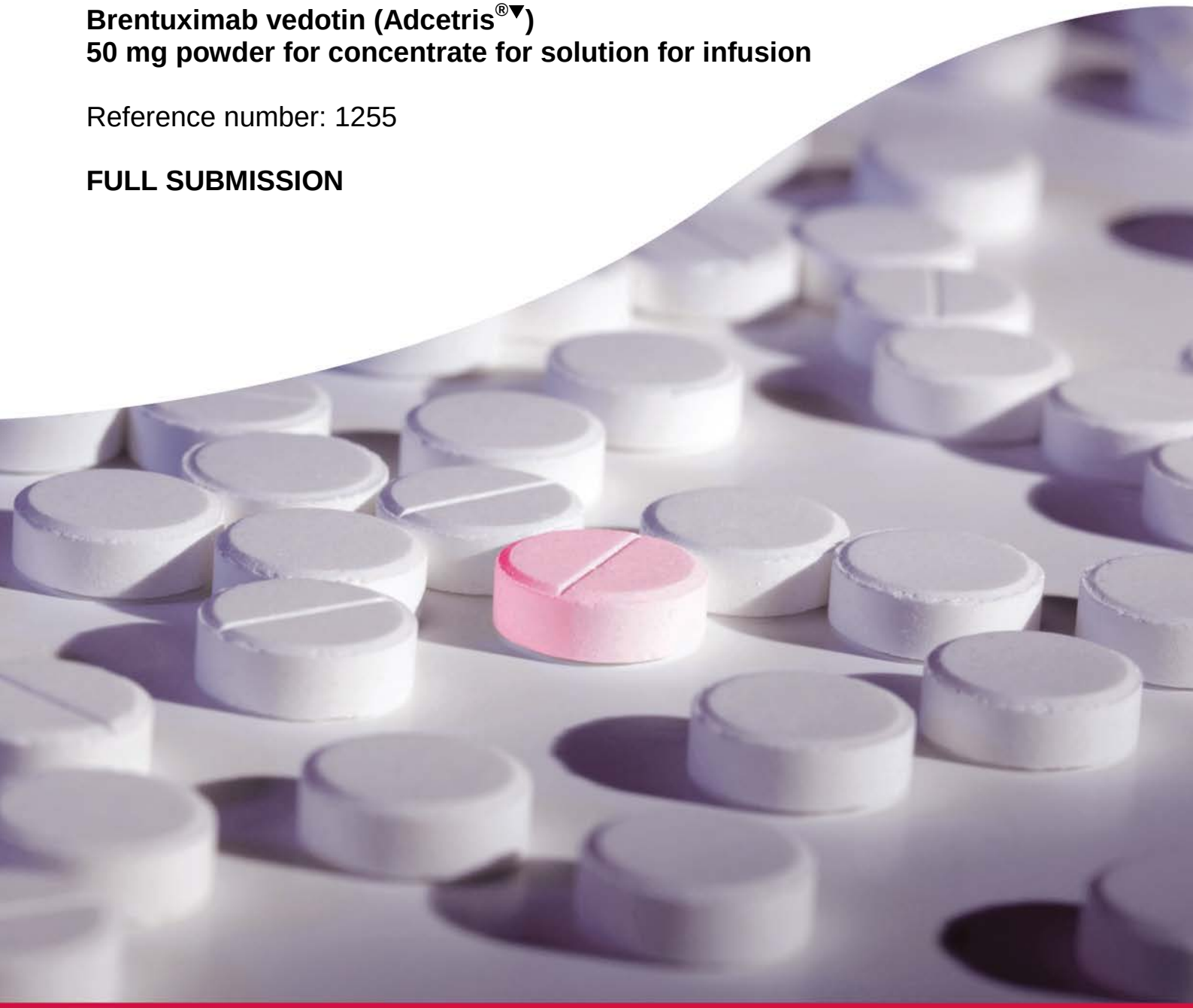
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Brentuximab vedotin (Adcetris®▼)
50 mg powder for concentrate for solution for infusion

Reference number: 1255

FULL SUBMISSION



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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Generic name (Trade Name®) strength formulation. Reference number: 1255. April 2015.

AWMSG Secretariat Assessment Report
Brentuximab vedotin (Adcetris®▼)
50 mg powder for concentrate for solution for infusion

This assessment report is based on evidence submitted by Takeda UK Limited on 17 December 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Brentuximab vedotin (Adcetris®▼) for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option; as well as for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)[2].
Dosing	The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every three weeks. Treatment should be continued until disease progression or unacceptable toxicity. Patients who achieve stable disease or better should receive a minimum of eight cycles and up to a maximum of 16 cycles (approximately one year). Refer to the Summary of Product Characteristics (SPC) for full dosing information[2].
Marketing authorisation date	25 October 2012[2].

