Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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1 Recommendations

1.1 Brentuximab vedotin is recommended as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:

- they have relapsed or refractory disease after autologous stem cell transplant and
- the company provides brentuximab vedotin at the price agreed with NHS England in the commercial access agreement.

1.2 Brentuximab vedotin is recommended for use within the Cancer Drugs Fund as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:

- they have relapsed or refractory disease after at least 2 previous therapies and
- they cannot have autologous stem cell transplant or multi-agent chemotherapy and
- the conditions of the managed access agreement are followed.

1.3 These recommendations are not intended to affect treatment with brentuximab vedotin that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding arrangements 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 lymphoma in adults:  
  - after autologous stem cell transplant or  
  - after at least 2 prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option.  
  Brentuximab vedotin most recently received an extension to the marketing authorisation for treating CD30-positive Hodgkin 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 pricing arrangement considered during guidance development was one in which the company (Takeda) had agreed a patient access scheme with the Department of Health. This scheme would have provided a simple discount to the list price of brentuximab vedotin with the discount applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS. The commercial access agreement between the company and NHS England incorporates this same simple discount applied at the point of purchase or invoice of all brentuximab vedotin but also includes additional and separate commercial arrangements that apply only to the population in the Cancer Drugs Fund (section 1.2). The financial terms of the agreement are commercial in confidence. |
3 Evidence

The appraisal committee (section 6) considered evidence submitted by Takeda UK and a review of this submission by the evidence review group. 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 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 lymphoma

4.1 The committee noted that there was no NICE technology appraisal guidance on Hodgkin 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, followed when possible by autologous stem cell transplant. The committee was aware that there is no standard therapy administered after autologous stem cell transplant to delay disease progression. Up to half the people who have had autologous stem cell transplant develop progressive disease with a life expectancy of less than 3 years. These people may be offered further, usually single-drug, chemotherapy. People whose disease does not respond after 2 previous lines of therapy would also be offered single-agent chemotherapy, but the committee was aware that these patients had a low chance of bridging to stem cell transplantation. Stem cell transplants give people the best chance of a curative treatment; so people who cannot bridge to stem cell transplantation have poor long-term survival prospects and a high clinical unmet need.

4.2 The committee understood that allogeneic stem cell transplant was the treatment of choice 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 circumstances, including their eligibility for stem cell transplant. The clinical experts advised that autologous stem cell transplant would not generally be recommended for relapsed or refractory Hodgkin 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 concluded that both of these groups would have a high clinical unmet need.

4.3 The committee considered the groups of people with CD30-positive Hodgkin lymphoma which reflected the marketing authorisation for brentuximab vedotin. These were:

- adults with relapsed or refractory disease after autologous stem cell transplant (population 1)
- adults with increased risk of disease relapse or progression after autologous stem cell transplant (population 2)
- 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 (population 3).

The committee heard from clinical experts that the most relevant populations in the UK were the first and third of the groups included in the marketing authorisation. The committee understood that there is currently no NICE guidance for these indications. Brentuximab vedotin is currently available through the Cancer Drugs Fund for populations 1 and 3. The UK marketing authorisation for brentuximab vedotin does not explicitly exclude retreatment as an option, but the company did not focus its submission on retreatment. Retreatment is not permitted through the Cancer Drugs Fund. Brentuximab vedotin offers the chance of a potentially curative stem cell transplant, which the clinical experts considered of great importance. The clinical experts also highlighted that in some instances brentuximab vedotin can be a curative treatment without stem cell transplant. For the second group, the committee heard from clinical experts that it was not routine practice in England to refer patients for transplant who are at increased risk of disease relapse or progression. 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 could be used as for the third group (that is, as a possible bridge to autologous stem cell transplant). The committee, however, noted that although the second group does not feature much in current UK
clinical practice, it should be appraised for the small subset of patients who may benefit. The committee concluded that based on current 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 of consultation, the Cancer Drugs Fund included brentuximab vedotin for the 2 relapsed or refractory CD30-positive Hodgkin lymphoma populations, administered once every 3 weeks (see summary of product characteristics) on the 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 to 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.

Clinical effectiveness

Population 1: adults with relapsed or refractory disease after autologous stem cell transplant

4.5 The committee noted that the trial evidence for this group was from SG035-0003 (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)

- 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 had 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 this 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 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). In its original submission, the company noted that because progression-free intervals are expected to shorten after each successive treatment, the effect of brentuximab vedotin can be considered clinically significant. The committee noted the evidence review group (ERG) 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.

Clinical-effectiveness conclusions

4.8 The committee noted that the company's clinical-effectiveness submission for this group came from non-randomised evidence, which provided an immature and limited evidence base (see section 4.5). The committee also noted that the outcomes presented included 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 relied on comparisons with historical controls, the validity of which is questionable. The committee
appreciated that it would be difficult to do a randomised controlled trial for brentuximab vedotin in part because Hodgkin lymphoma is rare. It also heard from clinical experts that there was little published evidence for the comparator treatments, preventing a clinically relevant comparison with brentuximab vedotin. Overall the committee concluded there was a large degree of uncertainty in the clinical evidence, but noted comments from clinical experts and positive results from the intra-patient comparison which suggested that brentuximab vedotin was more effective than chemotherapy.

**Population 2: adults with increased risk of disease relapse or progression after autologous stem cell transplant**

4.9 The committee noted the evidence base submitted by the company came from AETHERA (n=329), a double-blind, randomised, controlled, phase III trial comparing brentuximab vedotin with placebo. The trial collected data between April 2010 and September 2012. 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).

