presented a Category 2 submission to the March 2024 PBAC meeting requesting a Section 100 (Efficient Funding of Chemotherapy), Authority Required (Telephone/Online) listing for the first-line treatment of advanced classical Hodgkin lymphoma.

2.5 In July 2024, the PBAC did not recommend brentuximab vedotin, in combination with doxorubicin, vinblastine and dacarbazine (A+AVD), for the first-line treatment of advanced classical Hodgkin lymphoma. The PBAC considered the availability of alternative treatment options reduced the clinical need for A+AVD. The PBAC advised that the claim of superior effectiveness compared to PET-adapted ABVD was highly uncertain due to the indirect evidence presented and the high level of censoring in the key trial evidence, but considered it was likely reasonable. In addition, the PBAC considered the economic model structure used in the submission resulted in an incremental cost effectiveness ratio (ICER) that was highly uncertain and advised that the cost-effectiveness of A+AVD was unable to be reliably assessed (para 7.1, brentuximab vedotin Public Summary Document (PSD), March 2024 PBAC meeting).

2.6 The PBAC considered the primary reason for this outcome was due to the economic evaluation provided (para 7.2, brentuximab vedotin PSD, March 2024 PBAC meeting).

2.7 Table 2 summarises the key matters of concern identified at the March 2024 PBAC meeting and how these were addressed in the resubmission.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
Economic evaluation	
The submission presented a cost-utility analysis of A+AVD versus PET-adapted ABVD based on the ECHELON-1 trial of A+AVD versus non-PET-adapted ABVD. The PBAC considered the use of the ABVD arm from the ECHELON-1 trial as a proxy for the efficacy of PET-adapted ABVD was uncertain (para 7.11, brentuximab vedotin PSD, March 2024 PBAC meeting).	The resubmission argued that the ABVD arm in the ECHELON-1 trial is a reasonable proxy for PET-adapted ABVD given most patients in the trial had a negative interim PET after 2 cycles of chemotherapy (iPET2) and that only some patients who are positive at iPET2 will escalate to eBEACOPP in clinical practice due to tolerability concerns. The resubmission also presented additional supportive evidence based on a more recent data cut from the RATHL trial and a conference abstract/poster (Kristo 2023) that presented results of two unanchored matching adjusted indirect comparisons (MAICs) of A+AVD and PET-adapted ABVD.
The economic model structure resulted in an ICER that was highly uncertain and the cost-effectiveness of A+AVD was unable to be reliably assessed. The use of a partitioned survival analysis was inadequately justified given multiple structural limitations, which had an impact on the validity of extrapolated outcomes and the ability to appropriately model the impact of subsequent anti-cancer treatments; and limited the ability to quantify any uncertainties through sensitivity analyses (para 7.11, brentuximab vedotin PSD, March 2024 PBAC meeting). The PBAC considered that a resubmission should provide a revised economic analysis using a Markov model structure, which would provide a more flexible and transparent approach to assess the cost-effectiveness of A+AVD (para 7.11 and 7.13, brentuximab vedotin PSD, March 2024 PBAC meeting). The ESC considered a revised Markov model should consider inclusion of additional health states for relapse and subsequent treatments so that the impacts of assumptions around long term modelled outcomes may be appropriately tested and validated (para 6.80 and 7.11, brentuximab vedotin PSD, March 2024 PBAC meeting).	The model structure in the resubmission was substantially revised, described as a Markov model that included separate states for each line of therapy.
Further information and justification for the approach used in estimating utility values was required (para 6.80 and 7.11, brentuximab vedotin PSD, March 2024 PBAC meeting).	The resubmission used predicted utility estimates from the same regression model as the previous submission, applied to patients in the first-line treatment health state of the revised economic model. No further information for the approach used to estimate the utility values was presented.

Matter of concern	How the resubmission addresses it
Utilisation and financial estimates	
The PBAC noted that the DUSC considered the financial impact was underestimated due to the underestimated size of the eligible and treated populations and overestimated cost offsets. The PBAC noted revised financial estimates in the pre-PBAC response based on changes to the incidence rate, proportion at stage III/IV, ECOG requirements and uptake rates that were consistent with DUSC advice (para 6.87 and 7.12, brentuximab vedotin PSD, March 2024 PBAC meeting). The PBAC considered that a resubmission should utilise the pre-PBAC response inputs for incidence rate, proportion with stage III/IV disease and ECOG requirements but was concerned that the recommended use of PET-adapted regimens over non-PET-adapted regimens may impact uptake rates (para 7.12 and 7.13, brentuximab vedotin PSD, March 2024 PBAC meeting).	The resubmission included changes to the incidence rate, proportion with stage III/IV disease and ECOG requirements as requested. However, the uptake rates were also increased, consistent with inputs used in the March 2024 pre-PBAC response.

Source: Brentuximab Vedotin March 2024 Public Summary Document, Sections 1 to 4 of the resubmission
Abbreviations: A+AVD, brentuximab vedotin, in combination with doxorubicin, vinblastine and dacarbazine; ABVD, doxorubicin, bleomycin, vincristine and dacarbazine; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; ECOG, Easten Cooperative Oncology Group performance status

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT Form	PBS item code	Dispensed Price Max Amt	Max. Amount	№.of Rpts
BRENTUXIMAB VEDOTIN *Injection* ~~(50 mg injection, 1 vial)~~	NEW (Public) NEW (Private) MP	Published price Public : $14,055.13 Private DPMA: $14,295.31 Effective price Public: $[redacted] Private: $[redacted]	~~150 mg~~ *120mg*	11
Available brands				
Adcetris (brentuximab vedotin 50 mg injection, 1 vial)				
Restriction Summary [new] / Treatment of Concept: [new]				
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 - Efficient Funding of Chemotherapy Public/Private hospitals			
	Prescriber type: ☒Medical Practitioners			
	Restriction type: ☒Authority Required (in writing only via post/HPOS upload)			
Prescribing rule level	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.			
	Administrative Advice: No increase in the maximum number of repeats may be authorised			
	Administrative Advice:			

		Special Pricing Arrangements apply
		Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Episodicity: *[blank]*
		Severity: *[blank]*
		Condition: *Stage III or IV CD30 positive Hodgkin lymphoma*
		Indication: Stage III or IV CD30 positive Hodgkin lymphoma.
		Clinical criteria:
		The treatment must be for first line therapy for this condition.
		AND
		Clinical criteria:
		The treatment must be for curative intent.
		AND
		Clinical criteria:
		The treatment must be in combination with a multi-drug chemotherapy regimen.
		AND
		Clinical criteria:
		The treatment must not be for more than 6 treatment cycles under this restriction in a lifetime.
		Prescribing Instructions: Applications for authorisation of initial treatment must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail. If the application is submitted through HPOS upload or mail, it must include: (a) *details of the proposed prescription* ~~a completed authority prescription form~~; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

3.2 The resubmission proposed a special pricing arrangement with an effective AEMP of $[redacted] per vial and a published AEMP of $4,655 per vial. This is the same as the previous submission. The PBS listings of brentuximab vedotin for relapsed or refractory disease are subject to special pricing arrangements, with effective AEMPs per vial of $[redacted] for the ASCT naïve and $[redacted] for the post ASCT indications.

3.3 The requested restriction in the March 2024 submission specified that treatment with brentuximab vedotin must be in combination with doxorubicin, vinblastine and dacarbazine. However, it was noted that that while doxorubicin and vinblastine have unrestricted listings on the PBS/RPBS, dacarbazine is neither TGA-approved nor listed on the PBS for treatment of Hodgkin lymphoma, which may lead to equity of access

issues for the A+AVD regimen, although this would also apply to the nominated main comparator, PET-adapted ABVD (para 3.6. brentuximab vedotin PSD, March 2024 PBAC meeting). The ESC noted that ABVD has been standard of care in Hodgkin lymphoma for decades in Australia and access to dacarbazine has not been an issue.

3.4 The resubmission noted proposed amendments in the March 2024 Secretariat comments, that the clinical criteria specify use in combination with doxorubicin and vinblastine only (i.e. agnostic to the use of dacarbazine). However, the resubmission stated that the landscape for first-line treatment of advanced Hodgkin lymphoma is evolving, and that a less prescriptive criterion would allow greater flexibility for clinicians to prescribe brentuximab vedotin with different chemotherapy regimens (e.g. PET-adapted BrECADD). The resubmission proposed the clinical criterion be fully agnostic in terms of chemotherapy regimen. The evaluation noted that the proposed criterion allows broader use of brentuximab vedotin compared to the TGA indication, with no data presented to support the efficacy, safety, cost-effectiveness or financial implications of these regimens, including BrECADD, which is currently under TGA evaluation. Whilst the ESC acknowledged the changing clinical landscape in Hodgkin lymphoma, it considered it inappropriate for the restriction to be agnostic on the chemotherapy combination with brentuximab, noting it would allow use of brentuximab vedotin in other regimens including BrECADD, or combinations that had not been evaluated for efficacy, safety or cost effectiveness by PBAC. The pre-PBAC response amended its request for a chemotherapy regimen agnostic listing to a listing of brentuximab vedotin in combination with AVD.

3.5 The requested restriction has also been revised to be silent on age, and the ECOG status criterion was removed. The PBAC previously considered that these amendments were reasonable (para 7.4, brentuximab vedotin PSD, March 2024 PBAC meeting).

3.6 The resubmission also proposed amendments to current PBS listings for brentuximab vedotin in relapsed or refractory Hodgkin lymphoma, to allow for re-treatment following first-line therapy, and to change the restrictions from Authority Required to Authority Required (Streamlined). The PBAC previously considered that it would be appropriate to allow re-treatment with brentuximab vedotin for relapsed or refractory disease and considered a lifetime maximum of 16 treatment cycles in this setting remained appropriate (para 7.4, brentuximab vedotin PSD, March 2024 PBAC meeting). The ESC considered the March 2024 PBAC advice remained appropriate in the current clinical landscape.

3.7 The recommended dose of brentuximab vedotin according to the TGA approved PI is 1.2 mg/kg up to a maximum of 120 mg. The resubmission proposed a maximum amount of 150 mg to correspond with the minimum number of vials required to provide the maximum dose of 120 mg (each vial contains 50 mg i.e. 3 x 50 mg vials is equivalent to 150mg). The Secretariat noted that under the Section 100 (Efficient Funding of Chemotherapy) program, prescribing is based on the maximum amount of

active ingredient and not rounded to the nearest vial. As such, the maximum amount should be revised to 120mg, aligning with the TGA-approved Product Information.

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

4 Population and disease

4.1 Hodgkin lymphoma is a type of fast-growing (aggressive) blood cancer that affects a type of white blood cell called B-cell lymphocytes, which are part of the immune system. The disease is defined by the presence of unusually large, malignant (cancerous), Hodgkin-Reed-Sternberg cells, which help differentiate Hodgkin lymphoma from non-Hodgkin lymphoma. Classical Hodgkin lymphoma is typically characterised by the expression of CD30 surface markers on these cancer cells. The disease has a bimodal age distribution with peaks at 15 to 35 years of age and greater than 60 years of age. Classical Hodgkin lymphoma accounts for the majority of cases of Hodgkin lymphoma, with nodular lymphocyte predominant Hodgkin lymphoma comprising the minority of cases.

4.2 Disease staging is carried out according to the modified Ann Arbor classification that is based on the number and location of affected lymph nodes as well as whether the disease has spread to the bone marrow or other organs. The disease is further categorised by the presence or absence of B-type symptoms such as fevers, night sweats and weight loss exceeding 10% of the patient's baseline body weight. Advanced stage Hodgkin lymphoma includes stage III or IV disease (Ann Arbor classification) and stage IIB disease with bulk or extranodal disease (German Hodgkin Study Group classification).

4.3 The resubmission positioned A+AVD as a first-line treatment option for patients with previously untreated CD30 positive advanced (stage III or IV) Hodgkin lymphoma. This was unchanged from the previous submission.

4.4 The PBAC previously considered the clinical place in therapy of A+AVD was uncertain given treatment guidelines recommend the use of PET-adapted over non-PET-adapted regimens (para 7.5, brentuximab vedotin PSD, March 2024 PBAC meeting).

4.5 The resubmission stated that the National Comprehensive Cancer Network (NCCN) 2023 guidelines, presented in the March 2024 submission, have been superseded. The evaluation noted that the most recent NCCN guidelines (version 2.2025) have two preferred regimens as first-line options for stage III or IV disease: nivolumab plus AVD or BrECADD. Nivolumab plus AVD is recommended in all ages while BrECADD is recommended in patients aged 18-61 years. The evaluation noted that the guidelines state that A+AVD and PET-adapted ABVD remain useful in certain circumstances: A+AVD in patients who are not candidates for checkpoint inhibitors (e.g. nivolumab) and those without neuropathy; and PET-adapted ABVD when brentuximab vedotin and checkpoint inhibitors are not available or contraindicated. The resubmission acknowledged that the treatment landscape is evolving but made no changes to the proposed algorithm as neither nivolumab or brentuximab vedotin are listed on the

PBS for use as part of the newly recommended regimens in the updated NCCN guidelines (nivolumab plus AVD and BrECADD). The evaluation noted that this appeared inconsistent with the resubmission's requested listing that allows for the use of brentuximab vedotin as part of any multi-agent chemotherapy regimen including BrECADD. As outlined in paragraph 3.4, the ESC considered the listing should be for A+AVD only. In addition, as checkpoint inhibitors are not available for use in first-line Hodgkin lymphoma treatment in Australia the ESC considered it was reasonable that nivolumab was not included in the proposed treatment algorithm.

4.6 The resubmission also presented a current treatment algorithm for relapsed or refractory disease. Patients who fail first-line therapy may be treated with a range of salvage chemotherapy regimens (e.g. DHAP, dexamethasone, high dose cytarabine and cisplatin; IGEV, ifosfamide, gemcitabine and vinorelbine; ICE, ifosfamide, carboplatin, etoposide) with or without radiotherapy. Following salvage chemotherapy, patients are assessed for response (using Deauville scores) to determine subsequent treatment options including high dose chemotherapy (e.g. BEAM, carmustine, etoposide, cytarabine and melphalan; CBV, cyclophosphamide, carmustine, etoposide) and autologous/allogeneic stem cell transplant (ASCT).

