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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This guidance replaces TA446.

1 Recommendations

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

- they have already had autologous stem cell transplant or
- they have already had at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy are not suitable and
- the company provides brentuximab vedotin according to the commercial arrangement.

1.2 These recommendations are not intended to affect treatment with brentuximab vedotin that was started in the NHS before this guidance was published. People 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.

Why the committee made these recommendations (NICE technology appraisal guidance 446)

Hodgkin lymphoma is usually treated with chemotherapy, followed by stem cell transplant. Stem cell transplant gives people the best chance of a cure, so people who cannot have stem cell transplant have a high clinical unmet need. Brentuximab vedotin can be used as a 'bridging' treatment before stem cell transplant and, in some cases, as a curative treatment itself.

NICE technology appraisal guidance 446 recommended brentuximab vedotin as an option for treating adults with relapsed or refractory CD30-positive Hodgkin lymphoma after autologous stem cell transplant. However, it was not recommended for adults who are at increased risk of disease relapse or progression after autologous stem cell transplant because the cost-effectiveness estimates were too high.

For adults with relapsed or refractory disease after at least 2 previous therapies, when autologous stem cell transplant or multi-agent chemotherapy is not suitable, the cost-effectiveness evidence was less clear. So brentuximab vedotin was recommended for use within the Cancer Drugs Fund in this population to collect data on its effectiveness in practice.
Why the committee made these recommendations (Cancer Drugs Fund review of technology appraisal guidance 446)

Data collected through the Cancer Drugs Fund on rates of stem cell transplant after treatment with brentuximab vedotin show that it improved rates of stem cell transplant compared with chemotherapy. Also, the updated cost-effectiveness estimates for brentuximab vedotin are lower than £20,000 per quality-adjusted life year gained. Because of this, brentuximab vedotin is recommended as an option for treating relapsed or refractory CD30-positive Hodgkin lymphoma in adults, only if they have already had autologous stem cell transplant, or at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy are not suitable.
## 2 Information about brentuximab vedotin

| Marketing authorisation indication | Brentuximab vedotin (Adcetris) 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  
• at increased risk of relapse or progression after autologous stem cell transplant. |
| Dosage in the marketing authorisation | 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 has a commercial arrangement. This makes brentuximab vedotin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company’s responsibility to let relevant NHS organisations know details of the discount. |
3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Takeda and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Sections 3.1 to 3.33 reflect the committee's discussion during NICE technology appraisal 446. These sections are unchanged since the guidance was first published in June 2017.

Sections 3.37 to 3.47 reflect the committee's discussion during the Cancer Drugs Fund review of population 3 from NICE technology appraisal guidance 446.

The condition (NICE technology appraisal guidance 446)

Stem cell transplants give people the best chance of a cure for treating Hodgkin lymphoma

3.1 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.

There is a high clinical unmet need for people who cannot have stem cell transplant

3.2 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.

**Brentuximab vedotin will mainly be used for relapsed or refractory disease after autologous stem cell transplant, or after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option**

3.3 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 3.10). 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 for relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option.

Maximal response is expected after 4 to 5 cycles of brentuximab vedotin rather than 16

3.4 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 (NICE technology appraisal guidance 446)

The non-randomised evidence provides an immature and limited evidence base

3.5 Population 1 is adults with relapsed or refractory disease after autologous stem cell transplant. 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 months)
- median overall survival: 40.5 months.

Comparisons with historical controls are uncertain

3.6 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.
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 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.

Brentuximab vedotin may be more effective than chemotherapy in population 1 but the evidence is uncertain

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 3.5). 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.

Clinical-effectiveness evidence for population 2 came from the additional data cut of the AETHERA trial

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

The definition of patients at high risk of relapse in the trial is broader than that on which brentuximab vedotin's regulatory approval was based

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.

**Brentuximab vedotin improves progression-free survival more than placebo in population 2 but the data are uncertain**

3.11 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.

The clinical evidence for population 3 comes from non-randomised studies and is limited

3.12 Population 3 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 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).

