NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma

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

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers). [Add link to website in-development page on 'committee papers']

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

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

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

After consultation:

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

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 5pm 24 January 2019

Second appraisal committee meeting: 5 February 2019

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Brentuximab vedotin is not recommended, within its marketing authorisation, for treating CD30-positive cutaneous T-cell lymphoma (CTCL) after at least 1 systemic therapy in adults.

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

Brentuximab vedotin is licensed to treat CD30-positive CTCL after at least 1 systemic therapy. It is most likely to be used in the NHS to treat advanced disease. The most appropriate comparators in this indication are methotrexate, bexarotene and interferon alfa.

Clinical trial evidence shows that brentuximab vedotin is effective based on response rates and progression-free survival compared with methotrexate or bexarotene. However, it is uncertain whether brentuximab vedotin extends how long people live overall because there are limited data on the proportion of people who are able to bridge to an allogeneic stem cell transplant after brentuximab vedotin, and on whether brentuximab vedotin extends overall survival without bridging to transplant.

There is a wide range of cost-effectiveness estimates for brentuximab vedotin, but all estimates are uncertain and none of the analyses include all the preferred assumptions. Therefore, brentuximab vedotin is not recommended.

2 Information about brentuximab vedotin

Marketing authorisation	Brentuximab vedotin is indicated for the treatment of 'adult patients with CD30-positive cutaneous T-cell lymphoma after at least 1 prior systemic therapy'.
Dosage in the marketing authorisation	Brentuximab vedotin (Adcetris, Takeda) 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.
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 (simple discount patient access scheme), which would apply if the technology had been recommended.

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.

Potential new treatment option

Cutaneous T-cell lymphoma significantly affects quality of life

3.1 CTCL is a form of non-Hodgkin lymphoma that affects the skin. It may start as flat red patches or plaques on the surface of the skin, which progress to skin tumours. People may also have systemic symptoms, such as chronic pain and itching, that can severely limit activities of daily living. The clinical experts explained that CTCL is a rare disease and people usually live with their condition for many years. The patient experts explained that being diagnosed with CTCL can severely affect a person's physical and psychological wellbeing. It may take several years before CTCL is accurately diagnosed, and symptoms flare up unpredictably. The clinical and patient experts also explained that there is no uniform response to treatment; people with CTCL may be very self-conscious

about how their skin looks and uncertain about how the disease will respond to treatment, which has a negative psychological effect. The committee concluded that CTCL significantly affects quality of life.

There is an unmet need for more effective treatment options

3.2 There is no NICE guidance on treating CTCL. The disease can be divided into a number of distinct subtypes, only some of which express CD30. CD30 is expressed in both primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis, which together form the group of primary cutaneous CD30-positive lymphoproliferative disorders. Mycosis fungoides and Sézary syndrome can also express CD30. CTCL is treated based on the subtype and stage of the disease. Treatments either target the skin (skin-directed) or the entire body (systemic), but there is no standard therapy. The clinical experts highlighted that treatment options are diverse; they aim to relieve symptoms, control local disease and improve quality of life. The committee understood that compared with earlier stages of CTCL, advanced disease is associated with poorer prognosis, lower survival and significant impact on daily life. Although current treatments are palliative, the clinical experts noted that allogeneic stem cell transplants may consolidate treatment responses to achieve durable remissions or possibly cure and should be considered for certain patients with advanced CTCL. Without allogeneic stem cell transplants the disease has a cycle of remission and relapse. Because there are limited treatment options available, people with advanced CTCL may live for several years without treatment while having painful, itchy and uncomfortable symptoms on a daily basis. The committee agreed that there is an unmet need for effective treatments that extend the amount of time the disease is in remission and improve quality of life. The committee concluded that both patients and healthcare professionals would welcome potential new treatments.

Treatment pathway and comparators

The advanced disease subgroup is most relevant to NHS practice

3.3 The marketing authorisation does not specify whether brentuximab vedotin may be used for early-stage CTCL or advanced CTCL. The committee noted that the inclusion criteria for ALCANZA (the pivotal trial on which the marketing authorisation was based; see section 3.6) included patients with early-stage disease. The committee was also aware that the company's submission focused on a narrower population than the marketing authorisation, including only patients with advanced disease (mycosis fungoides [stage IIB and over], primary cutaneous anaplastic large cell lymphoma and Sézary syndrome) and excluding those with lymphomatoid papulosis. The clinical experts explained that skin-directed therapies are often effective for managing early-stage CTCL, but systemic agents (like brentuximab vedotin) are more commonly used for advanced disease. They also highlighted that lymphomatoid papulosis is usually treated with skin-directed therapies (because it is less aggressive), so brentuximab vedotin would not generally be used for this subtype of CTCL. The committee concluded that brentuximab vedotin would be used for people with advanced disease and it was therefore appropriate for the company to focus on the advanced disease subgroup because this was most relevant to NHS clinical practice.