4.7 Based on current PBS listings, patients with relapsed or refractory disease who have undergone ASCT are eligible for brentuximab vedotin or pembrolizumab. Patients with relapsed or refractory disease who have not undergone ASCT, are either unsuitable for ASCT or unsuitable for treatment with multi-agent chemotherapy and have had at least 2 prior treatments are also eligible for brentuximab vedotin or pembrolizumab. Brentuximab vedotin and pembrolizumab may be used sequentially as third- or fourth-line therapies, in no specific order. Brentuximab vedotin is TGA-approved but not PBS-listed for consolidation therapy after ASCT.

4.8 The treatment algorithm indicates that suitability for ASCT can be assessed at multiple lines of therapy. For example, patients who were not considered suitable for ASCT following second-line salvage chemotherapy can become suitable following third-line treatment with brentuximab vedotin or pembrolizumab.

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

5 Comparator

5.1 The resubmission nominated PET-adapted ABVD as the main comparator. PET-adapted ABVD consists of ABVD for the first 2 cycles with options to de-escalate to AVD for a further 4 cycles in PET-negative patients or escalate to eBEACOPP for a further 4 cycles in PET-positive patients. The PBAC previously considered that this was reasonable, noting that PET-adapted ABVD is the standard of care in Australia (para 7.6, brentuximab vedotin PSD, March 2024 PBAC meeting).

5.2 The resubmission noted that the previous submission nominated eBEACOPP as a supplementary comparator. However, the resubmission acknowledged ESC advice that eBEACOPP was standard of care for a specific subgroup of patients (used for at

least the first 2 cycles for fit patients who are less than 45 years of age) and that eBEACOPP (both non-PET adapted and PET-adapted) was unlikely to be replaced by A+AVD in clinical practice (para 5.5 and 6.53, brentuximab vedotin PSD, March 2024 PBAC meeting). Consequently, the resubmission did not consider eBEACOPP as a relevant comparator. The ESC agreed with the evaluation that this was reasonable.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (5) and organisations (4) via the Consumer Comments facility on the PBS website. The input from health care professionals described current treatment regimens with ABVD or BEACOPP as reasonably effective but noted they were associated with significant risks of short and longer term toxicity. Input highlighted that A+AVD is associated with relatively high rates of peripheral neuropathy and increased rates of infection but noted that the side effects experienced are often manageable through dosing guidelines and the use of growth factor support. The input from health care professionals also described the lower toxicity of A+AVD in terms of fertility and reduced risk of permanent lung damage. The input highlighted the importance of these aspects given Hodgkin-lymphoma commonly affects adolescents and young adults. Health care professional input also noted that access to brentuximab in the first-line setting may reduce the need for second-line treatment.

6.3 The PBAC noted the advice received from three consumer organisations. Input from Rare Cancers Australia described the impact of Hodgkin lymphoma on patients quality of life and the toxicity of the current treatment options available. Input from the Leukaemia Foundation provided comments from an individual living with Hodgkin Lymphoma which described the short and long term toxicities associated with current treatments, particularly in those diagnosed at a young age. The input from the Leukaemia Foundation highlighted that A+AVD does not necessarily provide a lower toxicity treatment option, rather an alternative toxicity profile to ABVD and highlighted it was important for more treatment options to be available to patients. The input from Lymphoma Australia highlighted the importance of having treatment options that have less impact on the future fertility of patients.

6.4 The PBAC specifically noted the advice from the Australasian Leukaemia and Lymphoma Group that the use of brentuximab vedotin may reduce the risk of relapse, and the risk of pulmonary and cardiac complications. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.5 The resubmission was based on a head-to-head trial comparing A+AVD with ABVD (as a proxy for PET-adapted ABVD) for the treatment of adult patients with previously untreated advanced (stage III or IV) Hodgkin lymphoma (ECHELON-1). The PBAC previously considered data from the primary analysis (April 2017 data cut) and an interim analysis (June 2021 data cut) of the trial. The resubmission presented new data from the March 2023 data cut.

6.6 The resubmission presented supportive evidence based on a trial of PET-adapted ABVD in adult patients with newly diagnosed advanced (Ann Arbor stage IIB, III, IV or stage IIA with adverse features) classical Hodgkin lymphoma (RATHL). The evaluation noted that the PBAC previously considered data from this trial based on the primary analysis at a median follow-up of 3.4 years (Johnson 2016). The resubmission presented additional results based on a later data cut at a median follow-up of 7.3 years (Luminari 2024).

6.7 The resubmission identified a conference abstract/poster (Kristo 2023) that presented the results of two unanchored matching adjusted indirect comparisons (MAICs) comparing the A+AVD regimen (based on individual patient data from the ECHELON-1 trial) with PET-adapted ABVD (escalation in PET-positive patients; unchanged or de-escalation in PET-negative patients; based on aggregate data from the RATHL trial) or PET-adapted ABVD (escalation in PET-positive patients, unchanged in PET-negative patients; based on aggregate data from the SWOG S0816 study). This had not previously been considered by the PBAC.

6.8 The resubmission identified two recently published Phase III trials of brentuximab vedotin-containing regimens for first-line treatment of stage III or IV Hodgkin lymphoma:

- A Phase III non-inferiority trial of PET-adapted BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone) compared to eBEACOPP in patients aged 18-60 years (HD21 trial, Borchmann 2024). At a median follow-up of 4 years, PET-adapted BrECADD was associated with improved progression-free survival (94.3%) compared to eBEACOPP (90.9%) (HR 0.66; 95% CI: 0.45, 0.97). Overall survival at 4 years was similar between the PET-adapted BrECADD (98.6%; 95% CI: 97.7, 99.5) and eBEACOPP (98.2%, 95% CI: 97.2, 99.3) arms.

- A Phase III trial evaluating nivolumab + AVD and brentuximab vedotin + AVD for treatment of patients aged ≥12 years (S1826 trial, Herrera 2024). At a median follow-up of 2.1 years, the 2-year progression-free survival was 92% (95% CI: 89, 94) with nivolumab + AVD, compared to 83% (95% CI: 79, 86) with A+AVD (HR 0.45; 95% CI: 0.30, 0.65). Overall survival at 2 years was similar between nivolumab + AVD (99%) and A+AVD (98%).

6.9 The resubmission excluded the HD21 and S1826 trials due to wrong intervention. The evaluation considered that the exclusion of the HD21 trial was inadequately justified given the resubmission's request for the proposed listing to be agnostic in terms of backbone chemotherapy, which would allow use in other regimens including PET-adapted BrECADD. However, the ESC noted that the trial included a different patient group (eBEACOPP patients, aged <60 years) and considered it reasonable to exclude. The HD21 and S1826 trials were cited as references informing changes to preferred regimens for first-line treatment of advanced Hodgkin lymphoma based on the NCCN and UpToDate guidelines.

6.10 Details of the key trial presented in the resubmission are provided in Table 3.

Table 3: Key trial and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Trials of brentuximab vedotin		
ECHELON-1 (NCT01712490)	Clinical Study Report C25003. A randomized, open-label, Phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma.	Clinical Study Report, August 2017.
	Clinical Study Report Addendum 1. Study C25003 (ECHELON-1). A randomized, open-label, Phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma.	Clinical Study Report Addendum 1, May 2022.
	Clinical Study Report Addendum 3. Study C25003 (ECHELON-1). A randomized, open-label, Phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma.	Clinical Study Report Addendum 3, June 2024.
	Connors *et al*. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma.	*N Engl J Med* 2018; 378: 331-344.
	Straus *et al*. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial.	*Lancet Haematol* 2021; 8: e410-e421.
	Ansell *et al*. Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma.	*N Engl J Med* 2022; 387: 310-320.

Source: Table 2.3, p65; Table 2.43, p148 of the resubmission
Note: Blue shading delineates data presented in the March 2024 submission

6.11 The key features of the ECHELON-1 trial are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
A+AVD versus ABVD						
ECHELON-1	1,334	Phase III, MC, OL, RCT. Primary analysis period (median 24 months follow-up) and up to 10 years follow-up	High	Adult patients with previously untreated stage III or IV classical Hodgkin lymphoma	mPFS, OS, complete remission, overall response	Patient characteristics, use of ASCT, mPFS, adverse events, EQ-5D-3L

Source: Section 2.4, pp71-90 of the resubmission
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, autologous or allogeneic stem cell transplant; MC, multi-centre; mPFS, modified progression-free survival; OL, open label; OS, overall survival; RCT, randomised controlled trial

6.12 The open-label trial design has the potential to introduce bias, as knowledge of treatment assignment may affect disease management decisions and assessment of

outcomes that are not centrally assessed. The risk of bias was minimised for efficacy and safety results that were reviewed by an independent review facility during the primary analysis period (April 2017 data cut). The independent review facility was disbanded after this period, therefore there is potential risk of bias for outcomes that were investigator-assessed only during the post-treatment follow-up period.

6.13 The resubmission noted that the use of ABVD for 6 cycles in the comparator arm of the key trial was not aligned with standard of care in the Australian setting, based on PET-adapted ABVD, which allows for treatment modifications after 2 cycles of ABVD (de-escalation to AVD or escalation to eBEACOPP for a further 4 cycles). ESC previously considered that this may affect the applicability of efficacy and safety data from the trial to the Australian setting (para 6.11, brentuximab vedotin PSD, March 2024 PBAC meeting).

6.14 The resubmission claimed the safety profile of A+AVD in the ECHELON-1 trial may be worse than in clinical practice as not all patients received G-CSF as primary prophylaxis in the trial. The use of G-CSF, which was permitted in the trial, was subsequently recommended for all patients randomised to receive A+AVD after an interim safety analysis. The brentuximab vedotin product information recommends primary prophylaxis with G-CSF for previously untreated Hodgkin lymphoma.

Comparative effectiveness

A+AVD versus ABVD

6.15 The primary outcome in the ECHELON-1 trial was modified progression-free survival which, in addition to progressive disease and death, included receipt of subsequent anti-cancer therapy in patients not in complete response after completion of frontline therapy, defined as Deauville scores ≥3. The PBAC previously stated that modified progression-free survival was more likely to reflect what would occur clinically in this context than the analyses of progression-free survival using standard definitions (para 7.7, brentuximab vedotin PSD, March 2024 PBAC meeting).

6.16 Table 5 presents a summary of modified progression-free survival, independently reviewed for the primary analysis period (April 2017 data cut) and investigator-assessed for the interim analysis (June 2021 data cut) and exploratory analysis (March 2023 data cut). Data from the June 2021 data cut were used in the economic model of the resubmission, unchanged from the March 2024 submission.

Table 5: Modified progression-free survival in ECHELON-1

	A+AVD N=664	ABVD N=670
Primary analysis, independently reviewed (April 2017 data cut)		
Median follow-up, months (95% CI)	24.9 (24.6, 25.0)	24.9 (24.6, 25.1)
Events, n (%) - Disease progression - Death - Subsequent treatment after noncomplete response [a]	117 (18) 90 (14) 18 (3) 9 (1)	146 (22) 102 (15) 22 (3) 22 (3)
Censored, n (%)	547 (82.4) [b]	524 (78.2) [b]
Kaplan-Meier estimates, % (95% CI) - 6 months - 1 year - 2 years - 3 years	 95.5 (93.5, 96.8) 86.3 (83.3, 88.7) 82.1 (78.7, 85.0) 78.8 (74.7, 82.3)	 94.9 (92.9, 96.4) 80.7 (77.3, 83.6) 77.2 (73.7, 80.4) 74.7 (70.8, 78.2)
Hazard ratio (95% CI)	**0.770 (0.603, 0.982)**	
Interim analysis, investigator-assessed (June 2021 data cut)		
Median follow-up, months (95% CI)	73.3 (72.5, 74.1)	71.6 (70.4, 72.9)
Events, n (%) - Disease progression - Death - Subsequent treatment after noncomplete response [a]	135 (20) 80 (12) 16 (2) 39 (6)	183 (27) 111 (17) 28 (4) 44 (7)
Censored, n (%)	529 (79.7) [b]	487 (72.7) [b]
Kaplan-Meier estimates, % (95% CI) - 6 months - 1 year - 2 years - 3 years - 7 years	 95.5 (93.6, 96.9) 83.4 (80.3, 86.0) 81.1 (77.9, 84.0) 80.1 (76.8, 83.0) 78.8 (75.4, 81.7)	 93.5 (91.3, 95.1) 77.0 (73.5, 80.0) 74.4 (70.9, 77.6) 73.1 (69.4, 76.3) 70.9 (67.1, 74.3)
Hazard ratio (95% CI)	0.708 (0.566, 0.884) [c]	
Exploratory analysis, investigator-assessed (March 2023 data cut)		
Median follow-up, months (95% CI)	90.1 (87.7, 90.9)	86.4 (84.40, 89.7)
Events, n (%) - Disease progression - Death - Subsequent treatment after noncomplete response [a]	135 (20) 80 (12) 16 (2) 39 (6)	184 (27) 111 (17) 28 (4) 45 (7)
Censored, n (%)	529 (79.7) [b]	486 (72.7) [b]
Kaplan-Meier estimates, % (95% CI) - 6 months - 1 year - 2 years - 3 years - 7 years - 8 years	 95.5 (93.6, 96.9) 83.3 (80.2, 86.0) 81.1 (77.9, 83.9) 80.1 (76.8, 83.0) 78.7 (75.3, 81.7) 78.7 (75.3, 81.7)	 93.5 (91.3, 95.1) 76.8 (73.4, 79.9) 74.3 (70.7, 77.5) 72.9 (69.3, 76.2) 70.7 (67.0, 74.1) 70.7 (67.0, 74.1)
Hazard ratio (95% CI)	0.704 (0.564, 0.880) [c]	

Source: Tables 2.16, p81 of the resubmission; Table 11.g, p108 of the ECHELON-1 clinical study report and Table 3.n, p51 of the ECHELON-1 clinical study report addendum 1; Table 3.n, p51 of the ECHELON-1 clinical study report addendum 3

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; mPFS, modified progression-free survival

Bolded results were statistically significant

[a] Noncomplete response was defined as a Deauville score of ≤3 at the end-of-treatment PET scan