The company presented additional evidence in this population

3.13 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 population 3

<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></td>
<td>47</td>
<td>58</td>
<td>53</td>
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<td>--------------------------------</td>
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<tr>
<td><strong>Post-brentuximab SCT rate (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression-free survival (months)</strong></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><strong>Overall survival</strong></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><strong>Mean number of cycles</strong></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.*

**Patients in these studies reflected a fitter subset of the population covered in the marketing authorisation**

3.14 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 3.1). The committee concluded that the study populations reflected only a fitter subset of the population under consideration.

**The studies may be not be generalisable to UK clinical practice**

3.15 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.

The real-world UK dataset provides the most relevant evidence but any comparison in population 3 is uncertain

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 3.12 to 3.13). The committee agreed that although the clinical data in the pooled dataset provided an improved evidence base compared with that considered in the first appraisal consultation document, it was still associated with a large amount of uncertainly. 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.

Overall cost effectiveness (NICE technology appraisal guidance 446)

The cost-effectiveness analyses for populations 1 and 3 are based on clinical-effectiveness evidence that is uncertain

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.

Cost effectiveness: population 1 (NICE technology
appraisal guidance 446)

3.18 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.

The company's approach to modelling progression-free survival is plausible

3.19 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 3.5 to 3.7). 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 incremental cost-effectiveness ratio (ICER).
A mortality benefit of 10% is more plausible than the company's base case of 31%

3.20 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 about 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.

The company's approach to treatment dosing and stopping rule is plausible

3.21 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 3.4). 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.

The committee's preferred ICER for population 1 is within the range considered to be cost effective for routine use

3.22 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.

Cost effectiveness: population 2 (NICE technology appraisal guidance 446)

The most plausible mortality benefit is somewhere between the company's and the ERG's estimates

3.23 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.

The company's assumptions about long-term health-related quality of life are unrealistic

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.

The scenario analysis that incorporates costs for subsequent treatments is not appropriate

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.

The committee's preferred ICER for population 2 is over
£30,000 per QALY gained and does not have plausible potential to be cost effective through the Cancer Drugs Fund

3.26 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 3.10). 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 to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). It also noted a company comment in response to 2nd 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).

Cost effectiveness: population 3 (NICE technology appraisal guidance 446)

The model structure and rates of stem cell transplant after chemotherapy and brentuximab vedotin were key model drivers

3.27 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 3.16). 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.

The modelled population is not generalisable to the entire population presenting in clinical practice so any results are uncertain

3.28 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 3.15). 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.

Estimates of overall and progression-free survival are uncertain

3.29 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 with 4 clinical studies of chemotherapy identified from a literature search. The committee recalled that the main limitations of the brentuximab vedotin studies 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.
The company's model is overly optimistic and the ERG's adjustments are overly pessimistic so the preferred cost-effectiveness analysis is between the 2 approaches

3.30 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.

Rates of stem cell transplant after treatment are a source of uncertainty

3.31 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 28.0%, and the post-brentuximab vedotin rate could also be higher at approximately 58.0%. However, the clinical experts would expect a better outcome following a complete response which is much more likely with brentuximab vedotin. The committee noted that the ERG suggested a stem cell transplant rate of 14.3%, taken from Zinzani et al. (2000), in the calculation of its 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 35.0%, 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 source of uncertainty, and agreed that the differential in post-treatment rates applied in the economic modelling was too large.

The committee's preferred ICER for population 3 is around £40,000 per QALY gained

The committee agreed that although the company provided revised modelling to address its concerns about patients who progressed after stem cell transplant, it concluded that there remained a high degree of uncertainty in the cost-effectiveness analysis. 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). 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. 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 (NICE technology appraisal guidance 446)

The company considered that brentuximab vedotin met the end-of-life criteria in populations 1 and 3

3.33 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.

