

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Brentuximab vedotin for treating CD30-positive
Hodgkin's lymphoma**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using brentuximab vedotin in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using brentuximab vedotin in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 01 September 2016

Second appraisal committee meeting: 12 October 2016

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Brentuximab vedotin is not recommended within its marketing authorisation for treating CD30-positive Hodgkin's lymphoma in adults with:

- relapsed or refractory disease after autologous stem cell transplant
- increased risk of disease relapse or progression after autologous stem cell transplant or
- relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.

1.2 This guidance is not intended to affect the position of patients whose treatment with brentuximab vedotin was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Brentuximab vedotin (Adcetris, Takeda UK) is an antibody–drug conjugate comprising an anti-CD30 monoclonal antibody attached by an enzyme-cleavable linker to a potent chemotherapeutic agent, monomethyl auristatin E (MMAE). The antibody–drug conjugate allows for the selective targeting of CD30-expressing cancer cells.
Marketing authorisation	Brentuximab vedotin is indicated for treating relapsed or refractory CD30-positive Hodgkin’s lymphoma in adults: <ol style="list-style-type: none"> 1. after autologous stem cell transplant or 2. after at least 2 prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option. Brentuximab vedotin is also indicated for treating CD30-positive Hodgkin’s lymphoma in adults at increased risk of relapse or progression after autologous stem cell transplant.
Adverse reactions	The most common adverse events are nervous system disorders, including peripheral neuropathy, dizziness, and demyelinating polyneuropathy. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	The recommended dose is 1.8 mg/kg administered by intravenous infusion over 30 minutes every 3 weeks.
Price	The price of brentuximab vedotin is £2,500 for a 50 mg vial (excluding VAT; ‘British National Formulary’ edition 69). The company estimated the average cost of treatment to be £69,335 per person for relapsed or refractory CD30-positive Hodgkin’s lymphoma after autologous stem cell transplant, and £86,470 per person at high risk of residual disease after autologous stem cell transplant. Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Takeda UK and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of brentuximab vedotin, having considered evidence on the nature of Hodgkin's lymphoma and the value placed on the benefits of brentuximab vedotin by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management of Hodgkin's lymphoma

- 4.1 The committee noted that there was no NICE technology appraisal guidance on Hodgkin's lymphoma. It understood that current first-line treatment is chemotherapy with or without radiotherapy. If this fails to lead to long-term remission, people may have high-dose chemotherapy then autologous stem cell transplant. The committee was aware that there was no standard therapy administered after autologous stem cell transplant to delay disease progression. Up to half the people who have autologous stem cell transplant would be expected to have disease progression and a short life expectancy of less than 3 years. These people may be offered chemotherapy with a single drug, or a combination of drugs. The committee understood that allogeneic stem cell transplant was the treatment of choice for young people if there is a suitable donor and a good response to systemic therapy after autologous stem cell transplant has failed. The committee recognised that treatment largely depended on the person's individual circumstances, including their eligibility for stem cell transplant.
- 4.2 The committee discussed the role of autologous stem cell transplant. It was aware that stem cell transplant can potentially cure Hodgkin's lymphoma, but that not all people are fit enough to have it. The clinical experts advised that autologous stem cell transplant would not generally be recommended for relapsed or refractory Hodgkin's lymphoma unless there was an adequate response to previous (salvage) therapy. This

normally means at least a partial response, although they noted that the definition of 'adequate response' is uncertain. The committee heard from clinical experts that positron emission tomography (PET) scanning is the preferred method of assessing response to salvage therapy before autologous stem cell transplant, and that this was available in most UK transplant centres. The committee recognised that there were 2 groups who may not have an autologous stem cell transplant: people who are not fit enough for treatment and those for whom salvage therapy did not produce an adequate response. The committee appreciated that both of these groups would have a high clinical unmet need.

4.3 The committee considered the subpopulations of people with CD30-positive Hodgkin's lymphoma included in this appraisal:

- adults with relapsed or refractory disease after autologous stem cell transplant
- adults with increased risk of disease relapse or progression after autologous stem cell transplant and
- adults with relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.