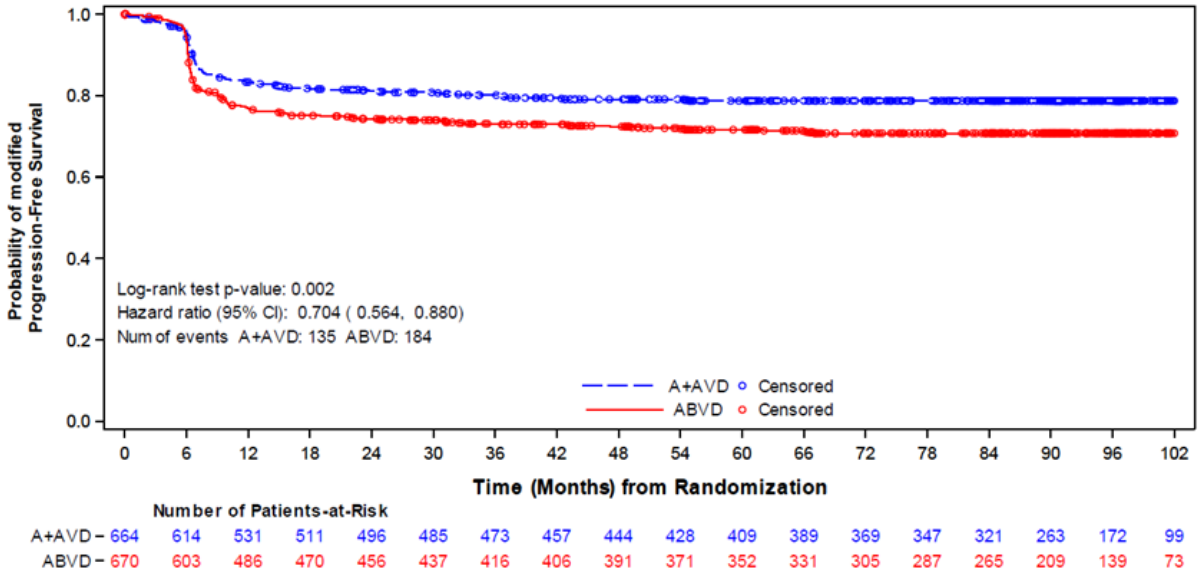
[b] The primary reason for censoring was no documented mPFS event at the time of analysis

[c] The 95% CI was descriptive and unadjusted for multiplicity

Note: Blue shading delineates data presented in the March 2024 submission

6.17 Figure 1 presents the Kaplan-Meier plot for investigator-assessed modified progression-free survival based on the March 2023 data cut.

Figure 1: Modified progression-free survival, investigator-assessed (ITT population, March 2023 data cut)



Source: Figure 2.5, p84 of the resubmission

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; ITT, intent to treat

6.18 Median modified progression-free survival was not reached in either treatment arm. For the primary analysis period (April 2017 cut-off), modified progression-free survival was statistically significantly improved in the A+AVD group compared to the ABVD group. Results based on later data cuts (June 2021 and March 2023) also favoured A+AVD, with greater numerical benefit compared to results from the primary analysis period. The PBAC previously considered that results from later data cuts that are not independently reviewed may be subject to bias (para 7.7, brentuximab vedotin PSD, March 2024 PBAC meeting).

6.19 The trial included pre-specified subgroup analyses for modified progression-free survival (primary analysis period only). Almost all subgroups demonstrated a consistent trend, with results favouring patients in the A+AVD arm compared to the ABVD arm (HR <1). However, there were subgroups where the hazard ratio was ≥1 including patients aged ≥60 years, patients aged ≥65 years and patients with no extranodal sites. There was also a numerically greater benefit for patients with stage IV disease treated with A+AVD (28.9% relative risk reduction) compared to patients with stage III disease (7.8% relative risk reduction). The evaluation considered that the magnitude of benefit of A+AVD in patients aged ≥60 years and patients with stage III disease is uncertain, however, the analyses were not powered to detect statistically significant differences. No interaction testing was performed.

6.20 Table 6 presents a summary of overall survival from the primary analysis period (April 2017 data cut), second interim analysis (June 2021 data cut) and final analysis (March 2023 data cut).

Table 6: Overall survival in ECHELON-1

	A+AVD N=664	ABVD N=670
Primary analysis period (April 2017 data cut)		
Median follow-up, months (95% CI)	28.0 (26.4, 28.3)	27.5 (25.9, 28.1)
Deaths, n (%)	28 (4)	39 (6)
Censored, n (%)	636 (96)	631 (94)
Kaplan-Meier estimates, % (95% CI)		
- 6 months	98.3 (97.0, 99.1)	98.1 (96.8, 98.9)
- 1 year	97.4 (95.8, 98.4)	96.9 (95.2, 98.0)
- 2 years	96.6 (94.8, 97.7)	94.9 (92.9, 96.4)
- 3 years	94.4 (91.4, 96.4)	92.9 (90.1, 95.0)
Hazard ratio (95% CI)	0.72 (0.44, 1.17)	
Interim analysis (June 2021 data cut)		
Median follow-up, months (95% CI)	73.3 (72.6, 74.1)	72.4 (71.1, 73.6)
Deaths, n (%)	39 (6)	64 (10)
Censored, n (%)	625 (94)	606 (90)
Kaplan-Meier estimates, % (95% CI)		
- 6 months	98.3 (97.0, 99.1)	98.1 (96.8, 98.9)
- 1 year	97.2 (95.7, 98.3)	96.7 (95.1, 97.9)
- 2 years	96.5 (94.7, 97.6)	94.7 (92.6, 96.2)
- 3 years	95.6 (93.7, 97.0)	93.3 (91.1, 95.0)
- 7 years	93.3 (90.7, 95.2)	88.7 (85.6, 91.1)
Hazard ratio (95% CI)	**0.59 (0.40, 0.88)**	
Final analysis (March 2023 data cut)		
Median follow-up, months (95% CI)	90.1 (87.69, 90.81)	88.3 (85.16, 89.86)
Deaths, n (%)	46 (7)	69 (10)
Censored, n (%)	618 (93)	601 (90)
Kaplan-Meier estimates, % (95% CI)		
- 6 months	98.3 (97.0, 99.1)	98.1 (96.8, 98.9)
- 1 year	97.2 (95.7, 98.3)	96.7 (95.1, 97.9)
- 2 years	96.5 (94.7, 97.6)	94.7 (92.6, 96.2)
- 3 years	95.6 (93.7, 97.0)	93.3 (91.1, 95.0)
- 7 years	93.5 (91.1, 95.2)	88.8 (85.8, 91.1)
- 8 years	92.6 (90.0, 94.5)	88.0 (84.9, 90.5)
Hazard ratio (95% CI)	0.62 (0.42, 0.90) [a]	

Source: Table 2.5-3, p99 of the resubmission; Table 11.q, p130 of the ECHELON-1 Clinical Study Report Addendum 1; Table 3.c, p24 of the ECHELON-1 Clinical Study Report Addendum 3

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; NE, not estimable; OS, overall survival

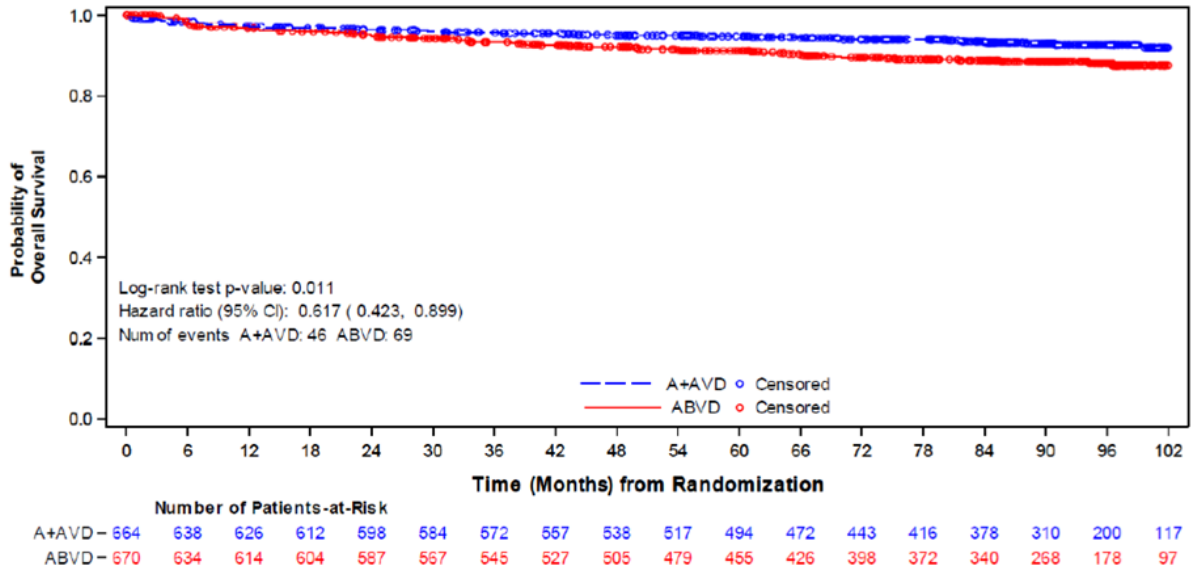
Bolded results were statistically significant

[a] The 95% confidence interval was descriptive only

Note: Blue shading delineates data presented in the March 2024 submission.

6.21 Figure 2 presents the Kaplan-Meier plot for overall survival based on the March 2023 data cut.

Figure 2: Overall survival (ITT population, March 2023 data cut)



Source: Figure 2.6, p87 of the resubmission

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; ITT, intent to treat

6.22 Median overall survival was not reached for either treatment arm. Results from the primary analysis indicated improved overall survival in the A+AVD arm compared to the ABVD arm, although the results did not achieve statistical significance. However, the second interim analysis (June 2021 data cut) showed statistically significantly improved overall survival for A+AVD compared to ABVD. Results from the final analysis (March 2023 data cut) showed improved overall survival in favour of A+AVD compared to ABVD and was of nominal statistical significance.

6.23 Pre-specified subgroup analyses were conducted based on data from the final analysis. The results suggest more favourable overall survival estimates for A+AVD compared to ABVD in patients aged <60 years and no apparent difference in overall survival between arms in patients aged ≥60 years. The analyses also showed more favourable overall survival estimates for A+AVD compared to ABVD in patients with stage IV disease and no apparent difference between arms in patients with stage III disease. There were also potential differences in the magnitude of benefit associated with A+AVD compared to ABVD in other subgroups according to region, international prognostic factors, presence of B symptoms, number of extra nodal sites, ECOG status and gender.

6.24 Overall, the evaluation considered that the subgroup analyses suggest that survival benefit in the overall population may have been driven primarily by patients with stage IV disease and those aged <60 years. However, the evaluation considered that the analyses should be interpreted with caution as the analyses were not powered to detect statistically significant differences between arms, with no interaction testing.

6.25 The PBAC previously noted both modified progression-free survival and overall survival data were subject to relatively high levels of censoring as most patients had

yet to experience an event, with potential confounding due to the use of subsequent treatments (para 7.7, brentuximab vedotin PSD, March 2024 PBAC meeting).

6.26 The resubmission presented patient-reported outcomes based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30 (EORTC QLQ-C30) and health utility values captured via the EQ-5D-3L instrument. Results from both instruments indicated worsening trends in both arms during the frontline treatment period that was worse for the A+AVD group compared to the ABVD group. Both arms improved during the post-treatment follow-up period (up to 36 months after the end of treatment) with no appreciable differences between arms.

6.27 The trial also captured the impact of lung toxicity using the Functional Assessment of Chronic Illness Therapy (FACIT) Dyspnea 10 and neurotoxicity using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) subscale during the frontline treatment period. A trend was observed for worsening dyspnoea and functional limitation for patients on A+AVD compared to ABVD, however, the trial report noted there is no established MCID for the FACIT-Dyspnea 10 and assumed no clinically important differences between arms based on a 0.5 standard deviation of baseline scores. Mean neurotoxicity scores were worse in the A+AVD arm compared to the ABVD arm during treatment. The trial investigators considered the differences to be clinically meaningful and reflective of the higher proportion of patients in the A+AVD arm experiencing peripheral neuropathy.

6.28 All patient-reported outcomes were also analysed according to whether patients had experienced a modified progression-free survival event within each treatment arm. The trial report noted no clinically meaningful differences associated with a modified progression-free survival event.

A+AVD versus PET-adapted ABVD

6.29 The PBAC previously considered evidence from the RATHL (PET-adapted ABVD with escalation in PET-positive patients; unchanged or de-escalation in PET-negative patients), AHL2011 (PET-adapted eBEACOPP; unchanged in PET-positive patients or de-escalation to ABVD in PET-negative patients versus non-PET-adapted eBEACOPP) and HD18 (PET-adapted eBEACOPP; unchanged or escalation in PET-positive patients and unchanged or de-escalation in PET-negative patients) trials. The trials contribute to the main body of evidence informing PET-adapted regimens in published guidelines.

6.30 The evaluation noted that the study designs of the RATHL, AHL2011 and HD18 trials were complex, with different points of randomisation and escalation/de-escalation of investigated treatment regimens which limited comparability between these trials and the key trial, ECHELON-1.

6.31 The PBAC previously considered the lack of a common reference and limited comparability between trials of PET-adapted regimens and ECHELON-1 precluded any useful indirect comparisons. The PBAC agreed with ESC that the RATHL trial was not designed to compare ABVD with BEACOPP-based regimens in PET-positive patients.

Therefore, the overall comparative efficacy and safety of PET-adapted ABVD (with options to escalate/de-escalate treatment) compared to non-PET-adapted ABVD remains uncertain (para 6.32 and 7.8, brentuximab vedotin PSD, March 2024 PBAC meeting).