In response to consultation on the second appraisal consultation document, the company provided a new data cut from the AETHERA trial (ASH 2015) which it used in all of its updated cost-effectiveness analyses for this population.

4.10 The committee noted that AETHERA included patients with Hodgkin 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 lymphoma (as determined by investigators)
- relapsed Hodgkin 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. In response to consultation on the second appraisal consultation document, the company created 2 definitions of high-risk patients which could be applied to the trial population to identify a subgroup of patients which better reflected the committee's preferences. The committee acknowledged that clinicians considered PET scanning to be valuable in assessing the risk of relapse or progression, and agreed that any definition of high-risk patients should include a positive PET scan result. The committee's preferred patient subgroup was defined as those with a positive PET scan result before autologous stem cell transplant and at least 1 of:

• relapsed disease within 12 months or disease refractory to front-line therapy
• extra-nodal disease at pre-autologous stem cell transplant relapse
• B symptoms at pre-autologous stem cell transplant relapse
• at least 2 previous salvage therapies.

The company did not present any clinical data for this subset of the trial population in its response to consultation on the second appraisal consultation document. It used the updated data cut and subgroup of patients that met the high-risk definition above in its modelled cost-effectiveness analysis.

Clinical-effectiveness conclusions

4.11 The committee noted that this was the only population for which randomised controlled trial evidence was available, but that even this was compromised to fit the data to the relevant high-risk group. The committee noted that the median progression-free survival assessed by independent review (primary outcome) for the whole trial population was 42.9 months for brentuximab vedotin and 24.1 months for placebo (HR 0.57, 95% CI 0.40 to 0.81; p=0.001). The committee, however, accepted the company's proposed high-risk patient definition (see section 4.10).
Population 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

4.12 The committee noted that the original evidence presented by the company 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; 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).

4.13 In response to the first appraisal consultation document, the company provided additional clinical-effectiveness evidence for this population, from 2 sources:

- C25007 (n=60): an ongoing phase IV, single-arm, open-label, multicentre study
- a real-world UK observational study (n=78): a retrospective study including multiple centres across England.

The company pooled the data from these sources to maximise the target patient population. Table 1 presents the results of the individual studies and the pooled dataset.

Table 1 Results for relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option

<table>
<thead>
<tr>
<th>Outcome</th>
<th>C25007 study (n=60)</th>
<th>Observational study (n=78)</th>
<th>Pooled dataset (n=138 for SCT, n=135 for response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (%)</td>
<td>48 (CR=15, PR=33)</td>
<td>51 (CR=24, PR=27)</td>
<td>50 (CR=20, PR=30)</td>
</tr>
<tr>
<td>Post-brentuximab SCT rate (%)</td>
<td>47</td>
<td>58</td>
<td>53</td>
</tr>
<tr>
<td>Progression-free survival (months)</td>
<td>4.8 (95% CI 2.96 to 5.32)</td>
<td>5.68 (95% CI 4.21 to 17.05)</td>
<td>-</td>
</tr>
<tr>
<td>Overall survival</td>
<td>74% at 24 months (95% CI 58.0 to 84.6)</td>
<td>37.2 months (95% CI 17.8 to not reached)</td>
<td>–</td>
</tr>
<tr>
<td>Mean number of cycles</td>
<td>7.4 (95% CI 6.5 to 8.4)</td>
<td>4.1 (95% CI 3.7 to 4.6)</td>
<td>5.7 (95% CI 5.1 to 6.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; SCT, stem cell transplant.

4.14 The committee discussed whether the results from these studies were representative of 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. It considered that in clinical practice, this population could be ineligible for autologous stem cell transplant or multi-agent chemotherapy either because the patient is frail, or because the response to previous treatment does not predict a favourable outcome after autologous stem cell transplant. The committee recognised that the latter group would represent fitter patients for whom brentuximab vedotin could act as a bridge to autologous stem cell transplant, and that it was this group that the pooled dataset reflected more closely. The committee heard from the clinical experts that the most likely treatment option for this population, in the absence of brentuximab vedotin, was single-agent chemotherapy (see section 4.1). The committee concluded that the study population reflected only a fitter subset of the population under consideration.

4.15 The committee recognised that all the data presented, although the best available for this population, was associated with a large amount of uncertainty, as is the case with single-arm studies and retrospective evidence. The committee heard from the ERG that it had a number of concerns about the pooled studies. The first concern was the generalisability of the C25007 data to the UK population. A proportion of patients (18%) in the study only had 1 previous treatment, so did not mirror the marketing authorisation for brentuximab vedotin. Also, 88% of patients in C25007 came from outside the UK, and clinical experts stated that routine clinical practice would be quite different to that of the UK. The ERG highlighted that these differences were seen in the study outcomes of mean treatment cycles and relative rates of allogeneic and autologous stem cell transplant.
Clinical-effectiveness conclusions

4.16 The committee noted that the company's clinical-effectiveness submission for this group came from non-randomised evidence which provided a limited evidence base (see sections 4.12 and 4.13). The committee agreed that although the clinical data in the pooled dataset provided an improved evidence base compared to that considered in the first appraisal consultation document, it was still associated with a large amount of uncertainty. The committee also agreed that the real-world UK dataset provided more relevant clinical data to estimate the clinical effectiveness of brentuximab vedotin from a NHS perspective.