The committee heard from clinical experts that the relevant populations in the UK were people with relapsed or refractory disease after autologous stem cell transplant, and those with relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option. The committee understood that there are currently no approved treatments for these indications. Also, brentuximab vedotin offers the chance of a potentially curative stem cell transplant, which the clinical experts considered of great importance. The committee heard from clinical experts that it was not routine practice in England to treat people at increased risk of disease relapse or progression after autologous stem cell transplant. This was because most

clinicians would aim for PET-negative remission (that is, no signs of disease on the PET scan) before autologous stem cell transplant (see section 4.2). If this is achieved, the risk of subsequent relapse or progression is reduced, and the adverse effects of brentuximab vedotin would likely outweigh its benefit, which is expected to be limited in this situation. If the PET scan is positive, brentuximab vedotin would be used as a 'bridge' to autologous stem cell transplant, that is, as a further treatment to reduce tumour burden and achieve PET-negative remission before autologous stem cell transplant. The committee was aware that submissions from professional groups also suggested that brentuximab vedotin would not be used to prevent relapse or progression after autologous stem transplant. The committee concluded that in clinical practice, brentuximab vedotin would mainly be used for relapsed or refractory disease after autologous stem cell transplant, and relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.

- 4.4 The committee asked whether rules for stopping treatment are used in clinical practice. It noted that, at the time the appraisal consultation document was issued, the Cancer Drugs Fund includes brentuximab vedotin for the 2 relapsed or refractory CD30-positive Hodgkin's lymphoma populations on condition that treatment is stopped if there is no partial or complete response after 6 treatment cycles. The committee heard from clinical experts that, although there was no robust evidence, maximal response would be expected after 4–5 treatment cycles. The committee noted that this was much lower than the maximum number of 16 cycles recommended in the summary of product characteristics. It concluded that stopping rules need further discussion for the economic modelling given their potential effect on the cost of treatment.

Clinical effectiveness

Adults with relapsed or refractory disease after autologous stem cell transplant

- 4.5 The committee noted that the main evidence was from the SG035-0003 trial (n=102); an open-label, single-arm, phase II trial. The key results were:
- overall response rate by independent review (primary outcome): 75% (76/102); complete response rate by independent review: 33% (34/102)
 - median progression-free survival by investigators: 9.3 months (95% confidence interval [CI] 7.1 to 12.2 months)
 - median overall survival: 40.5 months.
- 4.6 The committee noted that the company considered the anti-tumour effect of brentuximab vedotin to compare favourably with historical controls. It was aware that such comparisons are associated with a high risk of bias, not least because they may be based on studies that found no benefit for the controls. Also, the committee noted that the historical control data came from relatively old studies. It heard from clinical experts that the outcome of chemotherapy was likely to be better than reported in the literature, as shown by the increasing number of people who have allogeneic stem cell transplant. The committee agreed that no definite conclusions about the effect of brentuximab vedotin for this indication could be drawn from comparisons with historical controls.
- 4.7 The committee discussed the company's 'intra-patient' comparison, noting that this was done in a subset of patients (57/102) with relapsed or refractory Hodgkin's lymphoma who had 1 or more systemic therapies other than brentuximab vedotin after autologous stem cell transplant. Median progression-free survival (assessed by investigators) after the most recent systemic therapy before brentuximab vedotin was 4.1 months compared with 7.9 months when these same patients then had

brentuximab vedotin (hazard ratio [HR] 0.40; $p < 0.001$). Because progression-free intervals are expected to shorten after each successive treatment, the company considered the effect of brentuximab vedotin to be clinically significant. The committee noted the ERG's comment that the intra-patient comparison was only done for patients for whom systemic therapy had failed, excluding those who had a good outcome with chemotherapy. In contrast, the clinical experts considered that patients who had systemic therapies before brentuximab vedotin may be fitter and able to tolerate the adverse effects of chemotherapy. The committee acknowledged that the intra-patient comparison did not provide comparative evidence based on parallel and controlled assignment of patients to different treatment arms; nor did it compare the most effective, as opposed to the most recent, chemotherapy. Nevertheless, the committee concluded that the company's intra-patient comparison gave a useful indication of the effect of brentuximab vedotin compared with chemotherapy.