Brentuximab vedotin does not meet the end-of-life criteria in any population

3.34 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. 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.
Data collection through the Cancer Drugs Fund in population 3 would be beneficial to improve the accuracy of estimating transplant rates after treatment and to evaluate brentuximab vedotin against the end-of-life criteria

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. 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 (NICE technology appraisal guidance 446)

Brentuximab vedotin is recommended for use as an option within the Cancer Drugs Fund in population 3

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 it 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 brentuximab vedotin could be recommended within the Cancer Drugs Fund. It noted that during the second consultation the company proposed that brentuximab vedotin be considered for future use in the Cancer Drugs Fund in this population. However, it recalled that population 2 was the only population
which had 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 3.29), 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 in 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.
Cancer Drugs Fund review of technology appraisal guidance 446 for population 3

The company’s revised submission for the Cancer Drugs Fund review of population 3 includes new data and other changes

3.37 In technology appraisal guidance 446 the committee concluded that data collected through the Cancer Drugs Fund about stem cell transplant rates after brentuximab vedotin would address some uncertainty and allow for a more accurate estimation of cost effectiveness for population 3. In its revised submission for the Cancer Drugs Fund review, the company included:

- data collected through the Cancer Drugs Fund on rates of stem cell transplant after brentuximab vedotin
- a new lower rate of stem cell transplant after single-agent chemotherapy
- different data to inform overall and progression-free survival rates after stem cell transplant
- an updated economic model structure to include a new health state for patients whose disease has progressed after stem cell transplant.

New data for the Cancer Drugs Fund review of population 3

The data collection methods are suitable for decision-making

3.38 The company’s evidence on the rate of stem cell transplant after treatment with brentuximab vedotin was collected by Public Health England in a retrospective questionnaire. The questionnaire collected the rates of stem cell transplant in patients who had brentuximab vedotin through the Cancer Drugs Fund between April 2013 and March 2016. Of the 496 questionnaires sent to consultants, 436 (88%) were returned; the committee heard from the Cancer Drugs Fund clinical lead that this response rate was outstandingly high. The clinical experts stated that the data collected through the Cancer Drugs Fund were important for both clinicians and patients, and should address the uncertainties the committee raised in technology appraisal guidance 446 for population 3. The committee concluded that the data
collection methods were suitable for its decision-making.

**Table 2 Number of people who had stem cell transplant results from the Cancer Drugs Fund data collection**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Stem cell transplant after brentuximab vedotin</th>
<th>Stem cell transplant after brentuximab vedotin and salvage chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main cohort (brentuximab with the intention of bridging to stem cell transplant)</td>
<td>78/219 (36%)</td>
<td>128/219 (58%)</td>
</tr>
<tr>
<td>Sensitivity analysis 1 (main cohort plus 60 patients without data)</td>
<td>78/279 (28%)</td>
<td>128/279 (46%)</td>
</tr>
<tr>
<td>Sensitivity analysis 2 (main cohort plus patients having brentuximab with no intention of bridging to stem cell transplant)</td>
<td>78/312 (25%)</td>
<td>128/312 (41%)</td>
</tr>
<tr>
<td>Sensitivity analysis 3 (main cohort plus all patients in sensitivity analyses 1 and 2)</td>
<td>78/372 (21%)</td>
<td>128/372 (34%)</td>
</tr>
</tbody>
</table>

**Sensitivity analyses 2 and 3 are most relevant to the ICER calculations**

The committee was aware that the data had been stratified based on whether brentuximab vedotin was used with the intention of bridging to a stem cell transplant. The data were further divided by patients who had a stem cell transplant after brentuximab vedotin, and those who had a stem cell transplant after both brentuximab vedotin and salvage chemotherapy. The company also presented 3 sensitivity analyses. The company had included the results of sensitivity analysis 2 in its base-case analysis, because it included all patients having brentuximab vedotin (that is, regardless of the intention to bridge to a stem cell transplant) and did not include any effects of salvage chemotherapy. The ERG preferred sensitivity analysis 3, because it also accounted for the missing data of 60 patients and captured the full benefit of brentuximab vedotin (because it included all patients who had a stem cell transplant regardless of whether they had had salvage chemotherapy first). However, the clinical experts and the Cancer Drugs Fund clinical lead disagreed with including the missing
patient data. The ERG considered that missing data for 60 patients was a large proportion of the total data, and that it introduced a substantial amount of uncertainty in the estimated stem cell transplant rate. The committee was aware that the economic modelling included the stem cell transplant rates from both sensitivity analyses 2 and 3, so it agreed to consider both estimates in its most plausible ICER considerations.

