NICE National Institute for Health and Care Excellence

NICE guidance

Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell 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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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.

Contents

1 Guidance

1.1 Pixantrone monotherapy is recommended as an option for treating adults with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma only if:

- the person has previously been treated with rituximab and
- the person is receiving third- or fourth-line treatment and
- the manufacturer provides pixantrone with the discount agreed in the patient access scheme.

1.2 People currently receiving treatment initiated within the NHS with pixantrone monotherapy that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Pixantrone (Pixuvri, Cell Therapeutics) is an aza-anthracenedione analogue and inhibitor of topoisomerase II. The recommended dosage is pixantrone 50 mg/m^2 on days 1, 8 and 15 of each 28-day cycle for up to 6 cycles. It is administered intravenously. Pixantrone has a conditional marketing authorisation 'as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy'. The European public assessment report noted pixantrone had a reduced benefit in patients pretreated with rituximab. The marketing authorisation is linked to results being provided from the phase III PIX306 trial, which is investigating pixantrone plus rituximab compared with gemcitabine plus rituximab in patients with relapsed or refractory aggressive non-Hodgkin's B-cell lymphomas who have previously received a rituximab-containing regimen. Results are expected in 2015.

2.2 The summary of product characteristics states that the most common toxicity with pixantrone is bone marrow suppression (particularly the neutrophil lineage) and that other toxicities such as nausea, vomiting and diarrhoea are generally infrequent, mild, reversible, manageable and as expected in patients treated with cytotoxic agents. Although the occurrence of cardiac toxicity indicated by congestive heart failure appears to be lower than that expected with related drugs like anthracyclines, the summary of product characteristics recommends monitoring left ventricular ejection fraction. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Pixantrone is priced at £553.50 per 20-ml vial containing 29 mg free base pixantrone, which is equivalent to 50 mg pixantrone dimaleate (excluding VAT; 'British national formulary' [BNF] edition 66). The estimated cost of a course of treatment is £19,926 (costs calculated over 4 cycles using an average of 3 vials per dose based on the median length of treatment in the PIX301 trial, described in section 3.2). Costs

may vary in different settings because of negotiated procurement discounts. The manufacturer of pixantrone has agreed a patient access scheme with the Department of Health that makes pixantrone available with a discount. The size of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of pixantrone and a review of the submissions by the Evidence Review Group (ERG; section 9). The manufacturer submitted additional evidence (about the patient population, trial design and clinical effectiveness, a revised model, and support for consideration of end-of-life criteria) after consultation on the appraisal consultation document. The submission and the additional evidence did not incorporate a patient access scheme. The manufacturer later made a confidential simple discount patient access scheme submission in July 2013, which was superseded by an updated patient access scheme submitted in November 2013. The Committee's considerations and decision-making are based on the November 2013 patient access scheme.

Clinical effectiveness

Manufacturer's original submission

3.1 The manufacturer's systematic review identified 1 randomised controlled trial, which was included in its original submission. No other relevant randomised controlled trials or non-randomised controlled trials were identified. The manufacturer also included some supporting cardiotoxicity data from a randomised phase II study that did not meet the inclusion criteria of the literature review (because it evaluated pixantrone in combination with other drugs, not as monotherapy).

3.2 PIX301 is a randomised, controlled, open-label phase III study conducted in 66 centres, including the USA and Europe. Eligible patients were adults with aggressive de novo or transformed non-Hodgkin's lymphoma that had relapsed after 2 or more chemotherapy regimens, including at least 1 standard anthracycline-containing regimen with a response that had lasted at least 24 weeks. Seventy patients were randomised to pixantrone and 70 patients to a physician's choice of single-agent comparators. The full publication of PIX301 described how 67 patients went on to receive vinorelbine (n=11), oxaliplatin (n=30), ifosfamide (n=12), etoposide (n=9), mitoxantrone (n=4) or gemcitabine (n=1). Pixantrone was administered at a dosage of 85 mg/m^2 on days 1, 8 and

15 of a 28-day cycle for up to 6 cycles. Comparators were administered at predefined standard dosages for up to 6 cycles. Follow-up was for 18 months after completing study treatment.