2.0 DECISION CONTEXT

2.1 Background

Hodgkin lymphoma (HL) is a rare cancer of the immune system that is highly curable. Although it can occur at any age, most people diagnosed with HL are between the ages of 15 and 35 years or are aged 60 years and over[3]. First line treatment, combination chemotherapy, followed by radiotherapy cures approximately 80% of patients[4–6]. There is no standard treatment for the remaining patients with relapsed or primary refractory disease[1]. For this group, salvage chemotherapy is usually followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT), which has a cure rate of approximately 50%[1,4]. However, patients who are not cured at this stage have a poor prognosis: the median overall survival (OS) is 2.4 years, reducing to 1.2 years for those patients who relapse quickly (≤ 1 year) following their ASCT[1]. These patients may receive chemotherapy with or without radiotherapy, which may be followed by allogeneic stem cell transplantation (alloSCT) in patients who respond to chemotherapy and are considered eligible (i.e. < 60–70 years of age, no significant co-morbidities)[1,7]. For patients with relapsed or refractory disease who are not suitable for ASCT, the options are palliative care or to attempt ASCT with a very low probability of success[1]. Public Health Wales data shows the annual incidence of HL over the period 2009–2013 was 84 patients[8].

Brentuximab vedotin is an antibody-drug conjugate that delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Due to the CD30-targeted mechanism of action, brentuximab vedotin is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy[2].

Brentuximab vedotin has been licensed under a conditional approval scheme, which is granted if a medicinal product fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact additional data are still required[2,4]. The European Medicines Agency reviews new information on the medicine at least every year[2].

The applicant company have supplied clinical evidence for brentuximab vedotin for the treatment of adult patients with relapsed or refractory CD30+ HL following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. However, no evidence has been supplied to support the clinical efficacy of brentuximab vedotin in patients with relapsed or refractory sALCL[1].

2.2 Comparators

The comparator included in the company submission was best supportive care. The company states that there is no standard treatment for patients with relapsed or primary refractory disease[1].

2.3 Guidance and related advice

- South Wales Cancer Network. Hodgkin lymphoma. Haematological pathway. (2014)[9].
- British Committee for Standard in Haematology and British Society of Blood and Marrow Transplantation. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma (2014)[10].
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in Oncology. Hodgkin Lymphoma Version 4 (2014)[11].
- European Society for Medical Oncology. Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2014)[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company provided evidence for the use of brentuximab vedotin from a phase II study (SG035-0003), in which patients had received ASCT. Evidence from 41 patients who were ASCT-naive was also provided. Further evidence from supporting studies using brentuximab vedotin in both ASCT-experienced and ASCT-naive populations was supplied[1], but this was in smaller patient groups and is therefore not discussed further.

3.1 Study SG035-0003

SG035-0003 is a multicentre, open-label phase II study investigating the use of brentuximab vedotin in patients (n = 102) with relapsed or refractory HL, all of whom had received ASCT and high dose chemotherapy[1,2,13]. The median time to relapse after ASCT was 6.7 months (range 0–131 months). The median age of patients was 31 years, with a range of 15–77 years[13]. Brentuximab vedotin was given as a single agent at a dose of 1.8 mg/kg administered as an intravenous infusion once every three weeks on an out-patient basis. Dose delays of up to three weeks and a dose reduction to 1.2 mg/kg were allowed for toxicities. Patients could continue on study treatment until disease progression (according to the Revised Response Criteria for Malignant Lymphoma) or unacceptable toxicity. Patients who achieved stable disease or better were to receive a minimum of eight, but no more than 16 cycles[1]. The median number of treatment cycles was nine (range 1–16 cycles)[2]. After the discontinuation of treatment, follow-up assessment is being performed every 12 weeks until either the patient's death or study closure[13]. Endpoints of the study were assessed by an independent radiology review facility[1,13]. Follow-up of patients included in this trial remains ongoing; the most recent median observation time was approximately three years[14].