Cost effectiveness

4.17 The committee considered the company's amended economic analyses for populations 1 and 3 and the new data cut and subgroup analyses for population 2, all incorporating the updated patient access scheme. It agreed that the uncertainty in the clinical evidence base would be carried over in the economic modelling for populations 1 and 3.

Population 1: adults with relapsed or refractory disease after autologous stem cell transplant

4.18 For this group the committee noted that the cost-effectiveness analysis was sensitive to the progression-free survival extrapolation approach and the mortality benefit of brentuximab vedotin compared with chemotherapy.

Progression-free survival modelling

4.19 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 for chemotherapy (see sections 4.5 to 4.7). The company and the ERG extrapolated progression-free survival beyond the trial follow-up (6.08 years). They assumed that both brentuximab vedotin and chemotherapy had the same effect on progression-free survival as that measured in another study (Robinson et al. 2009), in which patients had allogeneic stem cell transplant. The committee noted that the ERG estimated progression risk from the entire curve in Robinson et al. (2009), and then applied the mean risk to the extrapolation of progression-free survival. The clinical experts considered it was not appropriate to apply a risk of progression...
rate estimated from the mean of the entire trial period, as it would incorporate patients with a different prognosis to those who are alive at least 18 months after allogeneic stem cell transplant. The committee agreed that this approach was too pessimistic because the progression-free survival extrapolation dropped too quickly at the end of the trial follow-up. In the original company submission, the company assumed that following the 6.08 year follow-up from start of treatment, the risk of progression would be equal to that after allogeneic stem cell transplant. The committee heard from the clinical experts that the curve displayed in the company's approach to progression-free survival modelling was a plausible extrapolation of progression-free survival beyond the within trial period. The committee was persuaded that the company's approach to the extrapolation of progression-free survival was plausible and accepted this assumption in its choice of a preferred ICER.

**Overall survival modelling**

4.20 The committee noted that to estimate overall survival from the model, the company compared brentuximab vedotin patients from SG035-0003 with chemotherapy patients from an earlier study (Martinez et al. 2010, 2013). The company adjusted the Martinez et al. survival to better reflect the patient characteristics in SG035-0003. In response to consultation on the second appraisal consultation document, the company provided 2 base-case analyses with different assumptions regarding mortality benefit and overall survival extrapolation. Base case 1 retained the 31% mortality benefit and reverted to fitting an exponential function to the overall survival data in Martinez et al. Base case 2 assumed a 10% mortality benefit for brentuximab vedotin and fit a lognormal function to the overall survival data in Martinez et al. The company also provided a scenario analysis in which it varied the mortality benefit of brentuximab vedotin between 10% and 40%. The committee heard from clinical experts that the 31% mortality benefit figure was possible and that brentuximab vedotin had served as a curative treatment for some people in this patient population. The committee heard from the ERG that any mortality benefit of brentuximab vedotin in the model was not based on robust evidence, but it incorporated a mortality benefit of 10% for brentuximab vedotin to reflect the committee's preferences as stated in the second appraisal committee document. The committee agreed that the company's modelled benefit of a 31% increase in survival did not reflect robust evidence, but considered that a mortality benefit of at least 10% was likely. The committee concluded that it would be reasonable
to incorporate a mortality benefit of 10% for brentuximab vedotin when calculating its preferred ICER.

**Dosage of brentuximab vedotin and chemotherapy**

4.21 After consultation on the second appraisal consultation document, the company reverted to the modelling approach from its original submission while incorporating changes to the relative dose intensity for chemotherapy (equal to brentuximab vedotin; that is, 94%) and the stopping rule proposed after consultation on the first appraisal consultation document. The stopping rule applied to patients whose disease did not respond to treatment after 4 or 5 cycles. The committee noted that in response to consultation, 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 that patients had in SG035-0003 (9.7 cycles), which was reduced after accounting for the stopping rule (8.5 cycles). The committee heard from clinical experts that people are likely to have fewer cycles than this because the maximal response to brentuximab vedotin would be expected after only 4 to 5 cycles (see section 4.4). The committee recognised that because brentuximab vedotin is more expensive than chemotherapy, the model was highly sensitive to the drug acquisition cost of brentuximab vedotin. On balance, it considered the company's approach to dosing and the stopping rule a plausible basis for discussion.

**Committee's preferred ICER (population 1)**

4.22 The committee agreed that the company and ERG had taken similar approaches in their assessment of cost effectiveness for this population, and that it could accept either if a mortality benefit of 10% was incorporated. The committee noted that with this adjustment, using either the company approach or the ERG approach, its preferred ICER was less than £30,000 per quality-adjusted life year (QALY) gained. The committee concluded that it could recommend brentuximab vedotin as cost effective for routine NHS use in this population.

**Population 2: adults with increased risk of disease relapse or progression after autologous stem cell transplant**

4.23 The committee agreed that the subgroup analyses reflecting the definition of high risk of relapse or progression after autologous stem cell transplant
including a positive PET scan should inform the modelling for this indication (see section 4.10). The committee understood that the key issues relating to cost effectiveness in this population were the approaches taken for modelling progression-free survival, overall survival and health-related quality of life.