Methotrexate, bexarotene and interferon alfa are the most appropriate comparators

3.4 The committee recalled that systemic agents are most commonly used for advanced CTCL. The clinical experts explained that patients are first offered retinoids (bexarotene), interferon alpha or single agent chemotherapy (methotrexate). They highlighted that low-dose methotrexate is not licensed for CTCL but that it has been used in UK clinical practice for over 40 years. The choice of treatment often depends on the associated adverse events and the patient's needs as all initial

therapies are considered to be equally effective. Multi-agent chemotherapy regimens are generally not used as standard care and are only considered when first-line systemic therapy options (referred to as Category A therapies by the company) have been exhausted. This is because of their lack of efficacy and associated toxicities, which are especially problematic in people with CTCL who are susceptible to infection. The clinical experts agreed with the company's positioning of brentuximab vedotin as an alternative to first-line systemic therapies for advanced CTCL. The committee concluded that the company's positioning of brentuximab vedotin was appropriate and based on current clinical practice methotrexate, bexarotene and interferon alfa were the most appropriate comparators.

Allogeneic stem cell transplant should be considered as part of the treatment pathway

3.5 The clinical experts explained that brentuximab vedotin would be used in 2 ways: as a bridge to stem cell transplant or as a treatment without future stem cell transplant. The committee recalled that allogeneic stem cell transplant may be a potentially curative therapy for certain patients with advanced CTCL. The clinical experts advised that allogeneic stem cell transplants should only be considered for patients whose disease adequately responds to therapy. This normally means at least a partial response, although they commented that current treatment options produce only short-term responses not adequate to allow for a bridge to transplant. The clinical experts explained that everyone who is newly referred to a specialist centre with a diagnosis of advanced CTCL would be assessed for eligibility for an allogeneic stem cell transplant. The committee was aware that there are clinical criteria to identify people for whom stem cell transplants are not appropriate (for example, people with comorbidities that would compromise their fitness for a stem cell transplant), but that it may not always be possible to decide whether a

stem cell transplant is appropriate before starting brentuximab vedotin. The committee concluded that it would consider the use of brentuximab vedotin as both a treatment without future stem cell transplant and a bridge to allogeneic stem cell transplant (if the evidence allowed) for advanced CTCL.

Clinical evidence

The clinical-effectiveness evidence is relevant to NHS clinical practice

3.6 The main evidence for brentuximab vedotin was from ALCANZA, an international, multicentre, open-label, randomised controlled trial. It included 128 adults median age 60 years with CTCL (mycosis fungoides or primary cutaneous anaplastic large cell lymphoma) who had 1 previous systemic therapy and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 and under; 95 patients had advanced CTCL. The trial compared brentuximab vedotin with physician's choice (either methotrexate or bexarotene). The committee noted that ALCANZA did not assess the comparative effectiveness of brentuximab vedotin and interferon alfa. It noted the company's comment that there was insufficient evidence for an indirect comparison. Having acknowledged that all first-line systemic treatments are equally effective, the committee agreed that the lack of a comparison between brentuximab vedotin and interferon alfa was not a major limitation in the evidence. The committee noted that the trial was international and multicentre, but only 4 centres were in the UK (24 patients). The clinical experts confirmed that patients in the trial were representative of UK patients who would be eligible for brentuximab vedotin. The committee concluded that the clinical-effectiveness evidence from ALCANZA was relevant to clinical practice in the NHS in England.