The primary endpoint determined after a median follow up of 22.6 months was the overall objective response rate (ORR): the sum of the patients who achieved complete remission (CR) plus those achieving a partial remission (PR)[2]. The ORR was 75% (76/102 patients; 95% confidence interval [CI] 65%–83%) with 33% (34/102 patients; 95%CI: 24%–43%) achieving a CR and 41% (42/102 patients: 95%CI: 31.5%–51.4%) achieving a PR[1]. The median time to objective response (CR or PR) was 5.7 weeks (range 5.1 to 56 weeks) with a median time to CR of 12 weeks (range 5.1 to 56 weeks)[13]. The most recent analysis at a median time of approximately three years from first dose, reported a median overall survival (OS) of 40.5 months (95% CI: 28.7 months–not estimable)[15]. The median duration of response for all patients with an objective response was 11.2 months (95% CI: 7.7–18.7)[14]. Eight patients (7.8%) went on to receive alloSCT after they had responded to brentuximab vedotin[13].

3.2 Studies in ASCT–naive patients

Clinical evidence in patients with relapsed or refractory HL was submitted by the company for 59 patients, who had not undergone ASCT and who had received ≥ one dose of brentuximab vedotin[1,4]. The median age of these patients was 35 years with a range of 12–88 years. The patients had been treated in phase I/II studies, in a Japanese study (TB-BC010088) and in Named Patient Programmes. The number of patients who had received at least two prior treatments and were treated with the licensed dose of brentuximab vedotin was 40. One additional patient received the licensed dose, but had only received one prior therapy before administration of brentuximab. The ORR and CR following a mean of 5.3 cycles of brentuximab vedotin were 22/41 patients (54%) and 9/41 patients (22%). Eight of the 41 patients (19%) who had been previously ineligible for ASCT because their disease was chemo-refractory went on to receive stem cell transplantation[1,4].

3.3 Comparative evidence from systematic review.

The key evidence for the use of brentuximab vedotin comes from the pivotal, SG035-0003 study for which there was no control group. The company have therefore carried out a systematic review of other treatment options in patients with relapsed HL post ASCT. The largest study identified in the review presented evidence for patients receiving treatment following ASCT failure: 294 patients received chemotherapy with or without radiotherapy, 35 patients received a second ASCT and 133 patients received an alloSCT[7]. OS estimated at two years, adjusted for baseline characteristics from the SG035-0003 study population was 48% in patients receiving chemotherapy and radiotherapy and 65% for those receiving an alloSCT versus 65% for brentuximab vedotin in SG035-0003[1,16].

3.4 Comparative safety

In study SG035-0003, 92% of patients had a treatment-related adverse event (AE). AEs leading to dose reduction occurred in 11% of patients; the reason for dose reduction was peripheral sensory neuropathy (PSN) for all but one patient. AEs that occurred in ≥ 20% of patients were: PSN (47%), fatigue (46%), nausea (42%), upper respiratory tract infection (37%), diarrhoea (36%), pyrexia (29%), neutropenia (22%), vomiting (22%), and cough (21%). Progressive multifocal leukoencephalopathy, a severe debilitating disease, occurred in two patients and resulted in one death, which may be related to use of brentuximab vedotin[4]. Treatment–related serious adverse events (SAEs) occurred in 14% of patients[4].

3.5 AWTTC critique

- Brentuximab vedotin is the only medicine licensed for the treatment of relapsed or refractory HL who relapse after ASCT and for those who are ineligible for ASCT and therefore provides a treatment option where there is an unmet need[4].
- The most recent median overall survival reported for brentuximab vedotin (40.5 months) compares very favourably with the overall survival of 1.2 years reported in the literature for patients who relapse within one year of ASCT[1].

- The Committee for Medicinal Products for Human Use (CHMP) considered brentuximab vedotin eligible for conditional marketing authorisation as it met EC criteria for orphan medicines: it is aimed at the treatment of seriously debilitating disease, the risk-benefit balance was considered positive, the applicant company is likely to be able to provide comprehensive clinical data, it fulfils an unmet medical need, and the benefit to patients of immediate availability outweighs the risks inherent in additional data being required[4].
- The pivotal study (SG0335-0003) using brentuximab vedotin in patients with HL was carried out without a control arm; however, the company conducted a systematic review to provide a naive comparison.
- Evidence from the European Named Patient Programme suggests that the number of cycles of brentuximab vedotin used in everyday clinical practice (6–8 cycles) is less than the number of cycles used in the pivotal study (median nine cycles)[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost-utility analysis (CUA) of brentuximab vedotin in the treatment of adults with relapsed or refractory CD30+ HL following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. The comparators are chemotherapy ± radiotherapy, or, in patients who are sufficiently fit and eligible, chemotherapy ± radiotherapy with the intention of undergoing alloSCT. In the base case, alloSCT is not permitted following brentuximab vedotin treatment[1].