Adults with increased risk of disease relapse or progression after autologous stem cell transplant

4.8 The committee noted that the main evidence was from the AETHERA trial ($n=329$); a double-blind, randomised, controlled, phase III trial comparing brentuximab vedotin with placebo. The key results were:

- median progression-free survival assessed by independent review (primary outcome): 42.9 months for brentuximab vedotin; 24.1 months for placebo (HR 0.57, 95% CI 0.40 to 0.81; $p=0.001$)
- median progression-free survival assessed by investigators: not reached for brentuximab vedotin; 15.8 months for placebo (HR 0.50, 95% CI 0.36 to 0.70)
- overall survival (without adjustment for treatment switching): median not reached for either treatment; HR 1.15 (95% CI 0.67 to 1.97).

4.9 The committee noted that AETHERA included patients with Hodgkin's lymphoma at risk of having residual disease after autologous stem cell transplant, defined as those who have 1 of the following risk factors:

- primary refractory Hodgkin's lymphoma (as determined by investigators)
- relapsed Hodgkin's lymphoma with initial remission of less than 12 months
- extra-nodal involvement before autologous stem cell transplant.

This definition was broader than the one on which brentuximab vedotin's regulatory approval was based, which defined high risk of relapse or progression as the presence of 2 or more of the above risk factors. It was also different from the definition in the final scope, which included a positive PET scan before autologous stem cell transplant as a high-risk factor. The committee was aware that clinicians considered PET scanning to be valuable in assessing the risk of relapse or progression. Autologous stem cell transplant would not be appropriate unless the PET scan is negative, in which case treatment after autologous stem cell transplant would not be needed (see sections 4.2 and 4.3). The committee agreed that the use of brentuximab vedotin in AETHERA did not reflect the regulatory approval for this indication, or clinical practice. The committee would have liked to consider subgroup analyses that mirror the definition adopted by the regulator for high risk of relapse or progression after autologous stem cell transplant. It was also aware of the clinical experts' advice that this was not a relevant population in clinical practice in England (see section 4.3).

Adults with relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option

4.10 The committee noted that the main evidence came from a group of patients who took part in phase I and II studies, a study in Japanese

patients only (TB-BC010088), and a named patient programme (n=59; only 41 patients had the recommended dosage of brentuximab vedotin of 1.8 mg/kg every 3 weeks). The key results were:

- overall response rate: 54% (22/41); complete response rate: 22% (9/41)
- patients who became eligible for autologous stem cell transplant: 19% (8/41).

4.11 The committee agreed that this evidence, although the best available for this population, was associated with a high risk of bias because it came from a heterogeneous group of patients, some of whom were included in phase I and II studies. These studies were unlikely to be powered to detect a meaningful clinical effect. The committee heard from the company that a single-arm, phase IV study is ongoing for this population. It understood that this study would report in May 2016 at the earliest. Despite not being a comparative study, the committee agreed that the phase IV study would provide better quality evidence than is currently available. The committee welcomed the company's suggestion that preliminary data from this study may be submitted during consultation on this appraisal consultation document. It agreed that until this evidence is submitted it would not consider the clinical effectiveness of brentuximab vedotin for this indication further.

Conclusion on clinical effectiveness

4.12 The committee noted that the company's submission mostly included retrospective, non-randomised evidence, with a randomised controlled trial for one of the indications. It recognised that the available evidence was immature and limited, particularly for the 2 populations in whom brentuximab vedotin would be used (see section 4.3). The committee noted that the outcomes presented mostly related to the anti-tumour effect of brentuximab vedotin measured as response rate, which is less clinically relevant than progression-free survival and overall survival. Also, the

company sometimes relied on comparisons with historical controls, the validity of which is questionable. Taken together, the committee found it difficult to interpret the available results and appraise the clinical effectiveness of brentuximab vedotin. The committee appreciated that it would be difficult to do a randomised controlled trial for brentuximab vedotin in part because Hodgkin's lymphoma is rare. Also, it heard from clinical experts that there was little published evidence for the comparator treatments, preventing a clinically relevant comparison with brentuximab vedotin. The committee would have liked to consider subgroup analyses that mirror the definition adopted by the regulator for people at high risk of disease relapse or progression after autologous stem cell transplant, but it also recalled that this population was not relevant to clinical practice in England (see section 4.9). The committee agreed that, as a minimum, it would need to consider available data from the phase IV study for relapsed or refractory CD30-positive Hodgkin's lymphoma after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option before it could conclude about the clinical effectiveness of brentuximab vedotin.