Brentuximab vedotin improves response rates and progression-free survival

3.7 The company presented results for all patients in the ALCANZA study and separate results for the advanced disease subgroup. The primary

outcome was the rate of objective response that lasted at least 4 months. Secondary outcomes included response rates, length of response, progression-free survival and health-related quality of life. Overall survival was not a prespecified end point but the company included these data in its submission. These outcomes were assessed per independent review facility at a median follow-up time of 33.9 months (see table 1). The company also presented complete trial data based on investigator assessment. The clinical experts stated that these results were clinically meaningful and important to people with advanced CTCL, because current treatments provide only short-term responses. They reiterated that the response rates found with brentuximab vedotin meant more patients could be offered allogeneic stem cell transplants. The committee concluded that brentuximab vedotin was clinically effective and produced durable clinical responses compared with methotrexate or bexarotene, and accepted that this would also be the case for interferon alfa (see section 3.6)

Table 1 Results from ALCANZA advanced subgroup

End point	Brentuximab vedotin (n=49)	Methotrexate or bexarotene (physician's choice; n=46)	P value
Objective response rate lasting for at least 4 months, n (%)	29 (59.2)	4 (8.7)	<0.001
Overall response rate, n (%)	34 (69.4)	8 (17.4)	<0.001
Complete response, n (%)	10 (20.4)	1 (2.2)	0.005
Partial response, n (%)	24 (49.0)	7 (15.2)	Not reported
Progression-free survival, months (95% confidence interval)	16.5 (15.5 to 27.5)	3.5 (2.4 to 4.9)	Not reported

The exact proportion of patient who have allogeneic stem cell transplants after having brentuximab vedotin is uncertain

3.8 The company presented results from a post-hoc analysis of allogeneic stem cell transplants in ALCANZA, which included 7 patients who had a transplant: 5 in the brentuximab vedotin group and 2 in the comparator group. Only 2 of the 5 patients in the brentuximab vedotin treatment group had a stem cell transplant directly after treatment; the other 3 had additional systemic therapies before their transplant. Both patients in the comparator group crossed over to have brentuximab vedotin before their transplant. The committee noted that the proportion of patients bridging to transplant was higher in the UK than any other country included in the ALCANZA study, but that the rate of transplant remained low. The clinical experts explained that the trial was done in 2013 and although allogeneic stem cell transplants were allowed in ALCANZA, their use was not a prespecified or exploratory end point. The clinical experts emphasised that UK clinical practice has evolved since 2013 and allogeneic stem cell transplants are now more common. A clinical expert who had used brentuximab vedotin on the compassionate use programme suggested that around 25% of patients bridged to transplant. The committee concluded that brentuximab vedotin could be used as a bridge to transplant for certain patients whose disease adequately responds to treatment, but the exact proportion in clinical practice was uncertain.

In the absence of a stem cell transplant, it is unclear whether brentuximab vedotin improves overall survival compared with current treatment

3.9 Overall survival was not a prespecified end point in ALCANZA because the primary goal of treatment for advanced CTCL is disease control and symptom relief. However, survival data were collected and provided by the company for the advanced disease subgroup. Median overall survival was 43.6 months (95% confident interval [41.0 months – not available]) in the brentuximab vedotin group and 41.6 months (95% confident interval

[21.1 months – not available]) in the comparator group. Based on these results the company considered that it was not possible to assume a difference in overall survival between the brentuximab vedotin and physicians choice treatment groups. They highlighted that the data were very immature, based on a relatively small sample size with few events and may be confounded by biases such as crossover. Almost half (46%) of patients crossed over from the comparator group and subsequently had brentuximab vedotin. The company explored various methods of adjusting for crossover. The committee agreed with the company that none of the available methods were suitable. The ERG explained that it was not possible to obtain robust estimates of clinical effectiveness for overall survival. The clinical experts agreed that there were limited data for overall survival after brentuximab vedotin. They stated that they had not seen a proven association between progression-free and overall survival in patients with CTCL for patients who were not able to bridge to transplant. The committee concluded that there was a high degree of uncertainty about whether brentuximab vedotin increased overall survival compared with current treatments for patients who were not able to bridge to transplant.

Data from ALCANZA can be extrapolated to other subgroups of cutaneous T-cell lymphoma

3.10 The committee recalled that the ALCANZA trial included patients with mycosis fungoides or primary cutaneous anaplastic large cell lymphoma, but did not include other subgroups of CTCL. Two phase II trials provided further non-randomised supportive evidence for Sézary syndrome and lymphomatoid papulosis, other subtypes of CTCL which are included in brentuximab vedotin's marketing authorisation. The committee noted that the studies included only a small number of patients with subtypes of CTCL other than mycosis fungoides, but it recalled that CTCL is a rare disease. The clinical experts explained that treatment would be similar for

most subtypes of CTCL, but that they would be unlikely to use brentuximab vedotin for lymphomatoid papulosis. Having reviewed the supporting data, the committee noted that the findings for response rates and median progression-free survival were generally consistent across the studies and subgroups, and that the European Public Assessment Report for brentuximab vedotin stated that 'the available data appears in support for the extrapolation of efficacy from mycosis fungoides and primary cutaneous anaplastic large cell lymphoma to other subtypes'. The committee concluded that the clinical-effectiveness data from ALCANZA could be extrapolated to othersubtypes of CTCL, such as Sézary syndrome.