6.32 The resubmission identified one conference abstract/poster (Kristo 2023) that presented the results of two unanchored MAICs comparing the A+AVD regimen (based on individual patient data from the ECHELON-1 trial) with PET-adapted ABVD (escalation in PET-positive patients; unchanged or de-escalation in PET-negative patients; based on aggregate data from the RATHL trial) or PET-adapted ABVD (escalation in PET-positive patients, unchanged in PET-negative patients; based on aggregate data from the SWOG S0816 study). The evaluation considered that the MAICs suggested that treatment with A+AVD was associated with statistically significant improvements in progression-free survival and potentially overall survival compared to PET-adapted ABVD regimens. The poster identified in the resubmission was based on a sponsor-commissioned report which was not provided with the resubmission (with no justification provided in the resubmission) and has not been published in a peer-reviewed publication. As a consequence, the evaluation considered that the there was insufficient documentation to adequately assess the validity of the MAICs and therefore these analyses should not be considered reliable.

Comparative harms

6.33 Table 7 summarises the safety outcomes in ECHELON-1 during the primary analysis period (April 2017 data cut). The evaluation noted that adverse event data were based on patient incidence only, which does not capture the occurrence of multiple events of the same type in individual patients.

Table 7: Key adverse events in ECHELON-1 (safety population, ≤30 days after last dose of frontline treatment)

Patients, n (%)	A+AVD N=662	ABVD N=659
Any adverse event	653 (99)	646 (98)
Grade 3 or higher adverse event	549 (83)	434 (66)
Serious adverse event	284 (43)	178 (27)
Adverse events resulting in study drug discontinuation	88 (13)	105 (16)
Adverse event resulting in dose modification	423 (64)	293 (44)
On-study deaths	9 (1)	13 (2)
Deaths due to study treatment-related adverse events	8 (1)	7 (1)
Adverse events of special interest		
Neutropenia	454 (69)	361 (55)
Febrile neutropenia	128 (19)	52 (8)
Peripheral neuropathy	442 (67)	286 (43)
Pulmonary toxicity	12 (2)	44 (7)
Infusion-related reactions	57 (9)	100 (15)

Source: Table 12.f, p234 of the ECHELON-1 clinical study report
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine
Note: Blue shading delineates data presented in the March 2024 submission

6.34 Almost all patients in both treatment arms experienced an adverse event. Treatment-emergent adverse events reported in ≥10% of patients in either treatment arm and in ≥10% more patients in the A+AVD arm compared to the ABVD arm were neutropenia, peripheral neuropathy, weight decreased, abdominal pain, anaemia and febrile neutropenia. Adverse events leading to premature discontinuation of study drug were reported more frequently for patients in the ABVD arm compared to the A+AVD arm. However, more patients in the A+AVD arm experienced adverse events resulting in dose modifications compared to ABVD, most commonly due to neutropenia and neuropathy.

6.35 More patients in the A+AVD arm experienced a serious adverse event compared to those in the ABVD arm. The most frequently reported serious adverse events in the A+AVD arm were febrile neutropenia, pyrexia, neutropenia, pneumonia, abdominal pain, sepsis, constipation, diarrhoea, pulmonary embolism, vomiting and dehydration. In the ABVD arm, the most frequently reported serious adverse events were febrile neutropenia, pyrexia, pneumonia and pneumonitis.

6.36 On-study death occurred in 9 patients in the A+AVD arm. Of these deaths, 8 were considered treatment related by the investigator. The majority of on-study deaths were associated with neutropenia and its complications, including neutropenic sepsis and septic shock. Most of the deaths (6 of 9) occurred in the first cycle of treatment. None of the A+AVD patients who died on-study had received G-CSF primary prophylaxis.

6.37 In the ABVD arm, on-study death occurred in 13 patients and 7 of these were considered treatment related by the investigator. The majority of on-study deaths

were associated with pulmonary toxicity. Most of the deaths (10 of 13) occurred in the fifth and sixth cycles of treatment.

6.38 As of the March 2023 cut off, there were 46 deaths (7%) in the A+AVD arm and 69 deaths (10%) in the ABVD arm. The deaths of 22 patients (3%) in the A+AVD arm and 30 patients (5%) in the ABVD arm were considered disease related.

6.39 The resubmission claimed the safety profile of A+AVD in the trial may be worse than in clinical practice due to differences in the use of G-CSF primary prophylaxis. Subgroup analyses indicated a lower incidence of febrile neutropenia, neutropenia, infections and infestations and deaths in both treatment arms with use of G-CSF by day 5 of the first treatment cycle. However, the proportion of patients with these adverse events (including serious adverse events) remained higher in the A+AVD arm compared to the ABVD arm regardless of G-CSF use.

6.40 The trial included a comprehensive review of the frequency and severity of peripheral neuropathy events. The most frequently reported peripheral neuropathy events were peripheral sensory neuropathy, peripheral neuropathy, paraesthesia and peripheral motor neuropathy. A higher proportion of patients in the A+AVD arm had peripheral neuropathy events of Grade 3 or higher severity (9%) compared to those in the ABVD arm (2%). At the latest follow-up (March 2023 data cut), more patients in the A+AVD arm (28%) had ongoing peripheral neuropathy compared to the ABVD arm (20%). A higher proportion of patients in the A+AVD arm (24%) had ongoing peripheral motor neuropathy events compared to the ABVD arm (10%).

6.41 Pulmonary toxicity is known to be associated with bleomycin, which is the likely contributor to the increased incidence of these events in the ABVD arm compared to the A+AVD arm. Serious pulmonary toxicity events were reported for 5 A+AVD patients (<1%) and 21 ABVD patients (3%), including 3 ABVD patients with a fatal event. No fatal events related to pulmonary toxicity were reported for the A+AVD arm. Pulmonary toxicity was not systematically assessed after the completion of frontline treatment.

6.42 Secondary malignancy was a long-term safety outcome reported in the trial. Based on the March 2023 data cut, a secondary malignancy (solid tumours and haematological malignancies) was reported for 33 patients in the A+AVD arm (5%) and 39 patients in the ABVD arm (6%). The incidence of secondary malignancies was higher among patients aged ≥60 years, occurring in 12 patients in the A+AVD arm (12%) and 17 patients in the ABVD arm (17%).

6.43 Fertility was not formally assessed in the trial; however, similar numbers of pregnancies were recorded in each arm at the March 2023 cut off. There were 165 pregnancies in 92 patients or partners in the A+AVD group (14%) and 73 pregnancies in patients or partners in the ABVD group (11%).

6.44 The resubmission presented data on potential safety concerns based on the Periodic Benefit-Risk Evaluation Report (PBRER) for the period from 19 August 2023 to 18 August 2024. Important identified risks included progressive multifocal

leukoencephalopathy, pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin, peripheral neuropathy, myelosuppression, infections, infusion-related reactions, hyperglycaemia, Steven-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), tumour lysis syndrome and anti-drug antibodies. Important potential risks were severe hepatotoxicity, pulmonary toxicity, gastrointestinal complications, reproductive toxicity and thymus depletion (paediatrics). Missing information included long term safety. No new safety signals were identified during the reporting period.

6.45 The evaluation noted that there are limited long-term safety data particularly for late complications such as secondary malignancies as these tend to occur 10 to 20 years post treatment, beyond the planned follow-up for the ECHELON-1 trial.

Benefits/harms

6.46 On the basis of direct evidence presented in the resubmission, after a median duration of follow-up of 2 years (April 2017 cut off), for every 100 patients treated with A+AVD compared to ABVD:

- Approximately 4 fewer patients would experience a modified progression-free survival event at 3 years (disease progression, death or subsequent treatment after incomplete response at the end of frontline treatment).
- There would be no apparent difference in deaths.
- Approximately 16 additional patients would experience a serious adverse event that is life-threatening or required hospitalisation.
- Approximately 14 additional patients would experience neutropenia.
- Approximately 11 additional patients would experience febrile neutropenia.
- Approximately 24 additional patients would experience peripheral neuropathy.
- Approximately 5 fewer patients would experience pulmonary toxicity.

6.47 On the basis of direct evidence presented in the submission, after a median duration of follow-up of 7.5 years (March 2023 data cut), for every 100 patients treated with A+AVD compared to ABVD:

- Approximately 8 fewer patients would experience a modified progression-free survival event at 8 years (disease progression, death or subsequent treatment after incomplete response at the end of frontline treatment).
- Approximately 5 fewer patients would have died at 8 years.

6.48 Comprehensive safety data were not available for the March 2023 data cut.

Clinical claim

6.49 The resubmission described A+AVD as superior in terms of efficacy compared to PET-adapted ABVD (using non-PET-adapted ABVD as a proxy). The PBAC previously

considered that the claim of superior efficacy for A+AVD compared to PET-adapted ABVD (with options to escalate/de-escalate treatment) was highly uncertain based on the supportive evidence presented and high level of censoring in the key trial, but likely to be reasonable (para 7.8, brentuximab vedotin PSD, March 2024 PBAC meeting). The ESC considered that the level of uncertainty associated with the claim of superior efficacy had been reduced with the extended patient follow-up data presented in the resubmission. The ESC considered the clinical claim of superior efficacy was met for both modified progression free survival and overall survival.

6.50 The resubmission claimed that non-PET-adapted ABVD is similar to PET-adapted ABVD in terms of efficacy and therefore the ABVD arm of ECHELON-1 is a reasonable proxy for the efficacy of PET-adapted ABVD. The evaluation considered that this claim was inadequately supported by the indirect evidence comparing A+AVD and PET-adapted ABVD. The ESC noted that the PBAC had previously considered the use of the ABVD arm from the ECHELON-1 trial as a proxy was uncertain but overall, the Committee had accepted the claim of superior comparative effectiveness was likely to be reasonable (para 7.8 and 7.9, brentuximab vedotin PSD, March 2024 PBAC meeting).

6.51 The resubmission described A+AVD as inferior in terms of safety compared to PET-adapted ABVD. The PBAC previously considered that this was reasonable (para 7.10, brentuximab vedotin PSD, March 2024 PBAC meeting). The resubmission did not present new comparative safety data. The ESC considered the claim of inferior safety remained reasonable.

6.52 The PBAC considered that the claim of superior comparative effectiveness was reasonable and agreed with the ESC that the level of uncertainty associated with the claim had been reduced with the extended follow-up data presented in the resubmission.

6.53 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.54 The resubmission presented a cost-utility analysis of A+AVD compared to ABVD (as a proxy for PET-adapted ABVD) in patients with previously untreated CD30+ stage III or IV Hodgkin lymphoma. The economic evaluation was based on data from the ECHELON-1 trial as well as other modelled variables.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness/cost-utility analysis
Treatments	A+AVD versus ABVD (as a proxy for PET-adapted ABVD)
Outcomes	Life years and quality-adjusted life years
Time horizon	65 years in the base case versus a maximum of 8.1 years (97 months) in ECHELON-1 (June 2021 data cut)
Cycle length	4 weeks
Methods used to generate results	Described as a Markov model in the resubmission but computationally also included features of a partitioned survival analysis
Health states	8 treatment health states based on fixed pathways according to ASCT eligibility:

Component	Description
	- 1st line A+AVD or ABVD - Transplant eligible: • 2nd line ICE+ASCT, • 3rd line pembrolizumab • 4th line GemVino - Transplant ineligible • 2nd line DHAP • 3rd line pembrolizumab • 4th line GemVino - Dead
Allocation to health states	1st line A+AVD or ABVD: Modified PFS Kaplan-Meier estimates from ECHELON-1 up to 6.6-6.8 years, extrapolated using loglogistic mixture cure models (weighted curves based on statistically cured and uncured fractions). Fixed proportion of progression events that are deaths based on ECHELON-1 data. Transplant eligible, 2nd line ICE+ASCT: PFS Kaplan-Meier estimates synthesised from Brockelmann 2021 and Viviani 2024 studies up to 7 years, extrapolated using a lognormal mixture cure model. Fixed proportion of progression events that are deaths, assumed to be the same as 1st line treatment. Transplant eligible, 3rd line pembrolizumab: PFS Kaplan-Meier estimates synthesised from the Younes 2012 study up to 1.7 years, extrapolated using a Weibull standard parametric function. The resubmission used the same source to inform OS in 3rd and 4th line treatment (see description for transplant eligible, 4th line GemVino). Transplant eligible, 4th line GemVino: Disease status was not explicitly modelled. OS was synthesised from the Younes 2012 study up to 1.83 years, extrapolated using a Weibull standard parametric function. The model used an inconsistent approach to estimate costs in patients who initiate 4th line treatment (based on patients who failed 3rd line treatment, excluding a fixed a proportion of progression events that are deaths, assumed to be the same as 1st line treatment) compared to life years and quality-adjusted life years (based on the difference between modelled OS and progression-free survival curves). Transplant ineligible, 2nd line DHAP: PFS Kaplan-Meier estimates synthesised from the Brockelmann 2021 study up to 9 years, extrapolated using a Weibull standard parametric function. Transplant ineligible, 3rd line pembrolizumab: PFS Kaplan-Meier estimates synthesised from the Brockelmann 2017 study up to 1.8 years, extrapolated using a Weibull standard parametric function. The source used to inform OS in 3rd and 4th line treatment is described below for transplant ineligible, 4th line GemVino. Transplant ineligible, 4th line GemVino: Disease status was not explicitly modelled. OS was synthesised from the Brockelmann 2017 study up to 1.75 years, extrapolated using a Weibull standard parametric function. The model used an inconsistent approach to estimate costs in patients who initiate 4th line treatment compared to life years and QALYs (same as described for transplant eligible, 4th line treatment). Background mortality was informed by age- and sex-specific general population mortality estimates from the Australian Life Tables 2020-2022. In the model, background mortality was applied from various extrapolation points. The estimates for first-line treatment were informed by mean baseline age and sex distribution in ECHELON-1 and separately for each subsequent line of therapy based on time of entry into these health states. Background mortality was also adjusted for excess mortality using a standardised mortality ratio of 2.2 (Dores 2020). Adverse events were modelled using trial-based incidence of adverse events in ECHELON-1.