The analysis is based on a 40-year Markov model. Three health states are modelled: progression-free survival (PFS); post-progression survival (PPS) and death. A cohort of patients aged 31 years, as per the median age of patients at baseline in the pivotal study (SG035-0003), commence treatment with brentuximab vedotin or the comparators in the PFS state, where they remain until they experience progression followed by death.

PFS data for brentuximab vedotin are based on the investigator-assessed PFS data estimated directly from the SG035-0003 study over 3.7 years of follow-up. For the chemotherapy ± radiotherapy comparator, PFS is estimated from a subset of 57 patients in that study with investigator-assessed PFS following their most recent post-ASCT treatment. For patients who go on to receive alloSCT, no progression is assumed during the average 3.9 months of chemotherapy, following which PFS is estimated from published retrospective analyses of outcomes in alloSCT recipients in Europe over a 5.2 year period[17]. The observed PFS data from these sources are extrapolated in the longer term by assuming a constant risk of progression beyond the 5.2 years of follow-up for alloSCT and chemotherapy ± radiotherapy, and assuming the risk of progression with brentuximab vedotin is the same as with alloSCT following the 3.7 year period of study follow-up.

OS data for patients receiving alloSCT or chemotherapy ± radiotherapy is based on published retrospective analyses of outcomes in European patients relapsing following ASCT, who were followed-up for a maximum of six years[7]. These data have been weighted to reflect the proportions expected to undergo alloSCT (56% in the base case), and adjusted to reflect the baseline risk factors of patients in SG035-0003. OS data for brentuximab vedotin is taken from SG035-0003, curtailed at 179 weeks and extrapolated exponentially beyond that point assuming the same constant risk of death as in patients receiving alloSCT or chemotherapy ± radiotherapy. The proportion of

patients progressing from the PFS state to the PPS state is modelled over time as the difference between the resulting OS and PFS curves[1].

Brentuximab vedotin acquisition costs are based on the weight of patients, dose intensity and average number of treatment cycles observed in SG035-0003, assuming vial wastage. Acquisition costs of standard chemotherapy, antiemetics and immunosuppressants (for alloSCT recipients) are estimated based on regimens identified in the literature and clinical expert opinion regarding the frequency of use of different regimens in the UK. Resource use associated with medicine administration and radiotherapy is costed using national reference costs; however, expert opinion is used to cost alloSCT instead of the lower national reference costs for this procedure[1]. AE costs are included in the model for events that were either grade 3–4 and occurred for any comparator in 5% or more of patients or grade 1–2 and occurred in 20% or more of patients.

Utility values for CR, PR, stable disease (SD) and progressive disease (PD) were elicited in a time trade-off vignette study reported to have been conducted in 100 members of the public in the UK. Values for CR, PR and SD were applied in the PFS health state to the proportions of patients with CR, PR and SD determined from SG035-0003 (for brentuximab vedotin treatment) and published retrospective analyses of outcomes in European patients[17]. These proportions of patients with CR, PR and SD in the PFS state are assumed to remain constant over time, but for alloSCT the same response rates as for chemotherapy ± radiotherapy are assumed in the first 100 days due to a lack of alloSCT specific data up to that point. In addition, utility decrements were elicited in the vignette study for adverse event states of acute and chronic graph versus host disease, grade 1–2 PSN, and grade 3 PSN, with decrements for other AEs sourced from the literature[1]. Costs and outcomes beyond one year are discounted at 3.5% per annum.

4.1.2 Results

The results of the base case analysis, in which alloSCT is not permitted following brentuximab vedotin treatment, are presented in Table 1. In patients for whom alloSCT may be a treatment option, brentuximab vedotin is estimated to be both more effective and less costly than chemotherapy with intention for alloSCT. The main driver of the results is the higher costs of AEs and the modelled smaller quality-adjusted life-year (QALY) gains in the PFS state for alloSCT compared with brentuximab vedotin. In patients ineligible for alloSCT, brentuximab vedotin has an incremental cost per QALY gained of £43,686. The main driver of the results is the greater acquisition costs and the greater retention of patients in the PFS state as modelled for brentuximab vedotin compared with chemotherapy ± radiotherapy.