**Progression-free and overall survival modelling**

4.24 The committee discussed the ERG’s concerns about the company’s overall approach to the modelling, specifically that the increase in progression-free survival with brentuximab vedotin translated into an equivalent but unproven overall survival gain. To correct this, the ERG rebuilt a partitioned survival model, assuming equal mortality in both treatment arms. The committee heard from the clinical experts that brentuximab vedotin has shown considerable gains in progression-free survival compared with best supportive care, but that overall survival data were not yet available. However, the clinical experts suggested that patients whose disease has not progressed after 2 years are unlikely to relapse, and gains in progression-free survival would be a good predictor of overall survival extensions in this population. The committee agreed that assuming a 1:1 relationship between progression-free survival and overall survival was optimistic, but that 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's 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**

4.25 In response to consultation on the second appraisal consultation document, the company updated the model to assume that 5 years after starting treatment, health-related quality of life for people whose disease did not progress would move back towards the age-adjusted population norm, with a small utility decrement being applied. In the ERG’s opinion, this assumption was not justified and contradicted the EQ-5D data collected from AETHERA. The committee concluded that the company’s assumption about long-term health-related quality of life remained unrealistic.
**Subsequent therapies**

4.26 In response to consultation on the second appraisal consultation document, the company presented a scenario analysis in which subsequent treatments were included as an additional cost. The company argued that patients on brentuximab vedotin would go on to have fewer subsequent treatments than those on best supportive care, improving the cost effectiveness of brentuximab vedotin. The ERG disagreed with the inclusion of these costs on the grounds that crossover was allowed in the AETHERA trial, meaning that these patients would be unlikely to represent a relevant part of the treatment pathway in UK clinical practice. The committee agreed with the ERG and further considered it unjustified to add the costs of brentuximab vedotin to the comparator arm in the model. It concluded that subsequent therapy costs should not be included in the estimation of the most plausible ICER.

**Committee's preferred ICER (population 2)**

4.27 Overall, the committee noted that it was not currently routine practice in the NHS to refer patients for transplant who are at increased risk of disease relapse or progression. The committee recognised that the clinical data did not reflect the definition of high risk of relapse or progression adopted by the regulator, but accepted the company's subgroup analysis because it included high-risk patients defined as having a positive PET scan plus 1 or more risk factors (see section 4.10). The committee agreed that the ERG's ICERs were generated from an overly pessimistic model which assumed no mortality benefit for brentuximab vedotin, and that the company model was more suitable for estimating its preferred ICER. However, it did not agree with the company model assumption of a 1:1 relationship between progression-free survival and overall survival, and so concluded that the company's cost-effectiveness estimates (an ICER of £35,606 per QALY gained) represented the lower limit of the committee's preferred ICER. The committee agreed that this ICER was higher than the range normally considered as cost effective for routine NHS use (£20,000 to £30,000 per QALY gained). It also noted a company comment in response to second consultation requesting brentuximab vedotin to be considered for future use within the Cancer Drugs Fund in this population. The committee considered that its preferred ICER of more than £35,606 per QALY gained did not indicate the plausible potential for satisfying the cost-effectiveness criteria for routine use through data collection. The committee therefore did not recommend brentuximab vedotin as cost effective for routine
NHS use in adults with increased risk of disease relapse or progression after autologous stem cell transplant (population 2).

Population 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

**Modelled population and comparator**

4.28 The committee noted that the evidence in the pooled dataset was uncertain and agreed that UK observation data was a more suitable source for the economic model (see section 4.16). The committee heard that the relative rate of post-chemotherapy and post-brentuximab stem cell transplants and the economic model structure were key points to consider in the assessment of cost effectiveness for this population.

4.29 The ERG noted that the modelled population from the pooled brentuximab dataset represented a fitter patient group than described in the indication under consideration. Therefore, the committee considered that the results of the studies were not generalisable to the entire population presenting in clinical practice (see section 4.14). However, the committee noted that the population from the UK observational data were more reflective of patients seen in clinical practice, and agreed that although these data formed a more suitable basis for economic modelling, any conclusions about cost effectiveness based on this evidence should be treated with considerable caution.

**Progression-free and overall survival modelling**

4.30 The committee noted from the outset that there was a lack of comparative data for this population. The company's base-case analysis compared the brentuximab vedotin single-arm studies (see section 4.13) with 4 clinical studies of chemotherapy identified from a literature search. The committee recalled that the main limitations of the brentuximab vedotin studies (see section 4.14) is that they were only generalisable to a subset of the population who would be seen in clinical practice and overall represented a fit population relatively likely to become eligible for stem cell transplant. Furthermore it heard from the ERG that the 4 chemotherapy trials identified were all single-arm studies, published between 1982 and 2000, all of which were poorly reported. The company used response rates as a surrogate for survival outcomes. The committee noted it
would have preferred to have seen estimates of progression-free survival and overall survival modelling from people who would have likely become eligible for a stem cell transplant after brentuximab vedotin or after single-agent chemotherapy. It agreed this information would have helped to inform a more accurate economic model structure. It concluded that there would be a high degree of uncertainty in any estimates of relative treatment effectiveness from the presented evidence.

**Economic model structure**

4.31 The committee agreed with the ERG that there was a structural flaw in the company’s original economic model. This was because patients who progressed to stem cell transplant in the model could not then move back to the event-free or post-progression survival states. In consultation on the second appraisal consultation document, the company amended the economic model structure for this population to include a palliative care health state in to which, patients would transition 1 year before death. The ERG disagreed with the company that this structural change corrected the underlying model flaw, because including a palliative state was not equivalent to including a post-progression survival state. The committee heard from the ERG that this flaw limited the model’s ability to accurately capture the costs and benefits associated with stem cell transplant; this was particularly problematic, in a model in which a change in stem cell transplant eligibility was the key effect of brentuximab vedotin. The model locked in an overly optimistic prognosis for people having stem cell transplant, derived from utility values of non-Hodgkin lymphoma and Hodgkin lymphoma for people having autologous stem cell transplant in van Agthoven et al. (2001), rather than from an originally stem cell transplant-ineligible population. To account for this model flaw, the ERG proposed:

- adjusting the utility value for patients who remain in the stem cell transplant state to 0.5 (incorporating any disutility for patients whose disease progressed after stem cell transplant)
- reducing the survival rate for patients having stem cell transplant by 20%.