Cost effectiveness

Adults with relapsed or refractory disease after autologous stem cell transplant

Survival modelling

4.13 The committee noted that to model progression-free survival the company used the Kaplan–Meier data from SG035-0003 for brentuximab vedotin, and data from the intra-patient comparison (see section 4.7) for chemotherapy. The company extrapolated progression-free survival beyond the trial follow-up (6.1 years) assuming that both brentuximab vedotin and chemotherapy had the same effect on progression-free survival as that measured after allogeneic stem cell transplant in a study

by Robinson et al. (2009). However, the ERG preferred fitting the following parametric functions to the progression-free survival data:

- generalised gamma for brentuximab vedotin during the trial follow-up period
- log-normal for the chemotherapy arm during the trial follow-up period
- generalised F for allogeneic stem cell transplant in Robinson et al. to extrapolate progression-free survival in both treatment arms.

The committee heard from the ERG that, of all 3 modifications, the last influenced the results most. It understood that the company did not extrapolate progression-free survival based on the entire curve reported in Robinson et al., but instead chose a portion of the tail of the curve, which it considered to reflect the period during which the risk of progression became stable. The committee agreed that the company's extrapolation relied on the tail of the curve, which provided imprecise and uncertain information because the number of patients at risk of progression was small near the end of the follow-up period. Therefore, the committee accepted the ERG's modifications to the company's base case.

- 4.14 The committee noted that to extrapolate overall survival in the model the company fitted an exponential function to data from Martinez et al. (2010, 2013). Because the probability of death in Martinez et al. was relatively constant from 30 to 66 months, the company assumed a constant rate of death during the extrapolation. The ERG did not agree with the company's arbitrary choice of timeframe to analyse the tail of the curve. Also, it found that the probability of death decreased over time in Martinez et al. The ERG considered the company's scenario analysis using the Weibull function to be more reliable than the base-case exponential extrapolation. After examining the evidence on the fits of both curves, the committee agreed that the Weibull function fitted the data better than the exponential function.

4.15 The committee noted that the company's model predicted a 30% increase in life expectancy among people having brentuximab vedotin compared with chemotherapy. The ERG considered that the mortality benefit of brentuximab vedotin in the model was not based on robust evidence, but on a naive indirect comparison between SG035-0003 and observational data from Martinez et al. Because of this, it preferred assuming no mortality benefit for brentuximab vedotin. The committee heard from clinical experts that there was evidence that brentuximab vedotin extends progression-free survival. This would be expected to translate to extended overall survival, although by how long was uncertain. The committee agreed that assuming no mortality benefit for brentuximab vedotin was too conservative, although it acknowledged that there was no evidence to robustly model overall survival. As a compromise, the committee agreed that it would need to consider sensitivity analyses in which the mortality benefit of brentuximab vedotin is varied within a clinically plausible range.

Dosage of brentuximab vedotin

4.16 The committee noted that the company used the actual dose that patients had in SG035-0003, rather than the scheduled dose, to account for missed, delayed or reduced doses, although it was unclear to the ERG how the company applied the actual dose. The committee understood that, because the company modelled a 'blended comparator' of single or combination chemotherapy regimens, the company estimated the cost of chemotherapy as a weighted average of the individual regimens. As a result, the entire cost of chemotherapy was applied to everyone in that treatment arm for the recommended duration of the regimen received, whether or not the person had disease progression, died, or reduced the dose. The committee preferred using the actual doses because they better reflected the dose that people would have in clinical practice than the scheduled doses. However, it considered that whether the actual or scheduled doses are used, they should be applied consistently in both treatment arms.

4.17 The committee noted that both the company's base case and the ERG's modified base case estimated the cost of brentuximab vedotin in the model based on the average number of treatment cycles patients had in SG035-0003 (9.7 cycles), although the ERG did a scenario analysis based on the company's base case in which it applied the recommended 16 cycles. The committee heard from clinical experts that people are unlikely to have the recommended number of cycles of brentuximab, and possibly not even the number of cycles in the trial. This was because the maximal response would be expected after fewer cycles of treatment (see section 4.4). The committee recognised that because brentuximab vedotin is considerably more expensive than chemotherapy, the model was highly sensitive to the cost of brentuximab vedotin. The committee recalled that stopping rules need further discussion for the economic modelling given their potential effect on the number of treatment cycles, and hence the cost, of brentuximab vedotin (see section 4.4). It concluded that stopping rules should be explored in the economic modelling as a way to improve the cost effectiveness of treatment. The committee agreed that ideally, this would need to be accompanied by outcome data to reflect the effect of stopping treatment, although it recognised the treatment effect might not differ as much as costs when treatment is stopped early because the maximum response is expected after 4–5 cycles (that is, before applying the stopping rule).