3.3 The primary outcome was complete and unconfirmed complete response, which was determined by a blinded independent assessment panel. Secondary outcomes were overall survival, response lasting at least 4 months and progression-free survival. Other predefined end points were overall response rate, time to response, time to complete response, duration of response and relative dose intensity. Health-related quality of life was not assessed. The primary analysis was the intention-to-treat population. Secondary analyses included a prespecified analysis of the response and survival end points for the histologically confirmed intention-to-treat population (that is, if the lymphoma had been classified according to retrospective independent central pathological assessment).

3.4 It was initially planned that 320 patients would be recruited to PIX301 but study enrolment was closed early because of slow accrual. The manufacturer's original submission stated that, with a final enrolment of 140 patients, the study was considered to be sufficiently powered (about 80%) to detect a 15% difference in the complete or unconfirmed complete response rate, assuming a rate of at least 18% in the pixantrone arm. In contrast, the full publication of PIX301 reported that the study was originally powered to detect a difference of 10% in the proportion of patients who achieved a complete or unconfirmed complete response. The publication further stated that, according to the original sample size assumptions, a sample of 70 patients per group would have about 40% power. It added that, to achieve 81% power with 70 patients per group, the true proportion of patients with a complete or unconfirmed complete response would have to be 22% in the pixantrone group and 5% in the comparator group.

3.5 The manufacturer's original submission reported that baseline demographic and disease characteristics were similar in the 2 arms. Previous treatment for non-Hodgkin's lymphoma was broadly similar for both groups, including number of chemotherapy regimens (median 8 regimens [range 2–9] in both arms). Aggressive histological features

were identified onsite in all patients before treatment was given and confirmed by central independent pathological review in 54 (77%) of 70 patients in the pixantrone arm and 50 (71%) of 70 patients in the comparator arm receiving treatment of physician's choice. Of the remaining 36 patients, reasons for non-confirmation were low-grade histology (n=13), lack of consensus (n=10), shortage of specimen (n=6), confirmation of a non-aggressive subtype other than non-Hodgkin's lymphoma (n=5), and the specimen reviewed by only 1 pathologist (n=2). Out of 140 patients, 36 patients completed 6 cycles of protocol treatment, and 104 patients discontinued early. The most common reason for early discontinuation in both groups was disease progression or relapse. After completing study treatment, 95 patients entered follow-up and 26 of these completed 18 months of follow-up.

3.6 The manufacturer's original submission reported that, at the end of treatment, confirmed and unconfirmed response rates for the intention-to-treat population (70 patients in each arm) were statistically significantly higher for the pixantrone group than the comparator group receiving treatment of physician's choice (20% compared with 5.7%; p=0.021). This was also the case at the end of the study after 18 months of follow-up (24.3% compared with 7.1%; p=0.009).

3.7 The manufacturer's original submission described the results for progression-free and overall survival in the intention-to-treat population. Median progression-free survival was statistically significantly longer for the group receiving pixantrone than the comparator group receiving treatment of physician's choice at 5.3 months compared with 2.6 months (hazard ratio 0.60 and 95% confidence interval [CI] 0.42 to 0.82; p=0.005). However, there was no statistically significant difference in median overall survival between the 2 groups (10.2 months in the pixantrone arm compared with 7.6 months in the comparator arm receiving treatment of physician's choice (hazard ratio 0.79 [95% CI 0.53 to 1.18]; p=0.251).

3.8 In addition to the results for the intention-to-treat population of PIX301, the manufacturer included clinical-effectiveness data for several post-hoc subgroups in its original submission for patients with aggressive B-cell lymphoma (classed as diffuse large B-cell lymphoma, transformed

indolent lymphoma or follicular lymphoma [grade III]):

- Disease confirmed by onsite pathological review (all lines of treatment, and third- or fourth-line treatment only).
- Disease confirmed by central independent pathological review (all lines of treatment, and third- or fourth-line treatment only).
- Disease confirmed by central independent pathological review in patients who had previously received rituximab treatment.

  The manufacturer also presented the results for a subgroup of patients with diffuse large B-cell lymphoma confirmed by onsite pathological review (over 80% of the total number of patients with aggressive B-cell lymphoma). The results of the subgroup analyses that were incorporated into the manufacturer's original economic model are described below. The results of other subgroup analyses included in the manufacturer's original submission have been previously reported in the appraisal consultation document.