Component	Description
Utilities	First-line on- and off-treatment utility values for A+AVD and ABVD were derived from a regression model of EQ-5D-3L individual patient data from ECHELON-1. Subsequent line treatment utility values (second-, third- and fourth-line, transplant eligible and transplant ineligible pathways) were derived using a multiplicative approach, based on calculated ratios using published estimates from Delea 2019 applied to the A+AVD on-treatment utility value in the model. Age-based utility adjustments were applied using a multiplicative approach based on Australian general population EQ-5D-3L utility estimates from Clemens 2014.
Costs	First-line drug costs were based on circumstances of use of A+AVD in ECHELON-1 and assumed for PET-adapted ABVD based on published guidelines. Subsequent treatment costs were pre-defined based on transplant eligibility following failure of first-line treatment. Chemotherapy and immunotherapy costs were based on recommended regimens as per eviQ protocols and PBS drug costs. ASCT costs were based on NHCDC 2021-22 Public Sector Acute Cost Weights. Treatment administration costs were based on MBS item fees and recommended dosing frequencies. Disease monitoring costs were based on MBS item fees and monitoring schedules as per published guidelines (ESMO, NCCN), the ECHELON-1 trial and expert opinion. Adverse event costs were based on hospitalisation costs for severe adverse events occurring in the ECHELON-1 trial using NHCDC 2021-22 Public Sector Acute Cost Weights.
Discounting	5% per year applied to costs and outcomes
Software package	Microsoft Excel

Source: Table 3.2, p185 of the resubmission

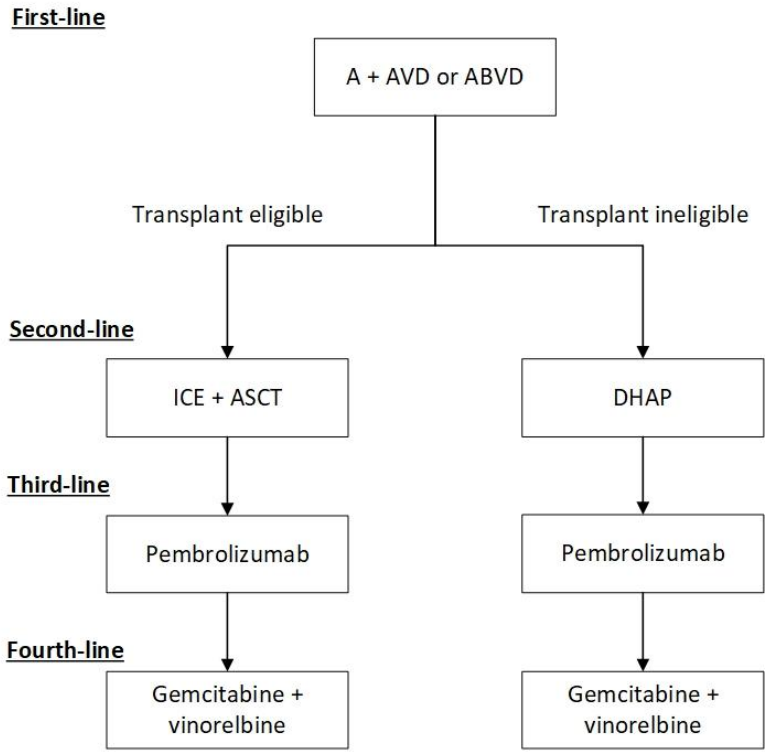
Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, allogeneic or autologous stem cell transplant; AR-DRG, Australian Refined Diagnosis Related Groups; DHAP, dexamethasone, cytarabine, cisplatin; GemVino, gemcitabine and vinorelbine; ICE, ifosfamide, carboplatin, etoposide; NHCDC, National Hospital Cost Data Collection; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival

6.55 The resubmission presented a new economic analysis, given substantial issues raised regarding the partitioned survival analysis structure in the previous submission (see Table 2).

6.56 The model structure was described in the resubmission as a Markov model that was broadly aligned with published economic evaluations. Computationally, the model included features of both a Markov model and partitioned survival analysis, given the mixed use of time-dependent transition probabilities and area under the curve for allocation of patients across health states.

6.57 All patients entering the model receive first-line treatment with either A+AVD or ABVD. In each 4-week cycle, patients can either remain in the same health state, experience disease progression, or die. Patients who experience disease progression are assumed to receive a subsequent line of therapy via an assigned treatment pathway based on transplant eligibility (illustrated in Figure 3 below).

Figure 3: Treatment pathways in the model



Source: constructed during the evaluation based on Section 3.2.2, p203 of the resubmission
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, allogeneic or autologous stem cell transplant; DHAP, dexamethasone, cytarabine, cisplatin; ICE, ifosfamide, carboplatin, etoposide

6.58 In each cycle, patients in subsequent treatment health states can either remain in the same health state, experience disease progression or die. A simplified approach was used to model the risk of death in patients in third- and fourth-line treatment health states (based on the same overall survival curve), assuming no difference in survival outcomes in patients initiating fourth-line treatment. Disease status was not explicitly modelled in patients who received fourth-line treatment and patients could either remain in the health state or die.

6.59 The model tracked time from entry into subsequent treatment health states to allow for implementation of time-dependent probabilities of disease progression or death from the point of treatment initiation.

6.60 The evaluation noted that subgroup analyses of the ECHELON-1 trial based on age and disease stage also indicated that survival benefit in the overall population may have been primarily driven by patients aged ≤60 years and those with stage IV disease. The evaluation considered that the cost-effectiveness of A+AVD in patients aged ≥60 years and those with stage III disease is uncertain.

6.61 Key drivers of the economic model are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Model structure (fixed treatment pathways)	The evaluation considered the fixed treatment pathways according to transplant eligibility were inconsistent with the proposed algorithm for relapsed or refractory disease in the resubmission. The treatment algorithm indicates that suitability for ASCT can be assessed at multiple points of care while the model assumed patients received ASCT at a specific time point, following failure of first-line treatment only. The model structure only allows for receipt of immunotherapies (pembrolizumab as a proxy for brentuximab vedotin) as third-line treatment, which does not reflect the potential for sequential use of brentuximab vedotin and pembrolizumab (consistent with current PBS listings). The model inappropriately assumes that subsequent treatments are initiated upon disease progression only and does not capture the use and associated benefits of consolidation treatments such as radiotherapy in patients at high risk of relapse. The resubmission acknowledged concerns with the applicability of published data used to inform modelled outcomes associated with subsequent treatments due to differences in known prognostic factors such as age, gender, disease severity and use of prior therapies. The resubmission acknowledged that outcomes in some health states may be underestimated. This appears to be the case, as data from relevant studies of brentuximab vedotin treatment after ASCT (Chen 2016, Moskowitz 2015) suggest substantially higher PFS and OS rates compared to model outputs. Overall, the structure and inputs used are likely to underestimate treatment benefits associated with subsequent therapies. The impact of this approach could not be quantified. The Pre-Sub-Committee Response (PSCR) acknowledged limitations of the model raised by the evaluation but argued that the model structure reflects the typical treatment pathway for 'average' patients with previously untreated classical Hodgkin lymphoma. The PSCR stated that the approach is consistent with that adopted in published economic models (e.g. Delea 2019 and Raymakers 2020) where the modelled cohort follows a fixed treatment pathway after being separated into ASCT eligible and ineligible populations following failure of frontline treatment. The PSCR argued that limitations must be considered in the context of the available clinical evidence, and what can reasonably be included in an economic model, noting that it cannot capture every possible combination and permutation of treatments that may occur in clinical practice. The ESC considered that it was reasonable to not add additional complexity to the model and considered the current structure provided a reasonable basis for decision making. The ESC noted that assumptions testing the halving of mortality rates associated with subsequent treatments in the model had negligible impacts on the ICER (see Table 13), suggesting any impact of underestimating treatment benefits is likely to be small.	Uncertain, favours A+AVD

Description	Method/Value	Impact
Baseline age	Based on mean age at baseline of 39.5 years in the ECHELON-1 trial, used to inform background mortality (adjusted for disease-related excess mortality). The resubmission did not adequately justify the use of mean age at baseline to estimate background mortality rather than weighted average estimates based on the distribution of patients in ECHELON-1 (as per the previous submission). It is unclear whether the resubmission's approach is appropriate given the bimodal age distribution of this condition. The PSCR noted this approach was applied due to the revised Markov model structure where use of a weighted average age could not be easily accommodated without significantly impacting computational complexity. The ESC agreed with the PSCR that the different approaches are unlikely to have a significant impact on the ICER. Additionally, the magnitude of benefit of A+AVD versus ABVD in patients aged ≥60 years is uncertain, with subgroup analyses indicating no apparent difference between arms in terms of PFS and OS. The pre-PBAC response acknowledged the uncertainty around the magnitude of benefit in this cohort of patients and noted that the ACM was of the view that the efficacy and safety of A+AVD was satisfactorily established in the subgroup of patients ≥60 years.	Uncertain, favours A+AVD
First-line PFS extrapolation	The resubmission claimed that the long, flat plateau of the Kaplan-Meier curves for modified progression-free survival in ECHELON-1 are suggestive of high cure rates. In the model, this was estimated as 79% in the A+AVD arm and 71% in the ABVD arm based on statistical cure fractions generated by the mixture cure model. The validity of extrapolated outcomes based on mixture cure models cannot be easily determined given the underlying assumptions appear clinically implausible (e.g. patients are cured/uncured at the time of diagnosis before any treatment is administered). Model outputs such as statistical cure fractions and predicted estimates in uncured patients only serve as mathematical functions to achieve goodness of fit to observed data. While there is known potential for cure with front-line treatments, the PBAC previously considered the use of the ABVD arm in ECHELON-1 as a proxy for the efficacy of PET-adapted ABVD was uncertain (para 7.11, brentuximab vedotin PSD, March 2024 PBAC meeting). The ESC considered the availability of longer term follow-up data presented in the current submission mitigated some of this uncertainty.	High, favours A+AVD

Description	Method/Value	Impact
First-line treatment health state utilities	Based on EQ-5D-3L data from the ECHELON-1 trial, with utility estimates predicted from a regression model with covariates for A+AVD (randomisation to this arm), on treatment, A+AVD on treatment (interaction effect), progressive disease, age, and baseline utility. The utility values were highly uncertain and difficult to validate due to limited documentation provided in the resubmission on the ad hoc analysis of trial-based data, choice of regression model and selected covariates. ESC previously considered that further information, and justification for the approach used in estimating the utility values was required (para 6.80, brentuximab vedotin PSD, March 2024 PBAC meeting). However, no further information was provided in the resubmission. The resubmission acknowledged that time since randomisation was a statistically significant predictor of utility estimates but claimed that including this covariate resulted in estimates that implausibly increased with time. The evaluation considered that the removal of the time since randomisation covariate was inadequately justified given predicted values with the inclusion of this covariate appeared to have better visual fit to observed data in the trial. The pre-PBAC response provided a sensitivity analysis which included time since randomisation covariate utility values in the model along with an assumption of the same off-treatment utilities between arms and noted that this had a small impact on the ICER (see Table 13). The resubmission stated that the difference in on treatment utility values between A+AVD and ABVD was reasonable as they are capturing quality of life impacts associated with treatment-related adverse events. However, the resubmission claimed that the predicted difference in off-treatment utility values may not be reasonable given any impacts from adverse events were likely to resolve upon treatment discontinuation. Therefore, the off-treatment utility value for ABVD was assumed to be the same as for A+AVD. This claim was inadequately justified given safety data suggest longer-term adverse events associated with prior use of brentuximab vedotin (peripheral neuropathy) that may have ongoing impacts on quality of life. The ESC noted the model was sensitive to the choice of selected covariates and assumptions regarding off-treatment utility values with small changes in utility values having a large impact on the ICER. The ESC acknowledged that differences in off-treatment utility may occur between treatment arms as highlighted by the evaluation. However, the ESC considered it was unlikely to be reasonable to extrapolate these differences across the 65 year time horizon of the model. While additional uncertainties regarding the utilities remain, the ESC considered the assumption of the same off-treatment utilities between arms was likely appropriate.	High, favours A+AVD

Source: Constructed during the evaluation based on Section 3, pp177-262 of the resubmission
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; ASCT, autologous or allogeneic stem cell transplant; OS, overall survival; PFS, progression-free survival;; PET, positron emission tomography

6.62 While the 65-year time horizon is a key driver of the model, the PBAC previously considered that it may be reasonable given the potential for cure with initial and subsequent treatments and the bimodal age distribution of this condition (para 7.11, brentuximab vedotin PSD, March 2024 PBAC meeting).

6.63 Table 10 summarises the incremental costs for health care resource items included in the economic evaluation. The cost categories have been simplified for ease of comparison with estimates from the previous submission.

Table 10: Health care resource items: disaggregated summary of cost impacts (discounted)

Resource item	A+AVD	ABVD	Incremental cost
Current resubmission			
First-line drug costs (including supportive therapies)	$[redacted]	$5,997 [a]	$[redacted]
Subsequent treatments (including supportive therapies)	$18,497	$24,140	-$5,643
- ICE+ASCT	$4,476	$7,154	-$2,473
- DHAP	$836	$925	-$89
- Pembrolizumab	$12,917	$15,728	-$2,811
- GemVino	$268	$333	-$65
Administration	$1,859	$2,169	-$310
Disease monitoring	$10,030	$10,530	-$500
Adverse events	$4,564	$2,888	$1,676
Total	$[redacted]	$45,723	$[redacted]
March 2024 submission			
First-line drug costs (including supportive therapies)	$[redacted]	$6,791 [b]	$[redacted]
Subsequent treatments (including supportive therapies)	$11,231	$24,501	-$13,270
- ASCT	$3,182	$5,924	-$2,742
- Pembrolizumab or brentuximab vedotin	$[redacted]	$[redacted]	-$[redacted]
- Chemotherapy	$865	$1,288	-$423
- Radiation therapy	$539	$632	-$94
Administration	$1,312	$1,336	-$23
Disease monitoring	$13,200	$14,859	-$1,658
Adverse events	$4,254	$2,696	$1,558
Total	$[redacted]	$50,182	$[redacted]

Source: Table 3.8-2, p244 and the brentuximab vedotin economic model of the resubmission; Table 3.8.1, brentuximab vedotin commentary March 2024 PBAC meeting

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, allogeneic or autologous stem cell transplant; DHAP, dexamethasone, cytarabine, cisplatin; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; GemVino, gemcitabine and vinorelbine; ICE, ifosfamide, carboplatin, etoposide; PET, positron emission tomography

[a] Based on drug costs associated with PET-adapted ABVD (2 cycles of ABVD followed by 4 cycles of AVD (91.3% of patients) and 4 cycles of eBEACOPP (8.7% of patients))

[b] Based on drug costs associated with ABVD given for 5.7 cycles

Note: Blue shading delineates data presented in the March 2024 submission

6.64 The difference in total cost between treatment arms was primarily driven by higher first-line drug costs in the A+AVD arm, partially offset by the reduced use of subsequent therapies.