Conclusion

4.18 The committee noted that the company estimated a base-case incremental cost-effectiveness ratio (ICER) for brentuximab vedotin of £39,327 per quality-adjusted life year (QALY) gained, and that the ERG's preferred ICER was £83,771 per QALY gained. The committee was aware that both of these ICERs were based on the average number of cycles of brentuximab vedotin that patients had in SG035-0003 (9.7 cycles), which the committee heard did not reflect clinical practice (see section 4.17). Overall, the committee agreed that the ERG's modified base case

mirrored its preferred analysis more closely than the company's base case. This was because the ERG included the following modifications:

- the generalised F function for allogeneic stem cell transplant in Robinson et al. to extrapolate progression-free survival in both treatment arms (see section 4.13)
- the Weibull function to extrapolate overall survival beyond the trial follow-up (see section 4.14)
- assuming that people in the chemotherapy arm have treatment only if they are alive and did not relapse (see section 4.16)
- applied the scheduled doses consistently in both treatment arms (see section 4.16).

However, the committee did not agree with the ERG's assumption of no mortality benefit for brentuximab vedotin. The committee would have preferred to have seen analyses based on the ERG's modified base case, including:

- scenario analyses in which the mortality benefit of brentuximab vedotin is varied within a clinically plausible range (see section 4.15)
- scenario analyses exploring the cost effectiveness of stopping treatment after 4 or 5 cycles of brentuximab vedotin if there was no partial or complete response (see section 4.17).

Until it considers these analyses, the committee concluded that it could not recommend brentuximab vedotin for relapsed or refractory Hodgkin's lymphoma after autologous stem cell transplant.

Adults with increased risk of disease relapse or progression after autologous stem cell transplant

Survival modelling

4.19 Overall, the committee was not persuaded of the relevance of this population to UK clinical practice. However, if it were to be modelled, the

committee agreed that the subgroup analyses reflecting the definition of high risk of relapse or progression after autologous stem cell transplant adopted by the regulator should inform the modelling for this indication (see section 4.9).

- 4.20 The committee noted that the ERG had doubts about the company's overall approach to the modelling, which led the ERG to believe that the model results were invalid. The ERG noted that the company assumed that all people in the model had equal life expectancy after relapse. As a result, the increase in progression-free survival with brentuximab vedotin unintentionally increased overall survival by an equal duration compared with best supportive care. This predicted that brentuximab vedotin would extend overall survival by 3.95 years compared with best supportive care, which the ERG considered an overestimate. To correct this, the ERG rebuilt a partitioned survival model, assuming equal mortality in both treatment arms. The committee agreed that assuming a 1:1 relationship between progression-free survival and overall survival was uncertain because there was no evidence on the relationship between these 2 outcomes, although it was reasonable to assume that an extension to progression-free survival would lead to some extension in overall survival. The committee concluded that the company and ERG's assumptions could both be considered extreme, and that the mortality benefit of brentuximab vedotin was likely to lie between the 2 estimates.

Health-related quality of life

- 4.21 The committee noted the ERG's comment that 5 years after starting treatment, the model assumed that the health-related quality of life of people who are alive and did not have disease progression was the same as the age-adjusted population norm. In the ERG's opinion, this assumption was not justified, and contradicted the EQ-5D data collected from AETHERA. The committee heard from clinical experts that health-related quality of life would nearly always be below the population norm because of the risk of complications after autologous stem cell transplant.

The committee concluded that the company's assumption about long-term health-related quality of life was not clinically plausible.

4.22 The committee noted the ERG's comment that, although the company estimated utility decrements on and off brentuximab vedotin or best supportive care, it did not apply the utility decrement for people who had stopped brentuximab vedotin in the model. The ERG noted that this decrement reflected the reduction in health-related quality of life that patients in AETHERA reported when brentuximab vedotin was stopped. Therefore, excluding it in the model would overestimate the utility in the brentuximab vedotin treatment arm. The committee considered the ERG's critique to be reasonable because the utility decrements were derived from the trial.