Table 1. Base case CUA results over 40-year (lifetime) horizon[1]

	Brentuximab vedotin	Chemotherapy ± radiotherapy	Chemotherapy with intention for alloSCT
Costs			
Medicine acquisition	£69,335	£3,729	£66,514
Medicine administration	£2,314	£2,714	
Health state costs	£14,510	£17,217	£16,271
AEs	£309	£1,123	£11,141
Total costs	**£86,468**	**£24,782**	**£93,925**
Outcomes			
Life years (total)	5.21	4.15	4.41
QALYs			
PFS	2.35	0.45	1.68
PPS	0.88	1.36	0.91
AEs	−0.04	−0.03	−0.08
Total QALYs	**3.19**	**1.78**	**2.51**
ICERs (£/QALY gained, brentuximab vedotin versus comparator)			
Patients eligible for alloSCT	**£43,686/QALY gained**		**Brentuximab vedotin more effective and less costly**
Patients not eligible for alloSCT	**£43,686/QALY gained**		n/a

ICER: incremental cost effectiveness ratio (incremental cost per QALY gained); PFS: progression free survival state; PPS:post-progression survival state; QALYs: quality-adjusted life years

In probabilistic sensitivity analyses, the probability of brentuximab vedotin treatment having an incremental cost per QALY gained below £30,000 was 3%, and below £50,000 was 66% in each population.

One-way sensitivity and scenario analyses included exploration of key assumptions on relative risks of PFS and OS beyond the SG035-0003 study follow-up, use of independently assessed response rates for brentuximab vedotin, the fitting of parametric functions for extrapolation of survival curves, inclusion of alloSCT in a proportion of patients following brentuximab vedotin treatment, and alternative time horizons of analysis. In patients eligible for alloSCT, brentuximab vedotin remained more effective and less costly than chemotherapy with intention for alloSCT, or else provided more QALYs at a lower incremental cost-effectiveness ratio (ICER) than could be achieved with chemotherapy with intention for alloSCT when compared against chemotherapy ± radiotherapy. In patients who are not eligible for alloSCT, the one-way sensitivity/scenario analyses to which the model results were most sensitive are presented in Table 2. No sensitivity/scenario analyses were presented to explore the combined impact of multiple key assumptions (e.g. alternative assumptions on relative risks of both PFS and OS).

Table 2. Key sensitivity/scenario analyses of brentuximab vedotin compared with chemotherapy ± radiotherapy

Scenario description	Scenario details	Incremental cost per QALY	Key plausibility considerations
Base case analyses	Brentuximab vedotin vs. chemotherapy ± radiotherapy	£43,686	Potential for significant bias in all analyses in post-ASCT setting due to: - relative efficacy based on unadjusted indirect comparisons or limited data from self controls -assumes patients treated with brentuximab vedotin alone, with risks of PFS and OS with brentuximab vedotin same as with alloSCT in the long term (but none of the costs of alloSCT included – see below) -quality of life benefits of alloSCT over chemotherapy ± radiotherapy not apparent until 3 months after transplant. Extent to which these analyses would reflect use in patients ineligible for ASCT or multi-agent chemotherapy is unclear, as response rates with brentuximab vedotin lower in these patients than in those post-ASCT[4]
	Brentuximab vedotin versus chemotherapy with intention to alloSCT	Brentuximab vedotin less costly and more effective	
Sensitivity/scenario analyses in patients eligible for alloSCT			
Inclusion of alloSCT following brentuximab vedotin treatment	Brentuximab vedotin versus chemotherapy ± radiotherapy, 8% on brentuximab vedotin receive alloSCT	£50,919	Brentuximab vedotin vs. chemotherapy ± radiotherapy only a relevant comparator in patients eligible for alloSCT because chemotherapy with intention for alloSCT is dominated by brentuximab vedotin in the incremental analysis In SG035-0003, brentuximab vedotin enabled a proportion of patients to undergo alloSCT. The assumptions of the base case analysis may reflect some of the benefits of alloSCT (as risk of PFS and OS assumed the same for brentuximab vedotin as for alloSCT), but does not reflect the additional costs involved with alloSCT. The scenarios of 8-18%% attracting the costs of alloSCT would seem to reflect more plausible costs and hence more plausible ICERs than the base case model. As real world data indicate that up to a quarter of patients on brentuximab vedotin went on to receive alloSCT[22], the ICER may increase even further.
	Brentuximab vedotin versus chemotherapy ± radiotherapy, 18% on brentuximab vedotin receive alloSCT	£59,960	
Sensitivity/scenario analyses in all patients			
Independent PFS assessment	Brentuximab vedotin versus chemotherapy ± radiotherapy	£56,055	Base case employs investigator assessment of PFS, which in an open-label single arm study may be subject to bias, but company argues is more likely to reflect assessment in practice. Independent review may be less open to bias and results in significantly increased ICER versus base case. Company has not explored impact of this alongside other assumptions