3.9 In its original submission, the manufacturer considered the post-hoc subgroup of patients with aggressive B-cell lymphoma confirmed by onsite pathological review to be similar to the population eligible for treatment according to pixantrone's European marketing authorisation, and indicated that this formed the basis of the population in the original base case of its cost-effectiveness analysis (however, it should be noted that the manufacturer stated that its economic evaluation focused on those who had received 2 or 3 previous therapies; see section 3.20 for details). This subgroup excluded patients with peripheral T-cell lymphoma not otherwise characterised and other disease subtypes not included in pixantrone's European marketing authorisation. Compared with the group that received treatment of physician's choice (n=62), complete or unconfirmed complete response rates at the end of the study in the pixantrone group (n=64) were statistically significantly higher (23.4% compared with 8.1%; p=0.027). Overall response rates were also statistically significantly higher in the pixantrone group (40.6% compared with 16.1%; p=0.003). Median progression-free survival was statistically significantly longer in patients who had received pixantrone than those who had received a comparator drug (5.7 months compared with 2.5 months, hazard ratio 0.56 [95% CI 0.38 to 0.81]; p=0.002). The

manufacturer advised that median overall survival was not included because the aggressive B-cell lymphoma analyses were exploratory.

3.10 In its original submission, the manufacturer presented a further analysis of patients with aggressive B-cell lymphoma confirmed by onsite pathological review who received pixantrone (n=50) or a comparator (n=49) as third- or fourth-line treatment, which it stated was more closely aligned with pixantrone's marketing authorisation. It is not clear from the manufacturer's submission how this population differs from that in the base case of its cost-effectiveness analyses (see section 3.20 for details). The group receiving pixantrone had a statistically significantly higher complete response or unconfirmed complete response rate (28.0% compared with 4.0%; p=0.002) and overall response rate (48.0% compared with 12.2%; p<0.001), and statistically significantly longer progression-free survival (5.8 months compared with 2.8 months, hazard ratio not stated; p=0.002) than the comparator group receiving treatment of physician's choice. Median overall survival in this population was numerically higher in the pixantrone arm than the comparator arm but this difference was not statistically significant (13.9 months compared with 7.8 months, hazard ratio 0.76 [95% CI 0.47 to 1.24]; p=0.275). The manufacturer's submission did not state whether the results were for end of treatment or end of study.

3.11 In addition to the histologically defined subgroups of the PIX301 population in its original submission, the manufacturer also supplied subgroup analyses that showed the influence of previous rituximab treatment on pixantrone's efficacy in the subgroup of patients who had aggressive non-Hodgkin's B-cell lymphoma confirmed by central independent pathological review. In this subgroup of patients who had previously received rituximab, there was no statistically significant difference between pixantrone (n=30) and the comparator arm (n=26) in the proportion of patients who had a complete or unconfirmed complete response at the end of treatment (16.7% compared with 7.7%; p=0.431). Median progression-free survival was longer in the pixantrone group than in the comparator group receiving treatment of physician's choice for this subgroup of patients but the difference did not reach statistical significance (3.5 months compared with 2.3 months, hazard ratio 0.66 [95% CI 0.38 to 1.14]). Similarly, median overall survival was longer in the

pixantrone group than in the comparator group receiving treatment of physician's choice but the between-group difference was not statistically significant (6.0 months compared with 4.6 months, hazard ratio 0.85 [95% CI 0.48 to 1.50]).

3.12 The manufacturer's original submission described the adverse events in PIX301 for 68 patients in the pixantrone group and 67 patients in the comparator group who received treatment of physician's choice. One dose reduction was allowed for patients who had neutropenia during treatment, and reductions were similar in the pixantrone and comparator groups (18% compared with 15%). Dose delay was more frequent with pixantrone (40% compared with 22%).

3.13 A similar number of patients had an adverse event of any grade but there was a higher incidence of grade 3 and 4 adverse events in the pixantrone group than in the comparator group (76.5% compared with 52.2%). Neutropenia occurred more frequently in the pixantrone group and was the most common adverse event of any grade (50.0% compared with 23.9%) and the most common grade 3 or 4 adverse event (41.2% compared with 19.4%). Grade 3 or 4 febrile neutropenia was also more common in the pixantrone group than in the comparator group (7.4% compared with 3.0%), and more patients in the pixantrone group than in the comparator group received an immunostimulant (51.5% compared with 26.9%). The manufacturer reported that severity of neutropenia did not increase with increasing cycle number and that the overall rates of grade 3 and 4 infections were similar in the 2 groups. It further stated that the common adverse events were similar to those expected in a heavily pretreated patient population, which reflected pixantrone's intended use in clinical practice in England and Wales (that is, third and subsequent lines of treatment).