4.23 The committee noted the ERG's comment that the model implicitly assumed the same utility for people having best supportive care as for patients who had placebo in AETHERA for the average duration of placebo treatment in the trial (33 weeks). However, patients who had placebo in the trial had intravenous injections, which needed frequent visits to hospital and caused adverse events. This does not apply to people having best supportive care in clinical practice. The committee agreed that people having best supportive care would likely have better health-related quality of life than patients who had placebo in AETHERA, and that it was reasonable not to assume a utility decrement for best supportive care in the model.

Conclusion

4.24 The committee noted that the company estimated a base-case ICER for brentuximab vedotin of £56,342 per QALY gained, and that the ERG's preferred ICER was £590,407 per QALY gained. Overall, the committee agreed that the ERG's modified base case mirrored its preferred analysis more closely than the company's base case. This was because the ERG:

- removed the assumption that the health-related quality of life of people who did not have disease progression 5 years after starting treatment was the same as the age-adjusted population norm (see section 4.21)
- applied the effect of brentuximab vedotin on health-related quality of life to everyone in the brentuximab vedotin arm (see section 4.22) and
- assumed no utility decrement in the best supportive care arm for the average duration of treatment with placebo in AETHERA (see section 4.23).

However, the committee did not agree with the ERG's assumption of no mortality benefit for brentuximab vedotin. The committee would have preferred the ERG's modified base case to model the subgroup reflecting the definition of high risk of relapse or progression adopted by the regulator (see section 4.9), with alternative assumptions about the mortality benefit of brentuximab vedotin explored (see section 4.20). However, the committee recognised that the ICER from the ERG's base case was too high. It also recalled that this population was not relevant to clinical practice in England. The committee concluded that revised analyses would have been needed had this been a relevant population in England, but that because it was not and the ICER was too high for brentuximab vedotin to be considered cost effective in this population, no further analyses need be considered.

Adults with relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option

4.25 The committee noted that the company did not submit an economic model for this indication. However, it was aware that data from a phase IV trial would be available (see section 4.11), and that the company plans to use these data to develop a model for this indication. Until it considers this model, the committee concluded that it could not make recommendations for relapsed or refractory CD30-positive Hodgkin's lymphoma after at least

2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.

End-of-life considerations

4.26 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [final Cancer Drugs Fund technology appraisal process and methods](#). It noted that the company made the case that brentuximab vedotin met the criteria for life-extending treatments for people with a short life expectancy for 2 populations:

- relapsed or refractory CD30-positive Hodgkin's lymphoma after autologous stem cell transplant and
- relapsed or refractory CD30-positive Hodgkin's lymphoma after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.

The committee was aware that for the second population, there was no robust clinical evidence or an economic model. It would discuss whether brentuximab vedotin fulfils the end-of-life criteria for relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option if evidence from the phase IV trial, and an economic model using that evidence, becomes available. Therefore, it concluded that it would focus on relapsed or refractory CD30-positive Hodgkin's lymphoma after autologous stem cell transplant for the end-of-life considerations.

4.27 The committee discussed whether brentuximab vedotin is indicated for patients with a short life expectancy, normally less than 24 months. It noted that both the company and ERG's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. The committee heard from clinical experts that life expectancy without brentuximab vedotin may be less than 24 months, particularly in people who relapse quickly after autologous stem cell transplant (within 1 year).

The committee noted this conflicting evidence, but agreed that its end-of-life estimates need to be consistent with the modelled benefits, and therefore the criterion for short life expectancy did not apply.

4.28 The committee discussed whether there was sufficient evidence to show that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The committee recalled that the cost-effectiveness analysis from which the survival benefit of brentuximab vedotin could be inferred did not reflect the committee's preferred analysis (see section 4.18). Therefore, it concluded that brentuximab vedotin did not fulfil the criterion for extending life. The committee agreed that it would be appropriate to re-consider whether brentuximab vedotin fulfilled this criterion based on a revised model addressing the committee's considerations.