The committee noted comments from the clinical experts who disagreed with the ERG’s adjustments to account for the model flaw, stating that fewer patients would progress than the ERG had assumed when generating an average utility of 0.5. The committee agreed that the ERG utility adjustments were overly pessimistic. It
concluded that the company's updated model structure did not address its concerns because it failed to accurately capture patients who progressed after stem cell transplants. It noted that, any patients transitioning in the model from a stem cell transplant state to a pre-death state should have progressed at a rate which is informed by the literature and fully described. The committee further concluded that the company's updated model was overly optimistic and that the ERG's adjustments were overly pessimistic, and agreed that its preferred cost-effectiveness analysis would lie between the 2 approaches.

Relative stem cell transplant rates

4.32 The committee understood that the relative rate of bridging to stem cell transplant from chemotherapy or brentuximab vedotin was a key driver in the ICER calculations. It was concerned that patients in the model having brentuximab vedotin were relatively fit, but for patients having the comparator the reverse might well be true. The committee heard from clinical experts that having a complete response to treatment is a key factor influencing the decision whether to progress to stem cell transplant, and that available evidence had found more than twice as many patients achieved a complete response on brentuximab vedotin compared with single-agent chemotherapy. Brentuximab vedotin offers these patients a new route to long-term survival because they are responding to treatment for the first time. However, the committee also heard from the clinical experts that the post-chemotherapy stem cell transplant rate estimated from the literature was likely to be an underestimate; in the UK this may be as high as 28%, and the post-brentuximab vedotin rate could also be higher at approximately 58%. However, the clinical experts would expect a better outcome following a complete response which is much more likely with brentuximab vedotin. The committee noted the ERG’s suggested stem cell transplant rate of 14.3%, taken from Zinzani et al. (2000) in the calculation of their modified base case. Although the company argued that this rate was based on few data points and therefore could not be considered robust, the committee agreed that the relative difference in rates should be smaller than that used in the company's modified base case. The ERG presented a scenario analysis in which it applied a post-chemotherapy stem cell transplant rate of 35%, based on clinical expert opinion, although some of the clinical experts said that it was overly optimistic. The committee concluded that post-treatment stem cell transplant rates remained a key source of uncertainty, and agreed that the differential in post-treatment rates applied in the economic modelling was too large.
Committee's preferred ICER (population 3)

4.33 The committee agreed that although the company provided revised modelling to address its concerns regarding patients who progressed after stem cell transplant, it concluded that there remained a high degree of uncertainty in the cost-effectiveness analysis (see section 4.31). The committee accepted that from the scenarios provided, modelling the post-treatment stem cell transplant rates at 14.3% and 53.0%, for chemotherapy and brentuximab vedotin respectively provided the most acceptable stem cell transplant rate differential. The committee considered that, taken together, the company scenario analysis that incorporated the stem cell transplant rates above the lower limit of its preferred ICER of £28,332 per QALY gained and the ERG’s modified base case (that also included these stem cell transplant rates and amended assumptions about utility and overall survival to account for the economic model flaw) would represent the upper limit (that is, £53,998 per QALY gained).

4.34 The committee concluded that because of the uncertainty in the model structure, overall survival and progression-free survival following stem cell transplant, and post-treatment stem cell transplant rates, it was difficult to determine a robust cost-effectiveness estimate (see sections 4.30 to 4.32). It concluded that its preferred ICER for this population would likely be approximately £40,000 per QALY gained at the mid-point of the range £28,332 and 53,998 per QALY gained, and so it did not recommend brentuximab vedotin as cost effective for routine NHS use in this population.

End-of-life considerations

4.35 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's technology appraisal process and methods. The company made the case that brentuximab vedotin met the criteria for life-extending treatments for people with a short life expectancy for population 1 (relapsed or refractory CD30-positive Hodgkin lymphoma after autologous stem cell transplant) and population 3 (relapsed or refractory CD30-positive Hodgkin lymphoma after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option). The committee noted that at the first appraisal committee meeting, the company had not considered brentuximab vedotin to meet the criteria for life-extending treatments in population 2.
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's and ERG's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. The committee concluded that its assessment of the short life expectancy criterion should be based on the modelled figures, and therefore this criterion did not apply for any of the 3 populations.

4.37 The committee also 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 noted that the cost-effectiveness analyses from which the survival benefit of brentuximab vedotin could be inferred were highly uncertain. In both population 1 and population 3, the modelled extension to life surpassed 3 months. In population 1 median overall survival was 40.5 months estimated from trial data, and estimates of median overall survival in population 3 ranged from 3.9 to 4.5 months. The committee concluded that although the modelled benefits demonstrated an extension to life of over 3 months, both criteria would have to have been met for the end-of-life criteria to apply.