6.65 The PBAC previously considered that the impact of subsequent treatments in the relapsed or refractory setting was a key driver of the economic model with a high level of impact in favour of A+AVD. Furthermore, the PBAC considered that there were additional uncertainties associated with the implementation of subsequent treatment costs that could not be quantified (para 7.11. brentuximab vedotin PSD, March 2024 PBAC meeting).

6.66 The estimated cost of subsequent treatments in the March 2024 submission was highly uncertain due to multiple issues associated with the implementation of these costs including the use of a weighted cost that effectively distributed the full cost of all treatments in a single model cycle irrespective of time on treatment or treatment modality. Additionally, the cost was likely overestimated given the relatively high cost of pembrolizumab based on the maximum length of treatment (35 × 21-day cycles).

6.67 The evaluation considered that costs associated with subsequent treatments in the resubmission were more appropriately applied in each model cycle, to patients who were alive and had not failed therapy.

6.68 Incremental costs were higher in the resubmission compared to the previous submission, which the evaluation noted was primarily driven by smaller cost offsets associated with the reduced use of subsequent therapies. The evaluation considered that the difference in incremental costs appears to be due to an increase in the cost of immunotherapies (pembrolizumab) in the A+AVD arm while costs in the ABVD arm appeared similar.

6.69 Table 11 summarises the incremental difference in health outcomes estimated in the economic evaluation. The health outcomes categories have been simplified for ease of comparison with estimates from the previous submission.

Table 11: Disaggregated summary of health outcomes included in the economic evaluation

Outcome	A+AVD	ABVD	Incremental outcome
Current resubmission			
First-line treatment, progression-free life years (undiscounted)	30.114	27.260	2.854
Subsequent treatments, post-progression life years (undiscounted)	3.318	4.549	-1.231
Total life years (undiscounted)	33.433	31.809	1.623
First-line treatment, progression-free QALYs (undiscounted)	23.984	21.735	2.249
Subsequent treatments, post-progression QALYs (undiscounted)	2.286	3.200	-0.914
Adverse events QALYs loss (undiscounted)	-0.003	-0.002	-0.001
Total QALYs (undiscounted)	26.267	24.933	1.333
Total QALYs (discounted)	12.262	11.723	0.539
March 2024 submission			
Progression-free life years (undiscounted)	24.199	21.896	2.303
Post-progression life years (undiscounted)	4.599	5.424	-0.826
Total life years (undiscounted)	28.798	27.320	1.478
Progression-free QALYs (undiscounted)	20.149	18.251	1.898
Post-progression QALYs (undiscounted)	3.694	4.357	-0.663
Total QALYs (undiscounted)	23.843	22.608	1.235
Total QALYs (discounted)	11.655	11.136	0.520

Source: Table 3.8-3, p244 and the brentuximab vedotin economic model of the submission; Table 3.8.2, brentuximab vedotin commentary March 2024 PBAC meeting

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; QALYs, quality adjusted life years

Note: Blue shading delineates data presented in the March 2024 submission

6.70 The difference in health outcomes between treatment arms was driven by improved survival in patients who were progression-free after first-line therapy.

6.71 Total undiscounted life years in patients who are progression-free after first-line treatment in the resubmission were substantially higher compared to the previous submission. The evaluation considered that this is primarily due to differences in background mortality estimates in the resubmission (general population mortality based on mean age and sex distribution, adjusted for excess mortality using an SMR of 2.20) compared to the previous submission (general population mortality based on individual patient data for age and sex, adjusted for excess mortality using an SMR of 2.87).

6.72 The outcomes also indicate poorer prognosis in patients who progressed after first-line treatment in the resubmission (based on published estimates and assumptions for progression-free survival and overall survival at each subsequent line of therapy) compared to the previous submission (based on the difference in area under the curve between modelled overall survival and progression-free survival curves, extrapolated using ECHELON-1 trial data).

6.73 The incremental life years and QALYs in the resubmission (undiscounted life years 1.623, undiscounted QALYs 1.333) were slightly higher compared to the previous submission (undiscounted life years 1.478, undiscounted QALYs 1.235).

6.74 The results of the stepped economic evaluation are presented in Table 12.

Table 12: Results of the stepped economic evaluation

Step and component	A+AVD	ABVD	Increment
Step 1: Time horizon 8.1 years (maximum follow-up, June 2021 data cut), modelled OS and PFS for all health states based on the ECHELON-1 trial (first-line treatment), Brockelmann 2021 and Viviani 2024 (second-line treatment) and Younes 2012 and Brockelmann 2017 (third- and fourth-line treatment) publications; includes costs for A+AVD and ABVD treatment, administration and supportive therapies; 5% discounting to costs and outcomes			
Costs	$[redacted]	$8,313	$[redacted]
Life years	6.494	6.324	0.169
Incremental cost per life year gained			**$[redacted] [1]**
Step 2: Extrapolate to 65 years			
Costs	$[redacted]	$8,313	$[redacted]
Life years	15.484	14.844	0.639
Incremental cost per life year gained			**$[redacted] [2]**
Step 3: Add costs of subsequent treatments, administration and supportive therapies; add costs of disease monitoring and adverse events (one-off, first-line treatment only)			
Costs	$[redacted]	$46,487	$[redacted]
Life years	15.440	14.797	0.643
Incremental cost per life year gained			**$[redacted] [3]**
Step 4: First-line treatment costs in the ABVD arm based on PET-adapted ABVD (2 cycles of ABVD followed by 91.3% receiving a further 4 cycles of AVD and 8.7% receiving a further 4 cycles of eBEACOPP)			
Costs	$[redacted]	$45,723	$[redacted]
Life years	15.440	14.797	0.643
Incremental cost per life year gained			**$[redacted] [3]**
Step 5: Add health state utilities and adverse event disutilities			
Costs	$[redacted]	$45,723	$[redacted]
QALYs	12.262	11.723	0.539
Incremental cost per QALY gained			**$[redacted] [2]**
March 2024 submission			
Costs	$[redacted]	$50,182	$[redacted]
QALYs	11.655	11.136	0.520
Incremental cost per QALY gained			**$[redacted] [a3]**

Source: pp183-185 and Table 3.28, p258 of the resubmission; Section 3 economic model of the resubmission

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year

[a] Revised base case corrected for errors identified during the evaluation

Note: Blue shading delineates data presented in the March 2024 submission

The redacted values correspond to the following ranges:

[1] *$155,000 to < $255,000*

[2] *$55,000 to < $75,000*

[3] *$45,000 to < $55,000*

6.75 Based on the economic model, treatment with A+AVD was associated with an incremental cost per QALY gained of $55,000 to < $75,000 compared to ABVD (as a proxy for PET-adapted ABVD). This was higher than estimated in the previous submission based on the revised base case for A+AVD versus ABVD $45,000 to < $55,000 per QALY gained). The evaluation and the ESC noted that the difference was primarily due to reduced cost offsets associated with subsequent treatments in the current resubmission, although there was also a marginal increase in incremental QALYs.

6.76 The extrapolation of survival benefits to 65 years had the largest impact on the economic analysis. In the model, 73% of incremental QALYs were accrued in the extrapolated period beyond 8.1 years. The incremental cost reduced by 2% during the extrapolated period due to increased cost offsets associated with the use of subsequent treatments. Acknowledging the PBAC had previously accepted a 65 year time horizon the ESC considered that it would be useful to explore impacts of a 45 year and a 55 year time horizon to see where QALYs are accrued given the bimodal distribution of the disease. As such additional sensitivity analyses around the time horizon were added to Table 13.

6.77 For every patient treated with A+AVD versus ABVD (as a proxy for PET-adapted ABVD) and followed up for 65 years, the economic model (without discounting) estimated that there would be:

- Additional treatment costs (drug acquisition, supportive therapies, administration) of $[redacted] and additional adverse event management costs of $1,676.
- Reduced costs of subsequent therapies (drug acquisition, supportive therapies, administration, stem cell transplantation) of $6,979 and reduced disease monitoring costs of $677.
- An additional 1.62 years of life lived and an additional 1.33 quality-adjusted life years.
- No difference in long term treatment-related or disease-related complications.

6.78 The results of key sensitivity analyses are summarised in Table 13.

Table 13: Sensitivity analyses

Analysis	Incremental cost	Incremental QALY	ICER	% change
Base case	**$[redacted]**	**0.539**	**$[redacted]**[1]	**-**
Discount rate (base case 5% costs and outcomes)				
0%	$[redacted]	1.333	$[redacted][2]	-[redacted]%
3.5%	$[redacted]	0.682	$[redacted][3]	-[redacted]%
Time horizon (base case 65 years)				
8.1 years	$[redacted]	0.148	$[redacted][4]	+[redacted]%
10 years	$[redacted]	0.191	$[redacted][4]	+[redacted]%
15 years	$[redacted]	0.292	$[redacted][5]	+[redacted]%
45 years	$[redacted]	0.534	$[redacted][1]	<[redacted]%
55 years	$[redacted]	0.539	$[redacted][1]	<[redacted]%
Baseline age (base case 39.5 years)				
30 years	$[redacted]	0.586	$[redacted][1]	-[redacted]%
60 years	$[redacted]	0.394	$[redacted][6]	+[redacted]%
Mortality due to disease progression (base case proportion of disease progression events that are death: 1L treatment: A+AVD 12%, ABVD 15% based on mPFS in ECHELON-1, 2- and 3L treatments: 17% based on PFS in ECHELON-1)				
1L mortality rates doubled	$[redacted]	0.673	$[redacted][3]	-[redacted]%
1L mortality rates halved	$[redacted]	0.472	$[redacted][1]	+[redacted]%
2L, transplant eligible, ICE+ASCT mortality rates doubled	$[redacted]	0.543	$[redacted][1]	+[redacted]%
2L, transplant eligible, ICE+ASCT mortality rates halved	$[redacted]	0.537	$[redacted][1]	<[redacted]%
2L, transplant ineligible, DHAP mortality rates doubled	$[redacted]	0.540	$[redacted][1]	<[redacted]%

Analysis	Incremental cost	Incremental QALY	ICER	% change
2L, transplant ineligible, DHAP mortality rates halved	$	0.538	$ [1]	< %
3L, transplant eligible, pembrolizumab mortality rates doubled	$	0.539	$ [1]	< %
3L, transplant eligible, pembrolizumab mortality rates halved	$	0.539	$ [1]	< %
3L, transplant ineligible, pembrolizumab mortality rates doubled	$	0.539	$ [1]	< %
3L, transplant ineligible, pembrolizumab mortality rates halved	$	0.539	$ [1]	< %
Background mortality (base case Australian general population mortality adjusted for excess mortality based on Dores 2020; SMR of 2.20)				
SMR 5.10 based on de Vries 2021	$	0.483	$ [1]	+ %
SMR 2.87 based on Nunez-Garcia 2023	$	0.523	$ [1]	+ %
No excess mortality (SMR 1.00)	$	0.578	$ [1]	- %
Transplant eligibility (base case A+AVD 40%, ABVD 49% derived from ECHELON-1 trial data)				
Decrease rate by 50% in both arms	$	0.622	$ [3]	- %
Increase rate by 50% in both arms	$	0.455	$ [1]	+ %
All patients are transplant eligible	$	0.495	$ [1]	+ %
All patients are transplant ineligible	$	0.706	$ [3]	- %
Health state utilities (base case 1L on- and off-treatment utilities based on ECHELON-1 regression model without time since randomisation covariate and ABVD off treatment utility assumed based on the A+AVD off treatment utility (A+AVD on treatment 0.7525; ABVD on treatment 0.8056; A+AVD and ABVD off treatment 0.8429), 2L ICE+ASCT based on Swinburn 2015 and all other subsequent treatment utilities based on Ramsey 2016; adjusted using age-specific general population utility estimates from Clemens 2014)				
1L treatment health state utilities based on ECHELON-1 regression model without time since randomisation covariate, and different off treatment utilities between arms (A+AVD 0.8429, ABVD 0.8665)	$	0.265	$ [7]	+ %
1L treatment health state utilities based on ECHELON-1 regression model with time since randomisation covariate, different off treatment utilities between arms (A+AVD on treatment 0.7356, A+AVD off treatment 0.8121; ABVD on treatment 0.7887, ABVD off treatment 0.8358)	$	0.237	$ [8]	+ %
1L treatment health state utilities based on ECHELON-1 regression model with time since randomisation covariate, with ABVD off treatment utility assumed based on A+AVD off treatment utility (A+AVD on treatment 0.7356, ABVD on treatment 0.7887, A+AVD and ABVD off treatment 0.8121) [a]	$	0.512	$ [1]	%
Subsequent line treatment health state utilities based on disease progression utility from the ECHELON-1 regression model without time since randomisation covariate (0.8037)	$	0.643	$ [1]	+ %
Subsequent line treatment health state utilities based on disease progression utility from the ECHELON-1 regression model with time since randomisation covariate (0.7729)	$	0.531	$ [1]	+ %
No age-related utility decrement	$	0.566	$ [1]	- %

Source: Table 3.31, p261 and the Section 3 economic model of the resubmission, [a] Table 1 pre-PBAC response

Abbreviations: 1L, First-line; 2L, Second-line; 3L, Third-line; A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, autologous stem cell transplant; DHAP, dexamethasone, high dose cytarabine, cisplatin; ICE, ifosfamide, carboplatin, etoposide; PET, positron emission tomography; SMR, standardised mortality ratio

The redacted values correspond to the following ranges:

[1] $55,000 to < $75,000

[2] $15,000 to < $25,000

[3] $45,000 to < $55,000

[4] $155,000 to < $255,000

[5] *$95,000 to < $115,000*
[6] *$75,000 to < $95,000*
[7] *$115,000 to < $135,000*
[8] *$135,000 to < $155,000*

6.79 The evaluation noted that the model was most sensitive to time horizon (due to extrapolated survival benefits over time), first-line treatment health state utilities and discount rate. The model was moderately sensitive to baseline age, transplant eligibility rates and mortality assumptions for first-line treatment (background mortality and mortality due to disease progression).