3.14 Approximately 40% of patients in both treatment arms presented with a history of cardiac disease at study enrolment, and cardiac risk factors were also similar in the 2 groups. The manufacturer stated that pixantrone is an innovative treatment because it has been specifically designed to reduce cardiotoxicity associated with anthracyclines without compromising efficacy. More cardiac adverse events occurred in the pixantrone group (24 patients [35.3%] than in the comparator group who

received treatment of physician's choice (14 patients [20.9%]). Thirteen (19.1%) patients in the pixantrone group experienced decreased left ventricular ejection fraction compared with 7 patients in the comparator group. The manufacturer provided supporting cardiotoxicity data from the randomised open-label phase II PIX203 trial, which closed before enrolment completed. This trial compared the combination of cyclophosphamide, pixantrone, vincristine, prednisone and rituximab with the standard of care (that is, rituximab in combination with a regimen of cyclophosphamide, doxorubicin, vincristine and prednisone) as first-line treatment in patients with diffuse large B-cell lymphoma. The cardiotoxicity results of PIX203 broadly supported those of PIX301.

Manufacturer's additional evidence in response to consultation on the first appraisal consultation document

3.15 In response to consultation on the first appraisal consultation document, the manufacturer requested and received permission from NICE to submit additional evidence. The additional evidence contained the results for 4 subgroups and showed the effect of treatment in patients who had previously received rituximab. Two of the subgroups were patients who had aggressive non-Hodgkin's B-cell lymphoma confirmed by central independent pathological review for all lines of therapy, and the other 2 subgroups were patients with aggressive B-cell lymphoma confirmed by central independent pathological review who were receiving third- or fourth-line treatment. During the second Committee meeting, the manufacturer clarified that the subgroups of all patients regardless of rituximab status (those patients who had previously received rituximab plus those who had not) were labelled as 'without rituximab' in its response to consultation.

3.16 In its additional evidence, the manufacturer presented amended results for the subgroup of patients who had aggressive non-Hodgkin's B-cell lymphoma confirmed by central independent pathological review and had previously received rituximab (see section 3.11). Complete or unconfirmed complete response rates were higher in the pixantrone arm than in the comparator arm (20% compared with 11%) but this difference was not statistically significant. Results for progression-free survival and overall survival were as before, except for median progression-free

survival in the comparator arm, which the manufacturer confirmed was an error. In its consultation response, the manufacturer also reiterated data for the subgroup of all patients who had aggressive non-Hodgkin's B-cell lymphoma confirmed by central independent pathological review regardless of whether they had previously received rituximab or not (n=50 in the pixantrone group, n=47 in the comparator group). At the end of the study, there was no statistically significant difference in complete or unconfirmed complete response rates between the pixantrone and comparator groups (9 patients compared with 4 patients; p=0.236). However, the overall response rate was statistically significantly higher in the pixantrone group (18 patients compared with 8 patients; p=0.041). Median progression-free survival was statistically significantly longer in the pixantrone arm than in the comparator arm (5.6 months compared with 2.5 months, hazard ratio 0.51 [95% CI 0.33 to 0.78]; p value not stated) but there was no statistically significant difference in median overall survival between the 2 groups (8.1 months compared with 6.3 months, hazard ratio 0.72 [95% CI 0.45 to 1.13]; p value not stated).

3.17 In its additional evidence, the manufacturer reiterated subgroup analyses for all patients (that is, patients who had previously received rituximab plus those who had not) with aggressive B-cell lymphoma confirmed by central independent pathological review who were receiving third- or fourth-line treatment with pixantrone (n=39) or treatment of physician's choice (n=39). Compared with the group receiving treatment of physician's choice, the pixantrone group had a statistically significantly higher complete or unconfirmed complete response rate (23.1% compared with 5.1%; p=0.047) and overall response rate (43.6% compared with 12.8%; p=0.005). Median progression-free survival was statistically significantly longer with pixantrone than with treatment of physician's choice (5.7 months compared with 2.8 months, hazard ratio 0.44 [95% CI 0.27 to 0.71]) but there was no statistically significant difference in median overall survival between treatment groups (11.9 months with pixantrone compared with 7.0 months with treatment of physician's choice, hazard ratio 0.67 [95% CI 0.40 to 1.12]).