People may have fewer cycles of brentuximab vedotin in clinical practice than in both ALCANZA and the summary of product characteristics

3.11 The committee noted that the summary of product characteristics for brentuximab vedotin states that it should be used up to a maximum of 16 cycles. The clinical experts explained that the number of cycles used depended on whether brentuximab vedotin was being used to bridge to allogeneic stem cell transplant. They explained that when brentuximab vedotin is used without future stem cell transplant, 16 cycles are common and in some cases patients are offered retreatment with brentuximab vedotin (even though this is outside its marketing authorisation). The committee also heard that although there was no robust evidence available, treatment with brentuximab vedotin may be stopped after only 2 or 3 cycles if the response is sufficient to allow for an allogeneic stem cell transplant. The committee noted that this was much lower than the maximum number of cycles specified in the summary of product characteristics. It concluded that the number of cycles of brentuximab vedotin used in clinical practice varied, and that this should be factored into its considerations of the cost-effectiveness evidence.

Brentuximab vedotin's effect on health-related quality of life is unclear from the trial data

3.12 The company provided health-related quality of life and symptom relief data for the advanced disease subgroup using the Skindex-29 and EQ-5D-3L tools. The data showed that patients who had brentuximab vedotin had better symptom relief compared with those who had the comparators. However, the committee noted that there was no statistically significant difference in overall Skindex-29 score or EQ-5D-3L values between the brentuximab vedotin and comparator groups. The clinical experts explained that neither tool fully capture both the skin related and physiological symptoms of CTCL. They further explained that a health-related quality-of-life tool specific to CTCL was being developed but was not yet available. The committee was also aware that the European Public Assessment Report stated that 'no firm conclusions can be drawn'. It concluded that brentuximab vedotin's effect on health-related quality of life was unclear.

Adverse effects

Brentuximab vedotin is generally well tolerated

3.13 The committee noted that the adverse effects reported in the ALCANZA study were broadly comparable between the brentuximab vedotin and comparator groups. It noted that there was 1 treatment-related death caused by tumour lysis, but that this was not unique to brentuximab vedotin. A patient expert commented that they had found brentuximab vedotin to be more tolerable than other treatments, but they noted that each patient was likely to react differently. The committee concluded that brentuximab vedotin was generally well tolerated.

Cost effectiveness

The company's model structure is appropriate for decision-making

3.14 The company presented cost-effectiveness analyses comparing brentuximab vedotin with 'physician's choice' (in clinical practice, methotrexate or bexarotene) using a partitioned survival model with 5 mutually exclusive health states. The model had a 45-year time horizon; this was expected to cover a lifetime because patients in the study had a median age of 60 years. The model comprised 2 pathways, 1 that included allogeneic stem cell transplant and 1 that did not. All patients start in the pre-progression health state. Eligibility for allogeneic stem cell transplant is based on response to treatment in this state. All eligible patients move to the allogeneic stem cell transplant health state at 18 weeks. Patients on either pathway can relapse and move into a post-progression or death state. The clinical experts confirmed that the model reflected the clinical pathway for CTCL. The model was informed by data from the advanced disease subgroup of ALCANZA. These included only patients with the mycosis fungoides and primary cutaneous anaplastic large cell lymphoma subgroups of CTCL, but the committee recalled that the data could be extrapolated to all subgroups included in the marketing authorisation (see section 3.10). The committee concluded that the model's structure was appropriate for decision-making.