4.29 Based on the discussion in sections 4.27 and 4.28, the committee agreed that the criteria for life-extending treatments at the end of life did not apply for brentuximab vedotin given the current evidence. Therefore the committee concluded that the current ICERs for brentuximab vedotin of £83,771 per QALY gained for adults with increased risk of disease relapse or progression after autologous stem cell transplant, and £590,407 per QALY gained for adults with increased risk of disease relapse or progression after autologous stem cell transplant were higher than the normally acceptable maximum ICER range of £20,000–30,000 per QALY gained considered to represent a cost effective use of NHS resources.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.30 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to

suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Cancer Drugs Fund considerations

4.31 The committee was aware of the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England. Under the new arrangements, drugs may be given a conditional recommendation by NICE and made available to NHS patients through the Cancer Drugs Fund. Such a drug will remain available within the Cancer Drugs Fund, normally for up to 2 years, while the company gathers more evidence. The committee considered that it could not determine the most plausible ICER for any of brentuximab vedotin's indications. The committee also heard from the company that it did not intend to submit a case to include brentuximab vedotin in the Cancer Drugs Fund because the eligible population was small (50–60 people), and it was unclear what information further data collection could provide. For these reasons, the committee concluded not to recommend that brentuximab vedotin is included in the Cancer Drugs Fund at this stage.

Overall conclusion

4.32 Based on the above considerations, the committee concluded not to recommend brentuximab vedotin within its marketing authorisation for treating CD30-positive Hodgkin's lymphoma in adults with:

- relapsed or refractory disease after autologous stem cell transplant
- increased risk of disease relapse or progression after autologous stem cell transplant or
- relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma	Section
Key conclusion		
<p>Brentuximab vedotin is not recommended within its marketing authorisation for treating CD30-positive Hodgkin's lymphoma in adults with:</p> <ul style="list-style-type: none"> • relapsed or refractory disease after autologous stem cell transplant • increased risk of disease relapse or progression after autologous stem cell transplant or • relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option. <p>The committee concluded that in clinical practice, brentuximab vedotin would mainly be used for relapsed or refractory disease after autologous stem cell transplant, and relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.</p> <p>Overall, the committee agreed that the ERG's modified base case mirrored its preferred analysis more closely than the company's base case. However, the ERG's modified base case did not include all of the committee's preferred assumptions, notably the mortality benefit of brentuximab vedotin.</p> <p>The committee agreed that the criteria for life-extending treatments at the end of life did not apply for brentuximab vedotin given the current evidence.</p>		<p>1.1, 4.3, 4.18, 4.24, 4.27–4.29</p>

Current practice		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The committee noted that there was no NICE technology appraisal guidance on Hodgkin's lymphoma.</p> <p>The committee recognised that there were 2 groups who may not have an autologous stem cell transplant: people who are not fit enough for treatment and those for whom salvage therapy did not produce an adequate response. The committee appreciated that both of these groups would have a high clinical unmet need.</p> <p>The committee understood that there are currently no approved treatments for the indications for which brentuximab vedotin would mainly be used in clinical practice.</p>	<p>4.1, 4.2, 4.3</p>
The technology		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee understood that brentuximab vedotin offers the chance of a potentially curative stem cell transplant, which the clinical experts considered of great importance.</p>	<p>4.3</p>

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The committee heard from clinical experts that the relevant populations in the UK were people with relapsed or refractory disease after autologous stem cell transplant, and those with relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.</p>	<p>4.3</p>
<p>Adverse reactions</p>	<p>The most common adverse events are nervous system disorders, including peripheral neuropathy, dizziness, and demyelinating polyneuropathy.</p>	<p>2</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The committee noted that the company's submission mostly included retrospective, non-randomised evidence, with a randomised controlled trial for one of the indications. It recognised that the available evidence was immature and limited, particularly for the 2 indications for which brentuximab vedotin would be used.</p>	<p>4.12</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The committee heard from clinical experts that it was not routine practice in England to treat people at increased risk of disease relapse or progression after autologous stem cell transplant.</p>	<p>4.3</p>