The most plausible rate of stem cell transplant after a single-agent chemotherapy is 5.3%

The committee was aware that rates of stem cell transplant after a single-agent chemotherapy had not been collected as part of the Cancer Drugs Fund data collection. In NICE technology appraisal guidance 446, the company's preferred rate was 5.3% based on a pooled estimate of 3 studies; the ERG's preferred rate was 14.0% based on 1 study by Zinzani et al. (2000; see section 3.31). The committee was aware that the published studies were at least 18 years old and unlikely to reflect current clinical practice. It considered the company's clinical expert's opinion that a rate of 5.3% was clinically plausible. This was further supported by the Cancer Drugs Fund clinical lead, who explained that because relevant patients will have had at least 2 chemotherapy regimens and still have relapsed and refractory disease, any responses to single-agent treatment are modest and generally short. The ERG had included both rates (5.3% and 14.0%) in its exploratory analyses but neither had a substantial effect on the results. The committee concluded that in the absence of any robust evidence, and based on clinical expert opinion, the most plausible rate of stem cell transplant after single-agent chemotherapy is 5.3%.

Rates of overall and progression-free survival after allogenic stem cell transplant taken from Reyal et al. are suitable for decision-making

The company presented data from Reyal et al. (2016) to inform rates of overall and progression-free survival after allogenic stem cell transplant. The company explained that the data presented during the development of NICE technology appraisal guidance 446 to inform these outcomes (Sureda et al. 2001) was no longer relevant because they did not include PET-based response-adjusted transplantation strategies. The clinical experts further explained that PET scanning is the preferred method of assessing response to treatment before
stem cell transplant. Sureda et al. also included patients that had previously failed an autologous stem cell transplant, which is not a relevant population for this appraisal. In its analysis, the company used a subgroup of the Reyal et al. dataset that excluded patients whose previous autologous stem cell transplant had failed. The results of this analysis were reported as commercial in confidence so cannot be reported here. However, in the full study population (in which 26% of patients had an autologous stem cell transplant that had failed), 4-year overall survival rates after stem cell transplant were 75.0% in people with a complete response and 67.3% in people with a partial response. The ERG considered the Reyal et al. subgroup to be relevant to NHS clinical practice. The committee concluded that the rates of overall and progression-free survival after allogenic stem cell transplant taken from the subgroup of Reyal et al. (that excluded patients whose previous autologous stem cell transplant had failed) were suitable for decision-making.

Rates of overall and progression-free survival after autologous stem cell transplant are less certain

The company presented data from Thomson et al. (2013) to inform overall and progression-free survival rates after autologous stem cell transplant. The ERG commented that the data were relevant to UK clinical practice because they included a PET-response-adjusted transplantation strategy. However, it was concerned with the small sample size (n=28) and noted that the data are very immature and suffer from substantial censoring, which makes any extrapolation of the data highly uncertain. Because of these limitations, the ERG preferred to use data from Reyal et al. (2016). It also commented that this would result in more conservative estimates of overall and progression-free survival. However, the clinical experts noted that patients having an allogenic stem cell transplant are not as healthy as those having autologous stem cell transplants so this assumption may not be valid. Furthermore, the clinical experts stated that the overall survival extrapolations using data from Thomson et al. were clinically plausible, and that the 2 years of overall survival after stem cell transplant would be similar to the general population. The committee acknowledged the ERG’s concerns about Thomson et al., and was aware that the ERG had included the outcomes from Reyal et al. in its exploratory analyses. It therefore concluded to explore both sources of data in the economic modelling.

Updated cost effectiveness for the Cancer Drugs Fund
The company's updated model and the ERG's exploratory analyses (using the company's original model) are both suitable for decision-making

3.43 In technology appraisal guidance 446, the committee raised concerns about the omission of a post-stem cell transplant disease progression state in the company's original model (see section 3.30). For the Cancer Drugs Fund review, the company included this health state as well as tunnel states to correct errors it identified in the way transitions between health states had been calculated. The committee heard from the ERG that it had serious concerns with the company's use of tunnel states in the updated model: it could not properly validate the model because of the volume of code and model running time. The ERG commented that the use of tunnel states was also inappropriate, because the change in the risk of death after a stem cell transplant is accounted for in the underlying hazard of the best fitting survival curve. The committee accepted the company's reasons for updating its model. It was also aware that the company had included a sensitivity analysis using the original model. The ERG had also presented exploratory analyses using the company's original model. The committee therefore concluded to consider both the results from the company's updated model, including sensitivity analyses, and the ERG's exploratory analyses (using the company's original model) in its decision-making.