Pathway including stem cell transplants

The rates of stem cell transplant used in the company's model are uncertain

3.15 The model assumed that 40% of patients whose disease showed at least a partial response to treatment (based on objective response rates) were eligible for an allogeneic stem cell transplant. This was based on clinical advice, which accounted for the eligibility of patients for a transplant based on age, comorbidities and likelihood of a matching donor, as well as patient choice. The clinical experts confirmed that the response rates

used to inform the assumption of 40% reflected those seen in clinical practice, but they highlighted that only limited numbers of patients have had brentuximab vedotin in England. The committee noted the ERG's concerns that there was insufficient evidence to allow the rate of allogeneic stem cell transplant to be modelled robustly. It also noted that only 2 of 128 patients in ALCANZA had a transplant after their first treatment. The committee concluded that the rate of allogeneic stem cell transplant after brentuximab vedotin was uncertain.

The modelling of survival for people having stem cell transplants is appropriate

3.16 The committee noted that for people who had an allogeneic stem cell transplant and crossed over to the allogeneic stem cell transplant pathway, disease-free and overall survival were modelled on real-world evidence from the London supra-regional centre for CTCL. The Kaplan–Meier data showed that relapse after an allogeneic stem cell transplant was likely to occur in the first 12 months after the transplant. The company digitalised the Kaplan–Meier disease-free survival data and fitted a single parametric curve for extrapolation. The company chose the Gompertz curve because it reflected the decreasing probability of relapse over time. Patients whose disease relapsed after a transplant were represented by the difference between the disease-free and overall survival curves, which was extrapolated using the log-normal parametric curve. The company also submitted an addendum that included an updated data-cut presented at the 2018 European Organisation for Research and Treatment of Cancer conference. The updated data-cut included longer follow-up and additional patients from 5 other centres in the UK. The updated data-cut used progression-free survival rather than disease-free survival. The company stated that although disease-free survival was a more stringent end point, progression-free survival was the more clinical relevant outcome. The results of the updated data-cut are

considered academic in confidence and cannot be reported here. The ERG explained that the updated data-cut did not resolve the uncertainty around the rate of transplant or provide additional data on transplants in patients who have had brentuximab vedotin. The clinical experts explained that although there had been few allogeneic stem cell transplants after brentuximab vedotin in clinical practice, there was no reason to expect any differences in outcomes after a transplant in patients having brentuximab vedotin compared with those having methotrexate or bexarotene. The committee agreed that the company's approach to modelling survival outcomes after an allogeneic stem cell transplant was appropriate.

Pathway not including stem cell transplants

The extrapolation of progression-free survival for people not having stem cell transplants is appropriate

3.17 The company explored various parametric survival curves for extrapolating the progression-free survival data. It considered the Weibull models to have the best statistical and visual fit for both the brentuximab vedotin and comparator groups. The committee concluded that the company's approach and its rationale for selecting the Weibull models for its base-case analysis were appropriately justified.

The modelling of overall survival for people not having stem cell transplants is uncertain

3.18 The committee recalled that the overall survival data from ALCANZA were immature and confounded by crossover that could not be adjusted for given the limited data. The company had therefore assumed that the unadjusted survival data for patients in the comparator group could be used to represent overall survival for all patients. The company fitted a parametric curve to each treatment group of the trial. It considered the log-logistic parametric model for overall survival in the comparator group

to have the best fit, and therefore used it in its base-case analysis to model overall survival for both brentuximab vedotin and the comparators. The company's choice was based on clinical plausibility and on how closely the parametric curves aligned with historical data collected from UK patients with CTCL. The committee noted that the company's assumption of equal overall survival for brentuximab vedotin and the comparator alongside a progression-free survival gain for people who had brentuximab vedotin meant that, after disease progression, patients who had brentuximab vedotin died more quickly than patients who had the comparator. Consequently, patients who had brentuximab vedotin spent less time in the resource-intensive post-progression state than patients who had the comparator. The committee recalled that there was uncertainty about whether brentuximab vedotin improved overall survival compared with current treatment (see section 3.9). It discussed an ERG scenario analysis which examined a potential survival gain with brentuximab vedotin. The ERG considered it plausible that there may be some survival gain attributable to brentuximab vedotin without also modelling allogeneic stem cell transplant as part of the treatment pathway (see section 3.9). The ERG's scenario analysis applied an acceleration factor to the company's base-case overall survival curve for the comparator to generate a 9.5 month mean gain in overall survival for brentuximab vedotin (equal to the gain in progression-free survival when allogeneic stem cell transplant is included in the treatment pathway). The committee noted that the cost-effectiveness estimates for brentuximab vedotin were much higher in this scenario than in the company's base case (see section 3.25). However, the committee was also aware that the ERG considered this scenario to be illustrative of the sensitivity of the cost-effectiveness results to the assumption of no overall survival, but cautioned that it may not accurately represent what is seen in clinical practice. The committee agreed that it should consider the uncertainty

around whether brentuximab vedotin increased overall survival compared with current treatment in its decision-making.