4.38 The committee agreed that although the short life expectancy criterion was not met for population 1, it was cost-effective for routine NHS use without meeting the end-of-life criteria because the committee's preferred ICER was less than £30,000 per QALY gained. The committee agreed that population 2 did not fulfil the end-of-life criteria, and was not cost effective for routine NHS use with a committee-preferred ICER higher than £35,606 per QALY gained. For population 3, the committee agreed that the available data for life expectancy and overall survival for brentuximab vedotin were promising but it failed to meet the short life expectancy criterion. The committee-preferred ICER was approximately £40,000 per QALY gained. It concluded that this population would benefit from additional data collection through the Cancer Drugs Fund to improve the accuracy of estimates relating to post-treatment transplant rates; when these are available, brentuximab vedotin will be reviewed against the end-of-life criteria in this population.
Cancer Drugs Fund considerations

4.39 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. The committee recommended brentuximab vedotin as cost effective for routine NHS use for population 1 (adults with relapsed or refractory CD30-positive Hodgkin lymphoma after autologous stem cell transplant), so was not considered for use within the Cancer Drugs Fund. For population 2, the committee did not recommend brentuximab vedotin as cost effective for routine NHS use and therefore considered if it could be recommended within the Cancer Drugs Fund. It noted that at second consultation the company proposed that brentuximab vedotin be considered for future use in the Cancer Drugs Fund for this population. However, it recalled that population 2 was the only population for whom there were randomised controlled trial data, therefore limiting the need for further evidence collection and weakening the case to be considered for the Cancer Drugs Fund. The committee considered its preferred ICER did not have the plausible potential to represent cost effectiveness by the addition of new data collected through the Cancer Drugs Fund for population 2. For these reasons, the committee concluded that brentuximab vedotin should not be included in the Cancer Drugs Fund for population 2 (that is, adults with increased risk of disease relapse or progression after autologous stem cell transplant). Having concluded that it did not recommend brentuximab vedotin as cost effective for routine NHS use in population 3 (that is, 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 considered if brentuximab vedotin could be recommended within the Cancer Drugs Fund for this population. In population 3, the ICER for brentuximab vedotin was approximately £40,000 per QALY gained (between £28,332 and £53,998 per QALY gained; see section 4.33), and the committee was aware that brentuximab vedotin had already been included in the Cancer Drugs Fund for this population, and gathering more information about post-treatment stem cell transplant rates could help alleviate some of the uncertainty and allow for a more accurate estimation of cost effectiveness in this population. The committee considered that collecting data on overall and progression-free survival would also provide valuable clinical-effectiveness information for this population, but it heard that this could take a long time and would be practically difficult given the low patient numbers in this population. The committee acknowledged that data on
post-treatment stem cell transplant rates collected from the drug’s use through the Cancer Drugs Fund would offer further insight on the clinical effectiveness of brentuximab vedotin, and provide a robust source of evidence for an influential factor in any further decisions about its cost effectiveness in this population. The committee was aware that NICE, NHS England and the company agreed the data collection arrangements as part of the managed access agreement. The committee concluded that for population 3, brentuximab vedotin met the criteria to be considered for inclusion in the Cancer Drugs Fund, and therefore recommended it as an option for use within the Cancer Drugs Fund for adults with CD30-positive Hodgkin lymphoma with relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option when the conditions of the managed access agreement are followed.

**Summary of appraisal committee's key conclusions**

<table>
<thead>
<tr>
<th>TA446</th>
<th>Appraisal title: Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusion</td>
<td></td>
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</tbody>
</table>
Brentuximab vedotin is recommended as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:

- they have relapsed or refractory disease after autologous stem cell transplant and
- the company provides brentuximab vedotin at the price agreed with NHS England in the commercial access agreement.

Brentuximab vedotin is recommended for use within the Cancer Drugs Fund as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:

- they have relapsed or refractory disease after at least 2 previous therapies and
- they cannot have autologous stem cell transplant or multi-agent chemotherapy and
- the conditions of the managed access agreement are followed.

The clinical-effectiveness evidence for the population with relapsed or refractory disease after autologous stem cell transplant (population 1) came from non-randomised evidence and provided an immature and limited evidence base with reliance on comparisons with historical controls, leading to a large degree of uncertainty. However, the committee noted the comments from the clinical experts and the positive results from the intra-patient comparison which suggested that brentuximab vedotin was more effective than chemotherapy. The committee's preferred ICER for this population was less than £30,000 per QALY gained. The committee concluded that it could recommend brentuximab vedotin as cost effective for routine NHS use.

The clinical effectiveness evidence for the population who are at increased risk of disease relapse or progression after autologous stem cell transplant (population 2) came from a randomised controlled trial comparing brentuximab vedotin with placebo. The trial showed that median progression-free survival was statistically significantly higher for brentuximab vedotin compared with placebo. However, the definition of high risk of relapse or progression used in the trial was broader than the one in the marketing authorisation for population 2 and the definition in the final NICE scope. The company redefined the high-risk patient criteria and identified a subgroup of patients, which was accepted by committee. The committee's preferred ICER for this population was significantly higher than the range normally considered to be a cost-effective use of NHS resources. This population did not fulfil the end-of-life criteria. The committee considered its
preferred ICER did not have the plausible potential to represent cost
effectiveness through the addition of new data collected through the Cancer
Drugs Fund and therefore did not meet the criteria to be recommended through
the Cancer Drugs Fund for this population.