3.18 In its additional evidence, the manufacturer also provided results for a subgroup described as patients with aggressive B-cell lymphoma confirmed by central independent pathological review who were

receiving third- or fourth-line treatment who had previously received rituximab (n=25 in both study arms), but confirmed at the second Committee meeting that this population was in fact a subgroup of patients whose disease had been confirmed by onsite (not central) pathological review. The correct population (that is, with pathology confirmed by central independent review), whose results had previously been included as part of the manufacturer's clarification response, showed an increase in complete response or unconfirmed complete response in the pixantrone arm (n=20) compared with the comparator arm (n=18; 30% compared with 5.6%; p=0.093). There was no statistically significant difference between treatment arms in median progression-free survival (5.4 months in the pixantrone group and 2.8 months in the comparator group, hazard ratio 0.52 [95% CI 0.26 to 1.04]). Similarly, there was no statistically significant difference in median or mean overall survival between treatment arms (hazard ratio 0.76 [95% CI 0.38 to 1.55]). Median overall survival was 7.5 months in the pixantrone group and 5.4 months in the comparator group. Mean overall survival was 9.9 months in the pixantrone arm and 7.9 months in the comparator group (difference of 2.0 months).

Cost effectiveness

3.19 The manufacturer did not identify any published economic evaluations or costing studies that were relevant to the decision problem. Consequently, it submitted a de novo economic analysis that assessed the cost effectiveness of pixantrone compared with treatment of physician's choice in treating multiply relapsed or refractory aggressive B-cell lymphoma, which was later revised as part of the manufacturer's response to consultation (see section 3.31 for details of changes in the revised model). Further minor updates were made in the manufacturer's model that formed part of a patient access scheme submission which was submitted in July 2013. In November 2013, this was superseded by another patient access scheme submission, which applied a further simple discount to the model (see sections 3.34–3.38 for details).

Manufacturer's submission

3.20 The manufacturer advised that the base-case model considered patients

who had received 2 or 3 prior therapies and whose disease was sensitive to treatment with anthracyclines because this population was consistent with pixantrone's European marketing authorisation for treating multiply relapsed or refractory aggressive non-Hodgkin's lymphoma (the marketing authorisation notes that a treatment benefit has not been established 'when used as fifth line or greater chemotherapy in patients who are refractory to last therapy'). The clinical data for this population were derived from PIX301. The analysis was conducted from an NHS and personal and social services perspective and a lifetime horizon of 23 years was used. Weekly cycles were chosen to capture the 4-week treatment cycles of pixantrone and 3-week treatment cycles of some of the comparator treatments and a half-cycle correction was applied. Costs and benefits were discounted at 3.5% per annum.

3.21 The manufacturer created a semi-Markov model that contained 3 health states: stable or no progression, progressive or relapsed disease, and death. The stable or no progression health state had 2 distinct subpopulations. The first of these was patients on initial third- or fourth-line treatment. The second was patients who had discontinued third- or fourth-line treatment (because of complete response, adverse event, completion of 6 months' treatment or a non-clinical reason) but had not experienced progression. All patients entered the model in the on-treatment subpopulation within the stable or no progression health state. During each cycle, patients could remain in the on-treatment subpopulation of this health state, discontinue treatment and move into the other subpopulation in this health state, progress and move into the progressive disease health state, or die. Patients who discontinued treatment before progression remained at risk of progression or death. Following progression, patients were at risk of death and unable to return to the stable or no progression health state. It was assumed that the original treatment was stopped following disease progression and patients received further treatment or palliative care. Adverse events were captured as events within the model by applying a utility decrement (disutility).

3.22 The manufacturer outlined how the transition between health states was calculated from the clinical data for any given weekly cycle. It noted that semi-Markov models allow the use of a partition approach, which has

been used extensively in oncology because it is particularly suited to progressive conditions that have ongoing risks that may vary over time. The distribution of the patient group between the different health states was estimated by calculating the area under the survival curves at each cycle. The progression-free survival curve defined the stable or no progression state, while the progressed state was defined by subtracting those patients who remained progression free from all surviving patients.