6.80 Alternative mixture cure models for progression-free survival for first-line treatment had minimal impact on the ICER as all models generated similar statistical cure fractions (78-79% A+AVD, 71% ABVD) and achieved plateaus at around 7-8 years.

6.81 The resubmission acknowledged concerns with the applicability of multiple sources used to inform progression-free survival and overall survival in subsequent lines of therapy due to differences in known prognostic factors such as age, disease severity, sex distribution and prior treatment exposure. The resubmission claimed that the impact of these differences could not be addressed other than by exploring the impact of alternative extrapolation functions in sensitivity analyses. The use of alternative extrapolation functions had minimal impact on the ICER per QALY gained, which ranged from $55,000 to < $75,000 to $55,000 to < $75,000.

Drug cost/patient/course

Table 14: Drug cost per patient for A+AVD and PET-adapted ABVD

	A+AVD			PET-adapted ABVD [a]	
	Trial	Economic model	Financial estimates	Economic model	Financial estimates
Mean cycles of treatment	5.6	5.6	5.6	6.0	6.0
Dose intensity	94-99% [b]	100%	94-100% [c]	100%	94-100% [c]
Cost/patient/course [d]	-	$[redacted]	$[redacted]	$4,818	$4,818

Source: constructed during the evaluation using the economic model and financial estimates in the submission
Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone
[a] 2 cycles of ABVD followed by 4 cycles of AVD in 91.3% of patients and 4 cycles of eBEACOPP in 8.7% of patients
[b] Reported relative dose intensities were lower for brentuximab vedotin (mean 94.0%) and bleomycin (mean 93.5%) compared to other components in the A+AVD and ABVD regimens of the trial (approximately 97-99%)
[c] Based on dose intensities in ECHELON-1 for A+AVD and ABVD (as a proxy for PET-adapted ABVD) and assumptions
[d] Based on 51%/49% public/private hospital split for dispensing fees and mark-ups
Note: The inclusion of dose intensity had minimal impact on the financial estimates as it did not change the number of vials required for chemotherapy agents based on the most efficient vial combination, with a small change in costs associated with oral prednisolone as part of the eBEACOPP regimen

Estimated PBS usage & financial implications

6.82 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS/RPBS listing of brentuximab vedotin.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Australian population	27,970,435 in Year 1, increasing to 29,931,725 in Year 6. ABS population 3222.0, Series B.	DUSC previously considered this to be reasonable for an age agnostic listing but noted the evidence primarily supports use in the 18–60 year old population (Table 12, brentuximab vedotin PSD, March 2024 PBAC meeting).
Incidence of Hodgkin lymphoma	3.0 per 100,000. Based on DUSC advice for the March 2024 submission.	DUSC previously considered data from the AIHW 2022 Cancer Data in Australia report and suggested that the incidence of Hodgkin lymphoma appears to plateau at 3 per 100,000 (Table 12, brentuximab vedotin PSD, March 2024 PBAC meeting).
Proportion of Hodgkin lymphoma that is classical Hodgkin lymphoma	94.2%. Based on the average of values reported by Cochrane 2021 (90 to 95%), Eichenauer 2018 (95%) and Cancer Council NSW 2023 (95%).	DUSC previously considered this to be reasonable, if not slightly underestimated (Table 12, brentuximab vedotin PSD, March 2024 PBAC meeting).
Proportion with stage III or IV disease	50.4%. Based on the characteristics of patients included in the Lymphoma and Related Diseases Registry (Wellard 2023).	This was consistent with DUSC advice that the previous proportion (48%) was underestimated as the calculation included patients with missing disease stage data in the denominator. DUSC also noted that the representativeness of Lymphoma and Related Diseases Registry data to the overall Australian population is unclear, as it is a voluntary register and is likely biased (Table 12, brentuximab vedotin PSD, March 2024 PBAC meeting). This estimate remains uncertain.

Parameter	Value applied and source	Comment
Uptake of A+AVD	Year 1: [redacted]% Year 2: [redacted]% Year 3: [redacted]% Year 4: [redacted]% Year 5: [redacted]% Year 6: [redacted]% Assumed based on DUSC advice for the March 2024 submission.	DUSC considered uptake rates in the March 2024 submission ([redacted]% over 6 years) to be underestimated, as brentuximab vedotin offers a better side effect profile compared to bleomycin. DUSC considered a range increasing by [redacted]% per year from [redacted]% and remaining steady at [redacted]% would be more appropriate (Table 12, brentuximab vedotin PSD, March 2024 PBAC meeting). The PBAC previously acknowledged the DUSC advice but noted treatment guidelines recommend the use of PET-adapted regimens over non-PET-adapted regimens and considered that this may impact uptake rates (para 7.12, brentuximab vedotin PSD, March 2024 PBAC meeting). Uptake rates are highly uncertain given the changing landscape for first-line treatments, with more recent guidelines suggesting a narrower place in therapy for the A+AVD regimen based on age, contraindications (peripheral neuropathy) and the availability of newer regimens. The ESC considered that iPET use will likely continue with A+AVD regardless of the fact that it was not used in ECHELON-1. As such, the ESC considered there would likely be high uptake of A+AVD to replace ABVD. The PBAC considered that uptake rates of 50% in Year 1 increasing to 65% in Year 6 would be more appropriate.
Number of cycles (A+AVD)	5.6 cycles. Based on the reported mean number of treatment cycles in the ECHELON-1 trial (5.5 cycles for brentuximab vedotin and 5.6 cycles for doxorubicin, vinblastine and dacarbazine), assuming the highest number of cycles among the individual treatments.	There were inconsistencies in the DUSC advice regarding this estimate (based on Table 12 and para 6.87, brentuximab vedotin PSD, March 2024 PBAC meeting). The assumption of imperfect compliance is reasonable, however the applicability of trial-based estimates to clinical practice is uncertain.
Substitution rate of PET-adapted ABVD	[redacted]%. Based on the assumption that patients treated with A+AVD would otherwise have received treatment with PET-adapted ABVD (2 cycles of ABVD followed by 4 cycles of either AVD or eBEACOPP).	DUSC previously considered that [redacted]% uptake (substitution rate) of comparators is inappropriate and would overestimate cost offsets (para 6.87, brentuximab vedotin PSD, March 2024 PBAC meeting).
Proportion of patients on PET-adapted ABVD who escalate/ de-escalate treatment	91.3% receive AVD, 8.7% receive eBEACOPP. Based on the proportion of patients in the ECHELON-1 trial with a Deauville score of 1 to 3 (86.1%) or no available Deauville score (5.2%).	DUSC previously considered that this was reasonable (Table 12, brentuximab vedotin PSD, March 2024 PBAC meeting).

Parameter	Value applied and source	Comment
Number of cycles (PET-adapted ABVD)	ABVD: 2 cycles, AVD/eBEACOPP: 4 cycles. Assumed based on 100% compliance.	DUSC previously considered that 100% compliance of substituted comparators is inappropriate and would overestimate cost offsets (para 6.87, brentuximab vedotin PSD, March 2024 PBAC meeting). The PBAC advised that an assumption of 90% compliance would be more appropriate.
Dose intensity (A+AVD and PET-adapted ABVD)	Variable (93.5% to 100%) based on ECHELON-1 data and assumptions.	DUSC previously considered the assumption of 100% dose intensity for all components in each regimen was inconsistent with trial data and may overestimate the costs of A+AVD given the higher costs of A+AVD compared to PET-adapted ABVD (Table 12, brentuximab vedotin PSD, March 2024 PBAC meeting). The use of trial-based dose intensities had minimal impact on the financial estimates given no change to the most efficient vial combination used to estimate the costs of each component in each regimen.

Source: Section 4, pp263-282 of the resubmission

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AIHW, Australian Institute of Health and Welfare; AVD, doxorubicin, vinblastine, and dacarbazine; ECOG, Eastern Cooperative Oncology Group; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; PET, positron emission tomography

6.83 The estimated utilisation and financial impact of listing brentuximab vedotin on the PBS/RPBS are summarised in Table 16.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Treated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost to the PBS/RPBS (less copayments)						
Cost to PBS/RPBS for A+AVD	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Cost offsets for substituted use of PET-adapted ABVD	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
Net cost to the PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Cost to the MBS						
Cost offset due to reduced chemotherapy administrations	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
Net financial implications						
Net cost to the PBS/RPBS/MBS	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Previous submission (March 2024)						
Net cost to PBS/RPBS/MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]

Source: Table 4.10, p274; Table 4.14, p277; Table 4.19, p279; Table 4.20, p280 and Table 4.23, p281 of the resubmission
Note: Blue shading delineates data presented in the March 2024 submission
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *$0 to < $10 million*

[3] *$10 million to < $20 million*

6.84 The estimated net cost to the PBS/RPBS/MBS was $0 to < $10 million in Year 1, increasing to $10 million to < $20 million in Year 6, a total cost of $60 million to < $70 million over the first 6 years of listing. The estimated net cost to the PBS/RPBS/MBS was larger than estimated in the March 2024 submission ($40 million to < $50 million over the first 6 years of listing). The evaluation and the ESC considered that the difference was primarily due to the increased size of the eligible population (increased incidence, increased proportion with stage III or IV disease, removal of the ECOG eligibility criterion) and increased size of the treated population (increased uptake rates).

6.85 The evaluation considered that treatment uptake rates are highly uncertain given the changing landscape for first-line treatments, with more recent guidelines suggesting a narrower place in therapy for the A+AVD regimen based on age, contraindications (peripheral neuropathy) and the availability of newer regimens. The Pre-Sub-Committee Response acknowledged concerns regarding the changing landscape for first-line treatments, but claimed inputs used in the resubmission were consistent with the PBAC's recommendation, aligned with DUSC advice at the March 2024 PBAC meeting. The pre-PBAC response agreed with the ESC that iPET use would likely continue with A+AVD and that there would likely be high uptake of A+AVD to replace ABVD. The PBAC considered that uptake rates of [redacted]% in Year 1 increasing to [redacted]% in Year 6 would be more appropriate.

6.86 The estimated financial implications included cost offsets associated with the use of supportive therapies in patients receiving ABVD or AVD as part of PET-adapted ABVD (total cost offset of $0 to < $10 million over 6 years, mainly due to the cost of netupitant + palonosetron). The evaluation considered that the inclusion of the costs of these therapies in patients receiving PET-adapted ABVD but not A+AVD was inadequately justified in the resubmission. The approach was inconsistent with trial data suggesting the use of antiemetics, corticosteroids and other supportive therapies was similar between arms in the ECHELON-1 trial. The evaluation considered that it may be simpler to remove the cost of these therapies from substituted ABVD and AVD regimens.

Quality Use of Medicines

6.87 No quality of use of medicines issues were identified in the resubmission.

6.88 The evaluation noted that DUSC previously considered multiple quality use of medicines issues including equity of access issues given the need for dacarbazine, safety concerns and the need for primary prophylaxis with granulocyte-colony stimulating factors; and the potential for a large degree of wastage in patients whose weight exceeds 100 kg given brentuximab vedotin is only supplied in 50 mg vials (para 6.90 to 6.92, brentuximab vedotin PSD, March 2024 PBAC meeting).

Financial Management – Risk Sharing Arrangements

No risk-sharing arrangements were proposed in the resubmission. The evaluation noted that brentuximab vedotin is currently subject to risk-sharing arrangements for relapsed or refractory disease (post-ASCT and ASCT-naïve listings). The available data indicate that Commonwealth payments have remained [redacted] than the nominated caps.*For more detail on PBAC's view, see section 7 PBAC outcome.*

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 Efficient Funding of Chemotherapy, Authority Required (Telephone/Online) listing of brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine (A+AVD) for the first-line treatment of advanced Hodgkin lymphoma. The PBAC was satisfied that A+AVD provides, for some patients, a significant improvement in efficacy over positron emission tomography (PET)-adapted doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). The PBAC considered that the resubmission had addressed the substantive outstanding issues identified at the March 2024 PBAC meeting with the provision of a revised economic model and advised that brentuximab vedotin was considered cost-effective at the price proposed in the resubmission.

7.2 The PBAC noted the input from health care professionals, Rare Cancers Australia, Leukaemia Foundation, Lymphoma Australia and the Australasian Leukaemia and Lymphoma group supporting the listing. The comments highlighted the need for

additional treatment options to address long term toxicity concerns associated with current treatments. The PBAC noted input that A+AVD does not necessarily provide a lower toxicity treatment option, rather an alternative toxicity profile to ABVD and acknowledged that it was important for more treatment options to be available.

7.3 With regard to the proposed restriction, the PBAC advised that:

- An Authority Required (Telephone/Online) listing was appropriate as the criteria proposed in the restriction could be answered in yes/no responses to Services Australia.
- A maximum amount of 120 mg was appropriate, consistent with the TGA-approved Product Information.
- The restriction should not be agnostic in terms of the chemotherapy regimen. Acknowledging that dacarbazine is not listed on the PBS for treatment of Hodgkin lymphoma, the PBAC agreed with the ESC that ABVD has been standard of care in Hodgkin lymphoma for decades in Australia and access to dacarbazine has not been an issue. As such, the Committee advised that the restriction should include clinical criteria which intend to restrict the chemotherapy regimen to doxorubicin, vinblastine and dacarbazine (AVD).
- The resubmission request to change the current PBS listings for brentuximab vedotin in relapsed or refractory Hodgkin lymphoma from Authority Required (Written) to Authority Required (Streamlined) was not considered appropriate. Instead, the PBAC advised that an Authority Required (Telephone/Online) listing would be appropriate for both initial and continuing treatment restrictions in the relapsed or refractory setting.
- The Committee reaffirmed its March 2024 advice that it would be appropriate to allow re-treatment with brentuximab vedotin for relapsed or refractory disease and considered a lifetime maximum of 16 treatment cycles in this setting remained appropriate (see paragraph 3.6). The PBAC advised that patients who had not failed PBS-subsidised treatment with brentuximab vedotin in the first-line setting could receive the balance of the lifetime maximum of 16 treatment cycles in the relapsed or refractory setting. The PBAC agreed with the flow on changes outlined in paragraph 8.1 to facilitate this approach.