Table 2. (continued)

Scenario description	Scenario details	Incremental cost per QALY	Key plausibility considerations
Hazard ratio for PFS beyond study period 1.5 to 2.0 for brentuximab vedotin/ chemotherapy versus alloSCT	Brentuximab vedotin versus chemotherapy ± radiotherapy	£49,635 to £53,783	Base case assumes the same risks of PFS and OS for brentuximab vedotin beyond the trial follow-up period as for alloSCT recipients, which is a source of uncertainty. The extent to which these scenario analyses may be more plausible than the base assumption is unclear, but removal of this assumption by increasing the relative risk of progression and mortality with brentuximab vedotin to 1.5 to 2 times that of alloSCT demonstrates the sensitivity of the model to the base case assumption, particularly on PFS.
Hazard ratio for OS beyond study period 1.5 to 2.0 for brentuximab vedotin/ chemotherapy versus alloSCT	Brentuximab vedotin versus chemotherapy ± radiotherapy	£47,810 to £48,451	
Hazard ratio for both PFS and OS beyond study period 1.5 to 2.0 for brentuximab vedotin/ chemotherapy versus alloSCT	Brentuximab vedotin versus chemotherapy ± radiotherapy	£55,059 to £61,258	
Log-normal curve fitting for PFS extrapolation	Brentuximab vedotin versus chemotherapy ± radiotherapy	£60,429	Base case model uses observed data for PFS, as parametric curve fitting was not felt to be adequate, and exponential function for OS. Exponential function may overestimate OS curves. Demonstrates model sensitivity to extrapolation of data
Weibull curve fitting for OS extrapolation	Brentuximab vedotin versus chemotherapy ± radiotherapy	£53,473	
Alternative time horizons	Brentuximab vedotin versus chemotherapy ± radiotherapy Time horizons: study follow-up; 5 years to 20 years;	£93,573; £81,172 to £46,052	Base case analysis appropriately uses lifetime horizon; however, given uncertainty in PFS and OS data it is useful to consider shorter time horizons. Demonstrates reliance of base case analysis on the uncertain PFS and OS benefits that are assumed to persist in the long term

4.1.3 AWTTC critique

Clinical study data for brentuximab vedotin used in the economic model are limited to a single arm study in patients post-ASCT, and there is a lack of robust comparative data against alternative treatment strategies. The company's analyses therefore rely on limited efficacy data from self controls in the single arm trial, or unadjusted indirect treatment comparisons, both of which are subject to risk of bias and significant uncertainty. Further uncertainties relate to the long term extrapolation of relative treatment effects and the assumptions on costs of progression to alloSCT following brentuximab vedotin treatment.

In all analyses, including sensitivity analyses exploring the impact of key assumptions, brentuximab vedotin was estimated to be more effective and less costly than chemotherapy with the intention for alloSCT. However compared with chemotherapy ± radiotherapy (as the next alternative) in patients eligible for alloSCT, and compared with chemotherapy ± radiotherapy as the only alternative for patients ineligible for alloSCT, the incremental cost per QALY gained exceeded usual thresholds for cost-effectiveness, and may be significantly underestimated. Collectively, all analyses

appear subject to considerable uncertainty and it is not clear they would reflect the cost-effectiveness of the use of brentuximab vedotin in NHS Wales in this post-ASCT population. It is further uncertain that the analyses would reflect the cost-effectiveness of the use of brentuximab vedotin in patients following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

The company suggests that brentuximab vedotin should be considered under the AWMSG policy for ultra-orphan medicines (see Section 6.5).

Key strengths of the economic evidence include:

- There are limited efficacy data for brentuximab vedotin in the treatment of this rare patient population, and no robust comparative data versus alternative treatment strategies. In this context, the company has made significant efforts to model the cost-effectiveness of brentuximab vedotin.
- A wide range of one-way sensitivity and scenario analyses has been conducted to explored the impact of key individual assumptions required in the modelling.