Treatment after disease progression

Neither the company's nor the ERG's approaches to modelling treatment after disease progression are appropriate

3.19 The committee recalled that the company's assumption of equal overall survival with brentuximab vedotin and the comparator alongside a progression-free survival gain with brentuximab vedotin meant that patients having brentuximab vedotin spend less time in the post-progression state than patients having the comparators (see section 3.18). The company assumed that patients in both groups spent equal time on subsequent active therapies after disease progression, based on data from the PROCLIPI study. Patients in the brentuximab vedotin group whose disease progressed after subsequent active therapies therefore had a higher risk of death and spent less time in the end-stage state compared with patients in the comparator group. The committee noted that spending less time in the resource-intensive end-stage state would equate to lower costs, so this may lead to brentuximab vedotin's cost effectiveness being overestimated. The clinical experts explained that the post-progression treatment pathway would likely be the same for people whose disease relapsed following treatment with brentuximab vedotin (who did not have an allogeneic stem cell transplant) and people whose disease relapsed after having methotrexate or bexarotene. The clinical experts also noted that people having brentuximab vedotin were not expected to have worse outcomes than those who had the comparator. The committee therefore agreed that the company's post-progression pathway did not reflect clinical practice. Because the model was sensitive to changes to the costs and benefits accrued in the post-progression state, the committee considered the ERG's scenario analysis which explored the uncertainty around post-progression treatment. In this

scenario analysis, the ERG assumed equal overall survival between brentuximab vedotin and the comparators and did not include allogeneic stem cell transplant as part of the clinical pathway. The committee considered the use of a best supportive care state in the ERG's scenario. It understood that clinical advice to the ERG suggested that patients would spend 5 years having subsequent active therapies, 1 year having best supportive care and 6 months having end-stage care. However, the clinical experts noted that best supportive care does not exist for CTCL because current treatments are unable to sustain a response. They explained that when there are no treatment options remaining, the only option for advanced CTCL is high-resource care. The ERG accepted that the term 'best supportive care' may not accurately represent the current pathway, but explained that the scenario was illustrative of a post-progression pathway in which patients whose disease relapses after either brentuximab vedotin or the comparators have equal mortality risk after they have exhausted all other treatment options, and the resource use for time without treatment increases as people move closer to death. The committee accepted that this scenario was for illustrative purposes to show the sensitivity of the model to the assumptions around overall survival. It noted that it would have preferred to have seen this exploratory analysis modelled with some proportion of patients having allogeneic stem cell transplants, despite these data not being robust (see section 3.15). The committee agreed that both the company's and the ERG's models of the post-progression pathway had limitations and were therefore not appropriate for decision-making. However, it noted that both the company's base case and ERG scenario analysis illustrated the importance of the assumption of equal overall survival for brentuximab vedotin and the comparators, and how this assumption affected the costs accrued in the post-progression state. The committee concluded that it should consider the assumption of equal overall survival and the post-

progression pathway for brentuximab vedotin and the comparators further in its decision-making.

Utility values

The ERG's approach to calculating utility values is more appropriate

3.20 To calculate the utility values for the progression-free state in the model, the company used EQ-5D-3L data from the ALCANZA trial but fitted a regression model including Skindex-29 scores as a covariate. The committee noted that the cost-effectiveness estimates calculated using Skindex-29 scores would differ to those based on an approach that excluded the Skindex-29 scores. It also noted that the utility values in ALCANZA were higher for brentuximab vedotin than for the comparators because of differences at baseline, and that the ERG considered it more appropriate to assume that the utility values for the progression-free state were equal for brentuximab vedotin and the comparator. The ERG's preferred utility value was calculated using an average of the EQ-5D-3L values from the brentuximab vedotin and comparator groups (0.689). The ERG also preferred not to include treatment-related disutilities based on descriptions of side effects in the model: the EQ-5D-3L data from ALCANZA would capture any changes in health-related quality of life as a result of adverse events, so further utility decrements would be unnecessary. The committee concluded that the ERG's approach to modelling utility values was more appropriate and suitable for decision-making.