7.4 The PBAC agreed with the ESC that PET use will likely continue with A+AVD regardless of the fact that it was not used in the ECHELON-1 trial and accepted the the resubmission's clinical place for brentuximab vedotin.

7.5 The PBAC accepted the nomination of PET-adapted ABVD as the main comparator, noting that it is the standard of care for ABVD treatment in Australia, and considered that ABVD (without PET, as per the ECHELON-1 trial) to be a suitable proxy.

7.6 The PBAC noted the ECHELON-1 trial remained the key clinical evidence with the resubmission presenting new data from the March 2023 data cut representing a median follow-up of 90.1 months and 86.4 months in the A+AVD and ABVD arms respectively. The PBAC recalled that a statistically significant benefit in modified

progression-free survival was reported in the A+AVD group compared to the ABVD group for the primary analysis period (HR 0.770; 95% CI: 0.603, 0.982). The PBAC noted that the results from the March 2023 data cut continued to favour A+AVD, with greater numerical benefit compared to the results from the primary analysis period (HR 0.704; 95% CI 0.564, 0.880). In addition, the PBAC noted that the results from the March 2023 data cut showed improved overall survival in favour of A+AVD compared to ABVD (HR 0.62; 95% CI 0.42, 0.90). The PBAC noted that median overall survival was not reached for either treatment arm. The PBAC recalled that it previously considered the claim of superior effectiveness compared to PET-adapted ABVD was highly uncertain, but likely reasonable. The PBAC considered that the claim of superior comparative effectiveness was reasonable and agreed with the ESC that the level of uncertainty associated with the claim had been reduced with the extended follow-up data presented in the resubmission.

7.7 The PBAC noted that more patients in the A+AVD arm experienced a serious adverse event or an adverse event leading to dose modification compared to those in the ABVD arm. The PBAC acknowledged the different toxicity profile of A+AVD compared to ABVD and considered there was evidence of different harms of a similar magnitude between the two treatments. Overall, the PBAC considered that the claim of inferior comparative safety was reasonable.

7.8 The PBAC recalled that the primary reason for not recommending brentuximab vedotin in March 2024 was due to the economic evaluation provided. The PBAC noted that, as requested in March 2024, the resubmission had provided a revised economic model that included separate states for each line of therapy. The PBAC acknowledged the concerns raised by the evaluation that the structure and inputs used in the model represent a simplification that may underestimate the treatment benefits associated with subsequent therapies in clinical practice. However, the PBAC noted ESC advice that it was reasonable in this instance to not add additional complexity to the model and that the current structure provided a reasonable basis for decision making. The PBAC also noted ESC advice that the approach taken in the model to determining baseline age was unlikely to have a significant impact on the incremental cost effectiveness ratio (ICER). In addition, the PBAC noted ESC advice that the availability of longer-term follow-up data mitigated some of the uncertainty regarding the approach taken to first-line progression-free survival extrapolation. In terms of the first-line treatment health state utilities, the PBAC noted ESC advice that the assumption of the same off-treatment utilities between arms was appropriate and accepted the approach taken to utilities in the revised model. The PBAC reaffirmed its March 2024 advice that a 65-year time horizon was reasonable (see paragraph 6.62). Overall, the PBAC accepted the revised economic model base case provided in the resubmission and considered it addressed the Committee's previous concerns. The PBAC advised that brentuximab vedotin was considered cost-effective at the price proposed in the resubmission.

7.9 The PBAC noted the revised financial estimates provided in the resubmission. The PBAC noted the uncertainty around the uptake of A+AVD and advised that uptake rates of [redacted]% in Year 1 increasing to [redacted]% in Year 6 would be more appropriate. In addition, the PBAC agreed with DUSC that the assumption of 100% compliance of the substituted comparators was not appropriate and advised that the number of cycles of PET-adapted ABVD should be amended to assume 90% compliance. The PBAC also agreed with the evaluation that the cost offsets associated with the use of supportive therapies should be removed (see paragraph 6.86). The PBAC advised that the financial estimates would be considered reliable with these changes.

7.10 The PBAC considered that the risk of use of A+AVD outside of the proposed indication was low and that the financial estimates were reliable and unlikely to be exceeded. As such, the PBAC advised that a risk sharing arrangement was not required.

7.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for brentuximab vedotin:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, as while clinically relevant improvements in modified progression-free survival were evident they were not considered substantial in magnitude;

b) The treatment is not expected to address a high and urgent unmet clinical need, as while the PBAC acknowledged there was an unmet need it was not considered high and urgent due to the availability of other therapies;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.12 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

MEDICINAL PRODUCT	PBS item code	Max. Amount	№.of Rpts
BRENTUXIMAB VEDOTIN Injection	NEW (Public) NEW (Private)	120mg	11

Available brands		
Adcetris (brentuximab vedotin 50 mg injection, 1 vial)		
Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 - Efficient Funding of Chemotherapy Public/Private hospitals
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (telephone/online)
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements apply
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Indication: Stage III or IV CD30 positive Hodgkin lymphoma.
		Clinical criteria:
		The treatment must be for first line therapy for this condition.
		AND
		Clinical criteria:
		The treatment must be for curative intent.
		AND
		Clinical criteria:
		The treatment must be in combination with at least the following: (i) doxorubicin, (ii) vinblastine
		AND
		Clinical criteria:
		The treatment must not be in combination with any of: (i) etoposide, (ii) cyclophosphamide, (iii) dexamethasone.
		Clinical criteria:
		The treatment must not be for more than 6 treatment cycles under this restriction in a lifetime.

Flow-on changes

Suggested additions are in italics and deletions are in strikethrough.

Proposed amended listing of brentuximab vedotin for patients with relapsed or refractory HL who have previously undergone ASCT (initial treatment).

MEDICINAL PRODUCT	PBS item code	Max. Amount	№.of Rpts
BRENTUXIMAB VEDOTIN Injection	11073T *(IP)* 11089P *(IN)*	200 mg	3

Available brands		
Adcetris (brentuximab vedotin 50 mg injection, 1 vial)		
Restriction Summary ~~13123~~ *(new)* / **Treatment of Concept:** ~~13259~~ *(new)*: **Authority Required *(telephone/online)***		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒~~Authority Required (in writing only via post/HPOS upload)~~ ☒*Authority Required (telephone/online)*
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised
		Administrative Advice: Special Pricing Arrangements apply
		~~Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).~~ ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au~~ ~~Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)~~ ~~Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos~~ ~~Or mailed to:~~ ~~Services Australia~~ ~~Complex Drugs~~ ~~Reply Paid 9826~~ ~~HOBART TAS 7001~~ ***Administrative Advice:*** *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*
		Indication: Relapsed or Refractory Hodgkin Lymphoma
		Treatment Phase: Initial treatment
		Clinical criteria:
		Patient must have undergone a primary autologous stem cell transplant (ASCT)
		AND
		Clinical criteria:
		Patient must have experienced a relapsed CD30+ Hodgkin lymphoma post ASCT; or
		Patient must have experienced a refractory CD30+ Hodgkin lymphoma post ASCT
		AND
		Clinical criteria:
		Patient must not receive more than 4 cycles of treatment under this restriction

	AND
	Clinical criteria:
	Patient must not have received prior treatment with this drug for this condition; or
	Patient must not have failed PBS-subsidised treatment with this drug for this condition in the first-line setting
t	~~**Prescribing Instructions:**~~ ~~Applications for authorisation of initial treatment must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail.~~ ~~If the application is submitted through HPOS upload or mail, it must include:~~ ~~(a) a completed authority prescription form; and~~ ~~(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).~~

Patients with relapsed or refractory HL who have previously undergone ASCT (continuing treatment)

<table>
<tr><th colspan="2">MEDICINAL PRODUCT</th><th>PBS item code</th><th>Max. Amount</th><th>№.of Rpts</th></tr>
<tr><td colspan="2">BRENTUXIMAB VEDOTIN
Injection</td><td>11067L (IN)
11096B (IP)</td><td>200 mg</td><td>11</td></tr>
<tr><td colspan="5">Available brands</td></tr>
<tr><td colspan="5">Adcetris
(brentuximab vedotin 50 mg injection, 1 vial)</td></tr>
<tr><td colspan="5">Restriction Summary 13244 / Treatment of Concept: 13208: Authority Required</td></tr>
<tr><td colspan="2" rowspan="3">Concept ID
(for internal Dept. use)</td><td colspan="3">Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals</td></tr>
<tr><td colspan="3">Prescriber type: ☒Medical Practitioners</td></tr>
<tr><td colspan="3">Restriction type: ☒Authority Required (telephone/online)</td></tr>
<tr><td rowspan="4">Prescribing rule level</td><td></td><td colspan="3">Administrative Advice:
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</td></tr>
<tr><td></td><td colspan="3">Administrative Advice:
No increase in the maximum quantity or number of units may be authorised.</td></tr>
<tr><td></td><td colspan="3">Administrative Advice:
No increase in the maximum number of repeats may be authorised</td></tr>
<tr><td></td><td colspan="3">Administrative Advice:
Special Pricing Arrangements apply</td></tr>
<tr><td colspan="2"></td><td colspan="3">Indication: Relapsed or Refractory Hodgkin Lymphoma</td></tr>
<tr><td colspan="2"></td><td colspan="3">Treatment Phase: Continuing treatment</td></tr>
<tr><td colspan="2"></td><td colspan="3">Clinical criteria:</td></tr>
<tr><td colspan="2"></td><td colspan="3">Patient must have undergone a primary autologous stem cell transplant (ASCT) for this condition</td></tr>
<tr><td colspan="2"></td><td colspan="3">AND</td></tr>
<tr><td colspan="2"></td><td colspan="3">Clinical criteria:</td></tr>
<tr><td colspan="2"></td><td colspan="3">Patient must have previously received PBS-subsidised treatment with this drug for this condition</td></tr>
<tr><td colspan="2"></td><td colspan="3">AND</td></tr>
<tr><td colspan="2"></td><td colspan="3">Clinical criteria:</td></tr>
<tr><td colspan="2"></td><td colspan="3">Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition</td></tr>
<tr><td colspan="2"></td><td colspan="3">AND</td></tr>
<tr><td colspan="2"></td><td colspan="3">Clinical criteria:</td></tr>
<tr><td colspan="2"></td><td colspan="3">Patient must not receive more than 12 cycles of treatment under this restriction</td></tr>
<tr><td colspan="2"></td><td colspan="3">Prescribing Instructions:
The treatment must not exceed a total of 16 cycles for this condition ~~of combined initial and continuing treatment~~ in a lifetime</td></tr>
</table>

Patients with relapsed or refractory HL who have not undergone ASCT (initial treatment).

MEDICINAL PRODUCT	**PBS item code**	**Max. Amount**	**№.of Rpts**
BRENTUXIMAB VEDOTIN Injection	11080E *(IN)* 11079D *(IP)*	200 mg	3

Available brands	
Adcetris (brentuximab vedotin 50 mg injection, 1 vial)	
Restriction Summary ~~13170~~ *(new)* / **Treatment of Concept:** ~~13209~~ *(new)*: **Authority Required *(telephone/online)***	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒~~Authority Required (in writing only via post/HPOS upload)~~ ☒*Authority Required (telephone/online)*
Prescribing rule level	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special Pricing Arrangements apply
	~~Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).~~ ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au~~ ~~Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)~~ ~~Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos~~ ~~Or mailed to:~~ ~~Services Australia~~ ~~Complex Drugs~~ ~~Reply Paid 9826~~ ~~HOBART TAS 7001~~ ***Administrative Advice:*** *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*
	Indication: Relapsed or Refractory Hodgkin Lymphoma
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must not have undergone an autologous stem cell transplant (ASCT) for this condition
	AND
	Clinical criteria:
	Patient must not be suitable for ASCT for this condition; or
	Patient must not be suitable for treatment with multi-agent chemotherapy for this condition
	AND
	Clinical criteria:
	Patient must have experienced a relapsed CD30+ Hodgkin lymphoma following at least two prior treatments for this condition; or
	Patient must have experienced a refractory CD30+ Hodgkin lymphoma following at least two prior treatments for this condition

	AND
	Clinical criteria:
	Patient must not receive more than 4 cycles of treatment under this restriction
	AND
	Clinical criteria:
	Patient must not have received prior treatment with this drug for this condition; or
	Patient must not have failed PBS-subsidised treatment with this drug for this condition in the first-line setting
	~~**Prescribing Instructions:**~~ ~~Applications for authorisation of initial treatment must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail.~~ ~~If the application is submitted through HPOS upload or mail, it must include:~~ ~~(a) a completed authority prescription form; and~~ ~~(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).~~

Patients with relapsed or refractory HL who have not previously undergone ASCT (continuation treatment)

MEDICINAL PRODUCT		PBS item code	Max. Amount	№.of Rpts
BRENTUXIMAB VEDOTIN Injection		11086L *(IN)* 11087M *(IP)*	200 mg	11
Available brands				
Adcetris (brentuximab vedotin 50 mg injection, 1 vial)				
Restriction Summary 13232 / **Treatment of Concept:** 13231: **Authority Required**				
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
		Prescriber type: ☒Medical Practitioners		
		Restriction type: ☒Authority Required (telephone/online)		
Prescribing rule level		**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).		
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.		
		Administrative Advice: No increase in the maximum number of repeats may be authorised		
		Administrative Advice: Special Pricing Arrangements apply		
		Indication: Relapsed or Refractory Hodgkin Lymphoma		
		Treatment Phase: Continuing treatment		
		Clinical criteria:		
		Patient must not have undergone an autologous stem cell transplant (ASCT) for this condition		
		AND		
		Clinical criteria:		
		Patient must not be suitable for ASCT for this condition; or		
		Patient must not be suitable for treatment with multi-agent chemotherapy for this condition		
		AND		
		Clinical criteria:		
		Patient must have previously received PBS-subsidised treatment with this drug for this condition		
		AND		
		Clinical criteria:		
		Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition		
		AND		
		Clinical criteria:		
		Patient must not receive more than 12 cycles of treatment under this restriction		
		Prescribing Instructions: The treatment must not exceed a total of 16 cycles *for this condition* ~~of combined initial and continuing treatment~~ in a lifetime.		

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.