Key limitations and uncertainties in the economic evidence include:

- Data with which to model outcomes and costs of the use of brentuximab vedotin and the comparators in patients post-ASCT are very limited. A lack of robust comparative data has resulted in several areas of significant uncertainty:
    - The relative efficacy of brentuximab vedotin and the comparators is based on unadjusted indirect comparisons or limited data from self controls.
    - Response to treatment is based on investigator assessment, which may be open to bias in a single-arm study. Use of independently assessed response rates from the study results in a significantly increased ICER estimates when comparing brentuximab vedotin with chemotherapy ± radiotherapy.
    - It is assumed that the risks of progression and survival for brentuximab vedotin in the period after study follow-up is the same as for alloSCT. The ICER estimates are sensitive to these assumptions and the methods of extrapolation in the long term.
- The base case excludes alloSCT as a treatment option following brentuximab vedotin treatment, despite the fact that the company reports real world data and company-sought expert opinion suggesting 25% to 30% of brentuximab vedotin recipients go on to receive alloSCT in practice. Scenario analyses incorporating the costs of alloSCT following brentuximab vedotin treatment would appear to be more plausible than the base case analysis and result in significantly higher ICER estimates.
- The company assumes that results of the analyses in patients post-ASCT also reflect the cost effectiveness of brentuximab vedotin in patients when ASCT or multi-agent chemotherapy is not a treatment option. This would appear subject to significant uncertainty as response to treatment in these patients appears lower than in patients post-ASCT[5].
- Deterministic sensitivity and scenario analyses are mainly limited to exploration of uncertainty in single parameters. Probabilistic sensitivity analysis, which considers joint uncertainty across parameter values, has been undertaken and suggests little chance of the ICER for brentuximab vedotin versus chemotherapy ± radiotherapy falling below the upper limit of the usual threshold for cost effectiveness. However, this relates only to parameter values assumed in the base case analysis and does not incorporate the alternative scenarios that may be more plausible than the base case analysis.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost effectiveness analyses of brentuximab vedotin relevant to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT
5.1 Budget impact evidence

5.1.1 Context and methods
Based on British Society of Blood and Marrow Transplantation (BSBMT) Registry data[18], the company reports there were 141 ASCT procedures for HL in the UK and Republic of Ireland in 2012, which would be equivalent to six procedures in Wales. Of these, it is assumed around half will relapse, which was rounded to four cases per year. Based on a range of assumptions, a further four cases of patients ineligible for ASCT are estimated[1]. An uptake of 80% is anticipated, equivalent to a total six patients eligible for treatment with brentuximab vedotin per year.

Costs of brentuximab vedotin and the comparators are derived from the economic model (Section 4), with additional assumptions on long term follow-up costs and the proportion of patients receiving best supportive care and their time in PFS and progressed disease states. Furthermore, in contrast to the base case cost-effectiveness analysis, 19% of patients who receive brentuximab vedotin are assumed to become eligible for stem cell therapy (SCT), the costs of which are included in the budget impact model[1].

5.1.2 Results
The company estimates the net budget impact in Wales in each of the next five years for patients post-ASCT and for patients who are ineligible for ASCT, as in Table 3.

Table 3. Company estimates of net cost implications associated with use of brentuximab vedotin in relapsed/refractory HL

	Year 1	Year 2	Year 3	Year 4	Year 5
Post-ASCT					
Number of eligible patients	4	4	4	4	4
Uptake (%)	80%	80%	80%	80%	80%
Treated patients	3	3	3	3	3
Net drug costs (brentuximab vedotin and chemotherapy)	£212,926	£212,926	£212,926	£212,926	£212,926
Administration and monitoring	−£873	−£873	−£873	−£873	−£873
Secondary & tertiary care	−£121,764	−£121,764	−£121,764	−£121,764	−£121,764
ASCT ineligible					
Number of eligible patients	4	4	4	4	4
Uptake (%)	80%	80%	80%	80%	80%
Treated patients	3	3	3	3	3
Net drug costs (brentuximab vedotin and chemotherapy)	£114,483	£114,483	£114,483	£114,483	£114,483
Administration and monitoring	−£4,183	−£4,183	−£4,183	−£4,183	−£4,183
Secondary & tertiary care	£43,598	£43,598	£43,598	£43,598	£43,598
Combined population relapse/refractory HL					
Company estimates of overall net cost*	£244,186	£244,186	£244,186	£244,186	£244,186
* Company estimates of overall net costs are underestimated as they include assumed cost savings relating to secondary and tertiary care, and administration and monitoring, that would not be realised as financial cost savings in practice					

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of patients eligible for treatment with brentuximab vedotin. The estimates are based on incident cases only and exclude patients with sALCL, who are not considered in the submission.
- The assumed net costs per patient are based on costs included in the company's economic model. The uncertainties and limitations of the economic model would feed through to the budget impact estimates.
- It should be noted that the cost savings to secondary and tertiary care, and administration and monitoring, as derived from the economic model reflect opportunity costs rather than financial costs. There is no evidence to suggest that these would be realised as budgetary cost savings in practice, and so the company's net budget impact estimates would appear to be underestimated.