<p>Uncertainties generated by the evidence</p>	<p>The committee noted that the outcomes presented mostly related to the anti-tumour effect of brentuximab vedotin measured as response rate, which is less clinically relevant than progression-free survival and overall survival. Also, the company sometimes relied on comparisons with historical controls, the validity of which is questionable.</p>	<p>4.6, 4.12</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>There are no clinically relevant subgroups for which there is evidence of differential effectiveness.</p>	<p>–</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>For relapsed or refractory disease after autologous stem cell transplant, the overall response rate by independent review (primary outcome) was 75%.</p> <p>For people at increased risk of disease relapse or progression after autologous stem cell transplant, the median progression-free survival assessed by independent review (primary outcome) was 42.9 months for brentuximab vedotin and 24.1 months for placebo (hazard ratio 0.57, 95% confidence interval 0.40 to 0.81; p=0.001).</p> <p>After at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option, the overall response rate was 54% (22/41).</p>	<p>4.5, 4.8, 4.10</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company submitted separate de novo economic models for relapsed or refractory disease after autologous stem cell transplant, and people at increased risk of disease relapse or progression after autologous stem cell transplant. The company made a statement about the potential cost effectiveness of brentuximab vedotin after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.</p>	<p>–</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The uncertainties for relapsed or refractory disease after autologous stem cell transplant were:</p> <ul style="list-style-type: none"> • the number of treatment cycles, and hence the cost, of brentuximab vedotin in clinical practice • the mortality benefit of brentuximab vedotin. <p>The uncertainties for people at increased risk of disease relapse or progression after autologous stem cell transplant were:</p> <ul style="list-style-type: none"> • the cost effectiveness of brentuximab vedotin when the definition of high risk of relapse or progression adopted by the regulator is applied • the mortality benefit of brentuximab vedotin. 	<p>4.15, 4.17 4.19, 4.20</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>For people at increased risk of disease relapse or progression after autologous stem cell transplant, the committee did not agree with the following assumptions about health-related quality of life in the company's model:</p> <ul style="list-style-type: none"> • the health-related quality of life of people who did not have disease progression 5 years after starting treatment was the same as the age-adjusted population norm • the effect of brentuximab vedotin on health-related quality of life did not apply to people who had stopped taking brentuximab vedotin • people having best supportive care in the model have the same utility as patients who had placebo in AETHERA for the average duration of placebo treatment in the trial (33 weeks). 	<p>4.21, 4.22, 4.23</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>There are no specific groups of people for whom the technology is particularly cost effective.</p>	<p>–</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee recognised that brentuximab vedotin is considerably more expensive than chemotherapy, and the model was highly sensitive to the cost of brentuximab vedotin.</p>	<p>4.17</p>
<p>Most likely cost-</p>	<p>For relapsed or refractory disease after</p>	<p>4.18,</p>

<p>effectiveness estimate (given as an ICER)</p>	<p>autologous stem cell transplant: the company estimated a base-case incremental cost-effectiveness ratio (ICER) for brentuximab vedotin of £39,327 per quality-adjusted life year (QALY) gained, and the ERG's preferred ICER was £83,771 per QALY gained. The committee was aware that both of these ICERs assumed an average number of cycles of brentuximab vedotin that did not reflect clinical practice. Overall, the committee agreed that the ERG's modified base case mirrored its preferred analysis more closely than the company's base case. However, it did not agree with the ERG's assumption of no mortality benefit for brentuximab vedotin.</p> <p>For people at increased risk of disease relapse or progression after autologous stem cell transplant: the company estimated a base-case ICER for brentuximab vedotin of £56,342 per QALY gained, and the ERG's preferred ICER was £590,407 per QALY gained. Overall, the committee agreed that the ERG's modified base case mirrored its preferred analysis more closely than the company's base case. However, it did not agree with the ERG's assumption of no mortality benefit for brentuximab vedotin. The committee also recognised that the clinical data did not reflect the definition of high risk of relapse or progression adopted by the</p>	<p>4.24</p>
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	regulator.	
Additional factors taken into account		
Patient access schemes (PPRS)	The committee concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.	4.30
End-of-life considerations	<p>The committee noted that both the company and ERG's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months.</p> <p>The committee agreed that there was insufficient evidence to show that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The committee agreed that it would be appropriate to consider whether brentuximab vedotin fulfilled this criterion based on a revised model addressing the committee's considerations.</p>	4.27– 4.29
Equalities considerations and social value judgements	The committee noted a comment suggesting that, without positive NICE guidance, there may be equity issues from variation in access within the UK because brentuximab vedotin is available in Scotland and Wales. The committee agreed that this does not represent a potential equality issue.	–

5 Proposed date for review of guidance

- 5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens

Chair, appraisal committee

July 2016

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser, an associate director and a project manager.

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