3.23 Clinical parameters for progression-free survival and overall survival were incorporated into the base case of the manufacturer's economic model by statistical analysis of patient-level data from the aggressive B-cell population of PIX301. Predictive equations for progression-free survival and overall survival were derived by fitting the patient-level data and extrapolating beyond the data from PIX301 (around 2 years). A log-normal distribution was used in the base case for both progression-free survival and overall survival.

3.24 Further clinical parameters were incorporated into the base case of the manufacturer's economic model. The cycle probability of treatment discontinuation distinguished between patients remaining on initial treatment and those who discontinued while stable. The frequency and duration of adverse events (grades 2–4) before progression while taking initial treatment were based on PIX301. Grade 3 and 4 adverse events occurring in at least 5% of the total patient population were considered to have cost and utility consequences. Some grade 2, and rarer grade 3 and 4, adverse events were included if considered important by clinical specialists in England. Other data from PIX301 that were used to inform the model were mean dose for the comparator treatments plus sex and body surface area.

3.25 There were no patient-reported outcomes in PIX301 and the manufacturer did not identify any utility data for any line of treatment in aggressive non-Hodgkin's lymphoma in its systematic literature review for studies on health-related quality of life. Utility data were identified from published sources for similar patient populations, and for disease areas with similar expected survival, disease progression, nature of the disease and quality of life. These were diffuse large B-cell lymphoma, chronic myelogenous leukaemia, chronic lymphocytic leukaemia,

follicular lymphoma, renal cell carcinoma and melanoma. For its original model, the manufacturer considered the self-reported quality of life in older patients with aggressive diffuse large B-cell lymphoma to give the estimation closest to the PIX301 trial population and used these values (pre-progression 0.81, post-progression 0.60) in its base-case analysis. The manufacturer did not provide a rationale for this decision. Utility values were assumed to depend only on the health state and any adverse events experienced, but not the treatment arm. Based on expert clinical opinion, the manufacturer assumed no difference in baseline health-related quality of life between the 2 subpopulations in the stable or no progression health state. All stable/no progression patients were assumed to have similar quality of life (that is, there was no difference according to complete response, partial response or stable disease).

3.26 The manufacturer determined disutilities associated with each adverse event that was included in the original model from relevant literature from other oncology indications. If no utility decrements were available, the maximum value of the range identified was assumed by the manufacturer to keep the calculations conservative (that is, so that pixantrone was not favoured).

3.27 Adverse events were modelled by the manufacturer as events rather than as health states and were assumed to be time independent because adverse events are likely to be experienced at different stages of treatment. Any grade 1–4 adverse event that occurred in less than 5% of the trial population was assumed to have no impact on quality of life. After consulting some clinical specialists in England, the manufacturer included some rarer grade 3 and 4 adverse events and some grade 2 adverse events that the clinical specialists considered to be important. Because no disutility values were available specifically for grade 2 and grade 3 or 4 adverse events, they were assumed to be the same for each grade. Within a health state, disutilities relating to an adverse event were applied to the proportion of patients assumed to experience the adverse event as weighted average disutilities. For each treatment, the manufacturer calculated a weighted average of grade-specific disutilities that were weighted by the number of effects of that particular grade. The disutility for each adverse event was then applied for the duration of that specific type of effect. The manufacturer's model limited the

consideration of adverse events to patients on original treatment upon entering the model (pixantrone or treatment of physician's choice).