5.2 Comparative unit costs

Brentuximab vedotin is the only agent licensed specifically for the treatment of relapsed or refractory HL. Other possible treatments include a range of salvage chemotherapy regimens. The British National Formulary list price of brentuximab vedotin is £2,500 per 50 mg vial (excluding VAT)[19] and the recommended dose is 1.8mg/kg. Assuming an average of three vials per patient per treatment cycle and the SPC-recommended number of cycles, which ranges from a minimum of 8 to a maximum of 16[2], the cost per patient treated would be £60,000 to £120,000. In the pivotal study, conducted in patients post-ASCT, the mean number of treatment cycles was 9.7[1], which would cost £72,750.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, brentuximab vedotin (Adcetris®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration. The company do not anticipate that brentuximab vedotin (Adcetris®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that other than updates of the SG035-0003 study, there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: January 2014
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to ultra orphan medicines

The company suggests that brentuximab vedotin should be considered under the AWMSG policy relating to ultra-orphan medicines[1]. The policy applies to medicines with orphan designation in the EU that are licensed for the treatment of disease with a prevalence of less than 1 in 50,000 in the EU[20]. At the time of the granting of orphan designation for brentuximab vedotin, the Committee for Orphan Medicinal Products (COMP) noted HL affected approximately 1 in 10,000 people in the EU, based on the information provided by the sponsor and the knowledge of the COMP[21]; this would equate to approximately 300 people in Wales. The majority of HL patients are effectively cured; 75–80% achieve complete remission[4,6]. The proportion of patients not

cured would be 20–25% (approximately 60–75 patients), of which an estimated 21% would be aged < 18 years, giving a population of approximately 47–59 patients in Wales. The target population for brentuximab vedotin, adult patients with relapsed or refractory CD30+ HL represent a small proportion of the wider HL population[4].

Should NMG/AWMSG consider the policy to apply to brentuximab vedotin, the same criteria for clinical effectiveness and cost-effectiveness of ultra-orphan medicines as those applied to other medicines will be considered, but recognising that the evidence base will necessarily be weaker. NMG/AWMSG would also recognise that the incremental cost-effectiveness ratios (ICERs) of many ultra-orphan medicines will exceed the threshold cost-effectiveness range. In such cases, NMG/AWMSG will consider evidence as detailed in Table 4 to inform their decisions (in descending order of priority)[20].

Table 4. Evidence considered by NMG/AWMSG for ultra-orphan medicines

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival	Relapsed or refractory HL is a severe condition in terms of its impact on quality of life and survival
Whether the medicine can reverse, rather than stabilise the condition	Limited study data demonstrate the efficacy of brentuximab vedotin in achieving ORR and CR in a proportion of patients (75% and 33%, respectively, in the pivotal study in patients post-ASCT). The EPAR notes that it is unknown at this time if brentuximab vedotin as a single agent can effect a cure[4]; however, there is evidence that brentuximab vedotin treatment may permit patients, who otherwise may have been ineligible, to undergo SCT.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development	Limited study data indicate 18-19% of patients were able to undergo SCT following brentuximab vedotin treatment, and data from a named patient programme in the UK indicates 25% of patients were progressed to alloSCT[22]. Brentuximab vedotin is therefore a potential bridge to SCT, which may be curative.
The innovative nature of the medicine. NMG/AWMSG will consider whether the medicine: -represents a significant improvement on existing therapy (e.g. the medicine is able to treat a condition where there was previously no effective treatment) and; -whether it can plausibly generate substantial health gains over existing treatments for the individual (e.g. > 1 QALY)	The licensed indication specifies use in patients with relapsed/refractory HL. There are no other treatments specifically licensed for this use and there is no one standard treatment. Limited single-arm study data demonstrate efficacy in achieving tumour response. The economic model generates QALY gains with brentuximab vedotin greater than 1 QALY compared against chemotherapy ± radiotherapy, and smaller gains over chemotherapy with intention for alloSCT, but these results are subject to significant limitations and uncertainties

There are many uncertainties and limitations of the economic evidence presented by the applicant company (see Section 4.1.3). Brentuximab vedotin dominated (i.e. was more effective and overall less costly) or yielded greater QALY gains at a lower ICER when compared against chemotherapy with intention for alloSCT in all sensitivity and scenario analyses that were undertaken; however, when compared against chemotherapy ± radiotherapy, brentuximab vedotin had an ICER that significantly exceeded the usual threshold range for cost effectiveness and which may be significantly underestimated.

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