The company's base-case ICER for brentuximab vedotin is less than £17,000 per QALY gained

3.44 The committee considered the results of the company's updated economic analyses, which incorporated the same patient access scheme for brentuximab vedotin that was considered during the development of technology appraisal guidance 446. It noted that the company had included:

- additional model health states for stem cell transplant after disease progression and tunnel states to correct errors in transition probability calculations (see section 3.43)
a 25% stem cell transplant rate after treatment with brentuximab vedotin from sensitivity analysis 2 of Cancer Drugs Fund data collection, and 41% in a scenario analysis (see section 3.38)

a 5.3% stem cell transplant rate after treatment with single-agent chemotherapy (see section 3.40)

data from Thomson et al. (2013) and Reyal et al. (2016) to inform overall and progression-free survival after stem cell transplant (see sections 3.41 and 3.42).

The company's base-case ICER for brentuximab vedotin compared with single-agent chemotherapy in the relevant population was £16,535 per QALY gained. Using a stem cell transplant rate of 41% (which includes patients who need salvage chemotherapy after brentuximab vedotin), the ICER fell to £13,503 per QALY gained.

The ERG's exploratory ICER for brentuximab vedotin is less than £18,000 per QALY gained

The committee considered the ERG's exploratory analyses, which were based on the company's original model and included:

- using a stem cell transplant rate after brentuximab vedotin of 34%, taken from sensitivity analysis 3 (see section 3.38)
- using a stem cell transplant rate after single-agent chemotherapy of 5.3%, and 14.0% in a scenario analyses (see section 3.40)
- using data from Reyal et al. (2016) to inform overall and progression-free survival rates after stem cell transplant (see sections 3.41 and 3.42).

With these changes, the ERG's exploratory ICER for brentuximab vedotin compared with single-agent chemotherapy in the relevant population was £17,885 per QALY gained. Using a stem cell transplant rate after single-agent chemotherapy of 14.0% increased the ICER to £21,339 per QALY gained.

The most plausible ICER is between £16,000 and £18,000 per QALY gained for population 3

The committee concluded that data on stem cell transplant rates after brentuximab vedotin collected through the Cancer Drugs Fund addressed some
of the uncertainty and allowed a more accurate estimation of cost effectiveness for population 3. However, the committee was aware of the limitations with both the company’s models. It noted that the main driver in the model were the rates of overall and progression-free survival after stem cell transplant, and that the rate of stem cell transplant after brentuximab vedotin had only a modest effect on the results. The committee therefore considered the most plausible ICER for brentuximab vedotin compared with single-agent chemotherapy in the relevant population to be between £16,535 (using data from Thomson et al. and Reyal) and £17,885 (using data from Reyal) per QALY gained. Because the ICER is within the range normally considered to be a cost-effective use of NHS resources, the committee concluded that brentuximab vedotin can be recommended for routine use to treat CD30-positive Hodgkin lymphoma in adults with relapsed or refractory disease, after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not suitable.

Updated end-of-life considerations for the Cancer Drugs Fund review of population 3

**Brentuximab vedotin does not meet the end-of-life criteria**

3.47 The committee recalled that during the development of technology appraisal guidance 446, it agreed to review brentuximab vedotin against the end-of-life criteria 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 suitable) once data collection in the Cancer Drugs Fund had ended (see section 3.32). The committee discussed whether brentuximab vedotin in this population is indicated for patients with a short life expectancy, normally less than 24 months. It noted that in technology appraisal guidance 446, both the company’s and ERG’s modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. For this Cancer Drugs Fund review, the modelled mean overall survival in the comparator treatment arm was more than 24 months. The committee therefore concluded that because it did not meet the short life expectancy criterion, it did not need to conclude on the life extension criterion. It agreed that brentuximab vedotin does not meet the end-of-life criteria for people with relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is suitable.
4 Implementation

4.1 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 this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have 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, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsed or refractory 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 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 and a project manager.

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Project Manager

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