Costs in the model

The company's base case may overestimate resource use frequencies and costs

3.21 The committee recalled that when there are no treatment options remaining, the only option for patients with advanced CTCL is high-

resource care (see section 3.19). End-stage care in the company's model included numerous outpatient appointments and regular visits from both palliative care and Macmillan nurse teams. The clinical experts reiterated that CTCL is a rare disease; any guidelines would likely recommend that patients have regular hospital admissions and visits from district nurses, but in practice it is likely that some patient care will be managed by families and carers. The committee considered whether there was capacity for these appointments and visits to be as frequent as the company had assumed. It considered the ERG's scenario analysis which reduced the frequency of outpatient appointments, district and Macmillan nurse visits and palliative support to be more reflective of clinical practice. The cost-effectiveness estimate for brentuximab vedotin was much higher in this scenario than in the company's base case (see section 3.25). The company also included costs for administering oral chemotherapy and for outpatient visits, tests and scans for patients having oral chemotherapy. The ERG considered this to be double counting of costs for the comparator group. The committee agreed that additional costs for oral chemotherapy should not be included in the base case. It concluded that the company's base case may overestimate resource unit costs for end-stage care.

The committee would have preferred to have seen analyses including a range of stopping rules

3.22 Both the company's base case and the ERG's revised base case estimated the cost of brentuximab vedotin based on the time-on-treatment data from the ALCANZA study. The company assumed that all patients having an allogeneic stem cell transplant have the transplant at 18 weeks, after 6 cycles of brentuximab vedotin. The committee recalled the clinical experts' suggestion that if a patient's disease had an adequate response to allow for an allogeneic stem cell transplant, brentuximab vedotin may be stopped after only a few cycles. The committee concluded that this

was unlikely to have a large effect on the cost-effectiveness estimates, but it would have preferred to have seen analyses that included a range of stopping rules for patients who go on to have allogeneic stem cell transplants.

Cost-effectiveness results

Brentuximab vedotin was more effective and less costly than methotrexate or bexarotene in the company's analysis

3.23 Brentuximab vedotin was more effective and less costly than methotrexate or bexarotene in the company's analysis The company's base-case analysis showed that, including the patient access scheme discount, the incremental cost-effectiveness ratio (ICER) for brentuximab vedotin compared with methotrexate or bexarotene was dominant (that is, brentuximab vedotin was both more effective and less costly). In the absence of an ICER the company also presented the net monetary benefit using a willingness-to-pay threshold of £30,000 per quality-adjusted life year (QALY). Net monetary benefit is a summary statistic that represents the difference between the monetary value of total expected QALYs (expected QALYs multiplied by the maximum acceptable ICER value) and total expected costs. The net monetary benefit for brentuximab vedotin in the company's base case was £134,218.

The ERG's cost-effectiveness estimates are higher than the company's cost effectiveness estimates

3.24 The ERG's cost-effectiveness estimates are higher than the company's cost effectiveness estimates The ERG made several revisions to the company's base case, specifically:

- removing allogeneic stem cell transplant from the model (see section 3.15),

- using the EQ-5D-3L utility estimates from the ALCANZA trial (see section 3.20),
- using equal utility values in the pre-progression health state for brentuximab vedotin and the comparators (see section 3.20),
- removing treatment-related disutilities (see section 3.20,
- removing extra oral chemotherapy costs (see section 3.21).

With these changes, the ERG's revised base-case analysis showed that the ICER for brentuximab vedotin compared with methotrexate or bexarotene continued to be dominant but that the net monetary benefit decreased to £59,804. The ERG also presented 3 scenario analyses to illustrate the sensitivity of the model to different assumptions. These each had a large effect on the ICERs:

- assuming an overall survival gain with brentuximab vedotin (see sections 3.9 and 3.18) increased the ICER to £47,570 per QALY gained.
- changing the post-progression pathway (see section 3.19) increased the ICER to £494,981 per QALY gained.
- changing resource use frequencies (see section 3.21) increased the ICER to £26,331 per QALY gained.

The ERG also presented results of combinations of these scenarios where the ICER ranged from £82,597 to £626,918 per QALY gained.