The clinical effectiveness evidence for the population with relapsed or refractory
disease after at least 2 previous therapies and who cannot have autologous stem
cell transplant or multi-agent chemotherapy (population 3) came from single-arm
studies which provided a limited evidence base, reflected only a fitter subset of
people, with different mean treatment cycles and relative rates of allogeneic and
autologous stem cell transplant compared with people in clinical practice in
England. Although the real-world UK dataset provided more relevant clinical data
it was still associated with a large degree of uncertainty. For this population, the
drivers of cost effectiveness were the economic model structure, relative rate of
post-chemotherapy and post-brentuximab vedotin stem cell transplants and the
modelled estimates of progression-free and overall survival. Although the
company provided revised modelling to address concerns regarding patients who
progressed after stem cell transplant, there remained a high degree of uncertainty
in the cost-effectiveness analysis. The company's model was overly optimistic but
the ERG's adjustments were overly pessimistic so the committee agreed that its
preferred cost-effectiveness analysis and ICERs would lie between the 2
approaches. The committee's preferred ICER for this population was significantly
higher than the range normally considered to be a cost-effective use of NHS
resources. The committee agreed that this population did not fulfil the end-of-life
criteria and therefore it could not recommend brentuximab vedotin as a cost-
effective use of NHS resources for routine use in this population. The committee
then considered if brentuximab vedotin could be recommended within the Cancer
Drugs Fund. It acknowledged that data on post-treatment stem cell transplant
rates collected from the drug's use through the Cancer Drugs Fund would offer
further insight on the clinical effectiveness and provide a robust source of
evidence for an influential factor in any further decisions about its cost
effectiveness in this population. It also considered that brentuximab vedotin had
the plausible potential to be cost effective in future and therefore it
recommended brentuximab vedotin as an option for use within the Cancer Drugs
Fund for this population.

Current practice
<table>
<thead>
<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>The committee noted that there was no NICE technology appraisal guidance on Hodgkin lymphoma. The committee concluded that based on current clinical practice, brentuximab vedotin would mainly be used in populations 1 and 3. Both of these groups would have a high clinical unmet need and 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 refer patients for transplant who are at increased risk of disease relapse or progression. However, the committee noted that although this group does not feature in current UK clinical practice, it could be relevant in the future.</th>
<th>4.1–4.4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The technology</strong></td>
<td>The committee understood that brentuximab vedotin offers the chance of a potentially curative stem cell transplant, which the clinical experts considered of great importance. It also heard from clinical experts that brentuximab vedotin had served as a curative treatment without stem cell transplants for a small group of patients.</td>
<td>4.3</td>
</tr>
</tbody>
</table>

**Proposed benefits of the technology**

**How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?**
<table>
<thead>
<tr>
<th>Position of the Treatment in the Pathway of Care for the Condition?</th>
<th>The committee heard from clinical experts that the relevant populations in the UK were adults 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. However, the committee noted that the population at high risk of disease progression or relapse could be clinically relevant in the future. It heard from clinical experts that there was a group of high-risk patients who differed to those in population 3, and for whom brentuximab vedotin would provide benefit.</th>
<th>4.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td>The most common adverse events are nervous system disorders, including peripheral neuropathy, dizziness and demyelinating polyneuropathy.</td>
<td>2</td>
</tr>
<tr>
<td>Evidence for Clinical Effectiveness</td>
<td>4.3, 4.11, 4.16</td>
<td></td>
</tr>
<tr>
<td>Availability, Nature and Quality of Evidence</td>
<td>For populations 1 and 3, the company’s submission mostly included retrospective, non-randomised evidence. The committee recognised that the available evidence was limited. For population 2, the company’s submission consisted of a randomised controlled trial (AETHERA). The committee considered this to be compromised to fit the data to the relevant high-risk group.</td>
<td>4.3, 4.11, 4.16</td>
</tr>
<tr>
<td>Relevance to general clinical practice in the NHS</td>
<td>The committee noted that AETHERA included patients with Hodgkin lymphoma at risk of having residual disease after autologous stem cell transplant defined as those who have 1 risk factor. This definition was broader than that on which brentuximab vedotin's regulatory approval was based and the definition in the final NICE scope. To identify the high-risk group reflecting clinical practice in England, the company redefined high-risk patient criteria and identified a subgroup of patients which was accepted by committee, that is, people with a positive PET scan result before autologous stem cell transplant, plus at least 1 more risk factor. The committee heard from the clinical experts that it was not routine practice in England to refer people for transplant who are at increased risk of disease relapse or progression, but it accepted that this population could be clinically relevant in the future.</td>
<td>4.3, 4.10, 4.11</td>
</tr>
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</table>

| Uncertainties generated by the evidence | The committee agreed that the clinical evidence base for all 3 populations was associated with uncertainty. | 4.6, 4.8, 4.11, 4.16 |

| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | There are no clinically relevant subgroups for which there is evidence of differential effectiveness. | – |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | For population 1, the overall response rate by independent review (primary outcome) was 75%.
For population 2, 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).
For population 3, the overall response rate (pooled dataset) investigator assessed was 50%. The overall response rates from C25007 and the UK observational dataset were 48% and 51% respectively.
The committee agreed that the clinical evidence base for all 3 populations was associated with uncertainty. | 4.5, 4.6, 4.8, 4.9, 4.11, 4.13, 4.16 |
| Evidence for cost effectiveness | | |
| Availability and nature of evidence | The company submitted separate de novo economic models for each population. | – |
The committee agreed that the uncertainty in the clinical evidence base would be carried over in the economic modelling. The uncertainties for population 1 were:

- estimated progression risk
- the mortality benefit of brentuximab vedotin
- the number of treatment cycles, and hence the cost, of brentuximab vedotin in clinical practice.