3.28 Costs captured in the manufacturer's model included drugs and their administration, plus those associated with health state and disease management, including adverse events. Drug and administration costs in the original model were calculated based on average dose per administration from the PIX301 trial using the British national formulary (BNF) edition 62 (published in September 2011) and the NHS reference costs. No patient access scheme was incorporated in the original model. From the second attendance onwards, administration costs were £206 for each attendance for all drugs except etoposide 50 mg (£163). At clarification, the manufacturer corrected an error in the vial price, which had been mistakenly quoted as £343.80 (based on the vial size given for pixantrone base) instead of £553.50 (equivalent to 50 mg pixantrone dimaleate). It advised that this error had a minimal impact on the cost-effectiveness estimates (which increased by 0.3%) because the drug costs in the model had been calculated based on cost per administration. The total number of administrations varied according to the dosing schedule for each drug. Drug wastage was incorporated in the base case. Personal and social services costs were £476.42 per 28 days for stable health state on treatment, £119.10 for stable health state on palliative care and £1993.89 for progressive health state. Disease management costs (comprising healthcare professional contact, disease follow-up and hospital-related costs) were different for active treatment and palliative care. For active treatment, health professional contact costs were £788.96 on treatment and £220.38 after treatment (per 28 days), disease follow-up costs were £86.63 per 28 days and annual hospital-related costs were £2357.28. For palliative care, health professional contact costs were £990.74 per 28 days, disease follow-up costs were £18.44 per 28 days and annual hospital-related costs were £1982.03. End-of-life care was excluded from the calculations because it affected only the last few weeks of life and estimates would be similar for pixantrone and its comparators. Within a health state, costs for managing an adverse event were applied to the proportion of patients assumed to experience the adverse event.

3.29 The manufacturer advised that the predicted median progression-free

survival and predicted median overall survival were similar to the results reported in PIX301. Compared with the clinical trial results, the manufacturer noted that the original model slightly underestimated the median overall survival with pixantrone (13.1 months compared with 13.8 months) while overestimating it for the comparator (9.2 months compared with 7.6 months). It reported that, conversely, the original model overestimated the median progression-free survival for the pixantrone arm (7.8 months compared with 6.4 months) and slightly underestimated it for the comparator arm (3.2 months compared with 3.5 months).

3.30 Using the original model, the manufacturer's base-case analyses for pixantrone compared with treatment of physician's choice in patients with aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line treatment) produced a deterministic incremental cost-effectiveness ratio (ICER) of £28,423 per quality-adjusted life year (QALY) gained. Incremental costs were £17,638 and incremental QALYs were 0.62. Using the correct vial price supplied at clarification increased the ICER to £28,503 per QALY gained. No probabilistic base-case ICER was presented. All economic analysis results generated using the manufacturer's original model have been superseded by those using the model provided with the patient access scheme submission submitted in November 2013 (see sections 3.34–3.38).

Manufacturer's additional evidence in response to consultation on the first appraisal consultation document

3.31 In response to the first appraisal consultation document, the manufacturer provided a revised economic model, which contained these amendments:

- The adverse-event disutilities used in the ERG's exploratory analyses were incorporated.

- Drug costs for comparator treatments were taken from the NHS Commercial Medicines Unit's Electronic Marketing Information Tool (eMIT) database instead of the BNF in line with NICE's Guide to the methods of technology appraisal (2013).

- Utility values were changed from self-reported quality of life in older patients with aggressive diffuse large B-cell lymphoma (0.81 for the pre-progression health state, 0.60 for the post-progression health state) to those for second- and subsequent-line treatment of renal cell carcinoma (0.76 for the pre-progression health state and 0.68 for the post-progression health state). This was in response to the Committee's conclusion in the first Committee meeting that the original utility values had overestimated quality of life for patients with multiply relapsed or refractory non-Hodgkin's lymphoma.

  The revised model did not incorporate a patient access scheme.

3.32 Using its revised model, the manufacturer provided cost-effectiveness estimates of pixantrone compared with treatment of physician's choice for several subgroups, including patients with aggressive B-cell lymphoma confirmed by central independent pathological review who were receiving third- or fourth-line treatment and had previously had rituximab. The deterministic ICER for this subgroup was £45,282 per QALY gained (incremental costs £9170; incremental QALYs 0.20). No probabilistic ICER was provided. All economic analysis results generated using the manufacturer's revised model have been superseded by those using the model provided with the patient access scheme submission submitted in November 2013 (see sections 3.34–3.38).

Manufacturer's patient access scheme submissions

3.33 The manufacturer agreed a patient access scheme in July 2013, which was a confidential simple discount on the list price of pixantrone. It further updated its economic model so that costs for treating adverse events and the cost for methotrexate were in line with the Committee's preferred values decided at the second Committee meeting. All economic analysis results generated using the manufacturer's model provided with the patient access scheme submitted in July 2013 have been superseded by those using the model provided with the patient access scheme submission submitted in November 2013 (see

sections 3.34–3.38).