None of the analyses includes all the committee's preferred assumptions

3.25 The committee noted that in both its revised base case and its scenario analyses, the ERG had removed allogeneic stem cell transplants from the modelling. It agreed that this did not represent clinical practice, and concluded that neither the company's nor the ERG's analyses included all of its preferred assumptions. These were:

- varying rates of allogeneic stem cell transplant to reflect the uncertainty in clinical practice (see section 3.15),
- varying the number of cycles of brentuximab vedotin for patients who have allogeneic stem cell transplants (see section 3.22),
- using equal utility values for both brentuximab vedotin and the comparators (see section 3.20),
- removing treatment-related disutilities (see section 3.20),
- removing the extra oral chemotherapy costs (see section 3.21).

Other factors

Brentuximab vedotin is innovative but there is no evidence of additional benefits not captured in the analyses

3.26 The company considered that brentuximab vedotin was an innovative treatment because it represents a step-change in managing a disease for which there is significant unmet need. Brentuximab vedotin may allow more patients to proceed to a potentially curative allogeneic stem cell transplant. The company also highlighted that brentuximab vedotin is given every 3 weeks in an outpatient setting, which means patients need to spend less time in hospital. The committee noted the limitations of EQ-5D-3L as a tool for measuring health-related quality of life in CTCL, but recalled that the extent of this is unknown (see section 3.12). The clinical experts agreed that brentuximab vedotin was innovative and that clinical trial results showed durable clinical responses which are rarely achieved with current treatments. The committee agreed that brentuximab vedotin would be beneficial for patients, but that it had not been presented with robust health related quality of life evidence to show a benefit for brentuximab vedotin or any additional benefits that were not captured in the measurement of QALYs.

There are no relevant equality issues

3.27 There were no relevant equality issues raised in the company submission or ERG report, or in patient and professional statements. During scoping, stakeholders highlighted that excluding CTCL with less than 5% CD30 expression from the recommendations may deny some patients access to the treatment because of evidence that 1 in 6 cases of CTCL with less than 5% CD30 expression may respond to treatment. However, the marketing authorisation for brentuximab vedotin does not specify a percentage of CD30 expression so this was not considered to be a relevant equality issue.

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

3.28 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It noted that the company had not provided any evidence to make a case for brentuximab vedotin meeting the criteria to be considered a life-extending treatment at the end of life. It was aware that the clinical experts considered that brentuximab vedotin did not fulfil either criteria for end of life as people with CTCL may survive for several years after treatment (see section 3.2) and agreed with the company assumption no overall survival gain after treatment with brentuximab vedotin (see section 3.9). Based on the testimony of the clinical experts and the data presented by the company and ERG the committee accepted that brentuximab vedotin did not meet the end-of-life criteria.

Brentuximab vedotin is not recommended for treating CD30-positive cutaneous T-cell lymphoma

3.29 The committee noted that although the company's base case showed the ICER for brentuximab vedotin to be dominant compared with methotrexate or bexarotene, the ERG's estimated ICERs ranged from dominant to £626,918 per QALY gained. However, the committee was aware that the ERG's estimated ICERs did not include the costs and

QALYs from allogeneic stem cell transplants. The committee recalled that the ERG's scenario analyses demonstrated the model to be sensitive to a number of assumptions, including the proportion of subsequent allogeneic stem cell transplants, overall survival gain with brentuximab vedotin or the comparators, the post-porgression treatment pathway and resource use in the post-progression state. The committee agreed that there was a high degree of uncertainty associated with all the cost-effectiveness estimates presented, and reiterated that it had not seen analyses including all its preferred assumptions. The committee concluded that based on the evidence presented, it could not recommend brentuximab vedotin for routine use for treating CD30-positive CTCL after at least 1 systemic therapy.

Cancer Drugs Fund

Brentuximab vedotin does not meet the criteria to be considered for inclusion in the Cancer Drugs Fund

3.30 Having concluded that brentuximab vedotin was not recommended for routine use, the committee then considered if it could be recommended use within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. It noted that the company had not made a case for brentuximab vedotin to be included in the Cancer Drugs Fund, and recalled that there was a high degree of uncertainty associated with all the cost-effectiveness estimates presented, and reiterated that it had not seen analyses including all its preferred assumptions. It agreed that it was unclear if brentuximab vedotin had the plausible potential to be cost-effective. Based on the available evidence, the committee agreed that brentuximab vedotin did not meet the criteria for inclusion in the Cancer Drugs Fund.

4 Proposed date for review of guidance

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

Peter Selby
Chair, Appraisal Committee
December 2018

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.

Lorna Dunning

Technical Lead

Nicola Hay

Technical Adviser

Stephanie Callaghan

Project Manager

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