The uncertainties for population 2 were:

- progression-free and overall survival modelling
- the mortality benefit of brentuximab vedotin
- the inclusion of subsequent therapy costs.

The uncertainties for population 3 were:

- relative post-chemotherapy and post-brentuximab stem cell transplant rate
- the economic model structure.

<table>
<thead>
<tr>
<th>Uncertainties around and plausibility of assumptions and inputs in the economic model</th>
<th>The committee agreed that the uncertainty in the clinical evidence base would be carried over in the economic modelling. The uncertainties for population 1 were:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- estimated progression risk</td>
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<td></td>
<td>- the mortality benefit of brentuximab vedotin</td>
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<tr>
<td></td>
<td>- the number of treatment cycles, and hence the cost, of brentuximab vedotin in clinical practice.</td>
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<tr>
<td></td>
<td>The uncertainties for population 2 were:</td>
</tr>
<tr>
<td></td>
<td>- progression-free and overall survival modelling</td>
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<td></td>
<td>- the mortality benefit of brentuximab vedotin</td>
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<td></td>
<td>- the inclusion of subsequent therapy costs.</td>
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<td>The uncertainties for population 3 were:</td>
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<td></td>
<td>- relative post-chemotherapy and post-brentuximab stem cell transplant rate</td>
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<td></td>
<td>- the economic model structure.</td>
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<tr>
<td>Question</td>
<td>Answer</td>
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<td>------------------------------------------------------------------------</td>
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<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>For population 2, the committee did not agree with the assumption that health-related quality of life of people who did not have disease progression 5 years after starting treatment rebounded towards the age-adjusted population norm. For population 3, the committee noted that the incorrect model structure limits its ability to capture benefits associated with stem cell transplant, in a model where stem cell transplant eligibility was the key effect of brentuximab vedotin.</td>
</tr>
<tr>
<td>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?</td>
<td>There are no specific groups of people for whom the technology is particularly cost effective.</td>
</tr>
<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>There are no specific groups of people for whom the technology is particularly cost effective.</td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>For population 1, the cost-effectiveness analysis was sensitive to the relative progression-free and overall survival of brentuximab vedotin and chemotherapy. For population 2, the key issues relating to cost effectiveness were the modelling of progression-free survival, overall survival and health-related quality of life. For population 3, the model was sensitive to the relative rate of post-chemotherapy and post-brentuximab stem cell transplants.</td>
</tr>
</tbody>
</table>
The committee’s preferred ICERs for brentuximab vedotin were:

- Less than £30,000 per QALY gained for adults with relapsed or refractory disease after autologous stem cell transplant.
- At least £35,606 per QALY gained for adults at increased risk of disease relapse or progression after autologous stem cell transplant.
- A preferred ICER of approximately £40,000 per QALY (between £28,332 and £53,998 per QALY gained) for adults with relapsed or refractory CD30-positive Hodgkin lymphoma after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.

### Additional factors taken into account

| Patient access schemes (PPRS) | The pricing arrangement considered during guidance development was that the company (Takeda) had agreed a patient access scheme with the Department of Health. The commercial access agreement between the company and NHS England replaces the simple discount patient access scheme under the same terms. The managed access agreement includes further commercial arrangements that apply only to the population in the Cancer Drugs Fund (section 1.2). The financial terms of the agreement are commercial in confidence. | 2 |
| End-of-life considerations | The committee concluded that based on the evidence presented, brentuximab vedotin did not fulfil the criterion for extending life for all 3 populations and therefore it could not be considered a life-extending, end-of-life treatment. | 4.35–4.37 |
| 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 also noted a comment that variation in donor availability between ethnic groups constitute an equalities issue under equalities legislation. The committee concluded that equality of access does not normally constitute an equalities issue under the legislation, because committee recommendations apply equally to all people.

The committee noted a comment that any decision not to recommend brentuximab vedotin would disproportionately affect people under the age of 30 years. The committee agreed that the increased prevalence in people under the age of 30 diagnosed with Hodgkin lymphoma is a feature of the disease. Age of disease prevalence is not a relevant issue under the Equalities Act as the appraisal recommendations apply to people of all ages equally. | 
5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in section 1.1 of this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology (as in section 1.1 of this appraisal), the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in paragraph 5.1 and 5.2 above. This means that, if a patient has CD30-positive Hodgkin lymphoma and the doctor responsible for their care thinks that brentuximab vedotin is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, as recommended in section 1.2, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has CD30-positive lymphoma and the doctor responsible for their care thinks that brentuximab vedotin is the right treatment, it should be available for use, in line with NICE's section 1.2 recommendation and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

5.5 NHS England and Takeda have agreed a commercial access agreement that makes brentuximab vedotin available to the NHS at a reduced cost. The commercial access agreement incorporates a simple discount applied at the point of purchase or invoice of brentuximab vedotin for the recommendation in section 1.1 but also includes additional and separate commercial arrangements.
that apply only to the population in the Cancer Drugs Fund for the recommendation in section 1.2. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the simple discount aspect of the commercial access agreement should be directed to gb.commercial@takeda.com.
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.

Thomas Paling and Ahmed Elsada
Technical leads

Nicola Hay
Technical adviser

Frances Sutcliffe
Associate director

Stephanie Yates
Project manager

Accreditation

NICE accredited

www.nice.org.uk/accreditation