3.34 In response to the second appraisal consultation document, the manufacturer submitted a patient access scheme in November 2013 that contained an additional discount to the patient access scheme proposed in July 2013. The November 2013 patient access scheme is a simple discount on the list price of pixantrone, and the economic model was further updated with this additional discount as part of this submission. The manufacturer advised that the patient access scheme would apply to patients with histologically confirmed aggressive non-Hodgkin's B-cell lymphoma who had previously received rituximab and would be receiving pixantrone as a third- or fourth-line treatment. The manufacturer made no other revisions to the economic model.

3.35 The manufacturer provided cost-effectiveness estimates incorporating the patient access scheme submitted in November 2013 for pixantrone compared with treatment of physician's choice for patients with aggressive B-cell lymphoma confirmed by central independent pathological review who were receiving third- or fourth-line treatment and had previously received rituximab. This additional discount reduced the deterministic ICER to £18,462 per QALY gained (incremental costs are commercial in confidence and so cannot be shown here; incremental QALYs 0.20).

3.36 The manufacturer tested the robustness of the model using one-way sensitivity analyses and reported that the key drivers of the cost-effectiveness estimates produced using its economic model were the parametric fitting methodology for progression-free survival and overall survival, and the utility estimate for the stable or no progression health state. The manufacturer noted that the ICER was sensitive to changes in the estimates for progression-free survival.

3.37 In its base-case patient access scheme submission provided in November 2013, the manufacturer used the same utility values as the revised version of the model, which were for patients receiving second- and subsequent-line treatment for renal cell carcinoma (0.76 for the pre-progression health state and 0.68 for the post-progression health state). The manufacturer provided alternative utility scenarios using data from

published sources for similar patient populations, and for disease areas with similar characteristics. These were second-line treatment in patients with chronic myelogenous leukaemia, third-line treatment in patients with chronic lymphocytic leukaemia, first-line maintenance treatment in patients with follicular lymphoma, first-line treatment in patients with metastatic renal cell carcinoma, self-reported quality of life during chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma and second-line treatment in patients with malignant melanoma. The ICERs ranged from £14,607 per QALY gained to £18,871 per QALY gained.

3.38 To explore uncertainty, the manufacturer undertook a probabilistic sensitivity analysis that incorporated the patient access scheme submitted in November 2013. The probabilistic mean ICER was £22,024 per QALY gained (incremental costs are commercial in confidence and so cannot be shown here; incremental QALYs 0.18). However the manufacturer asserted that there was structural uncertainty inherent in the probabilistic sensitivity analysis that reduced the advantage of pixantrone and skewed the probabilistic results. It explained that the model assumed that overall survival and progression-free survival were independent, leading to the survival curves crossing (that is, more patients were in the progression-free survival state than alive) and the model artificially reduced progression-free survival to avoid this, and that this applied to around 30% of the simulations. In order to illustrate the structural uncertainty arising from the probabilistic ICER, the manufacturer provided additional analyses; for example, if it is assumed that overall survival and progression-free survival are not independent (by assuming the same random numbers for progression-free survival and overall survival using the Cholesky decomposition), the probabilistic mean ICER is £9938 per QALY gained (incremental costs are commercial in confidence and so cannot be shown here; incremental QALYs 0.21). The manufacturer also noted that the joint uncertainty of incremental QALYs and incremental costs did not follow a normal distribution, and reported that the median probabilistic ICER was £14,692 per QALY gained (incremental costs are commercial in confidence and so cannot be shown here; incremental QALYs 0.18). The manufacturer reported that pixantrone was more likely to be cost effective compared with treatment of physician's choice in patients with aggressive B-cell lymphoma

confirmed by central pathological review who were receiving third- or fourth-line treatment at a maximum acceptable ICER of £25,000 per QALY gained.

Evidence Review Group's comments

3.39 The ERG considered the evidence included by the manufacturer to be relevant to the decision problem in its analysis. No additional relevant trials were identified and the ERG found that the manufacturer's systematic review followed standard practices.

3.40 The ERG had concerns about the generalisability of the PIX301 population to clinical practice in England and Wales, particularly the potential effect of previous rituximab treatment on the response to pixantrone because rituximab is given as part of standard first-line treatment in the UK. The ERG noted that about 50% of patients in PIX301 had previously received treatment with a biological agent (for example, rituximab). The ERG considered the clinical benefit of pixantrone in patients who have previously been treated with rituximab to be a key area of uncertainty, given that there were no statistically significant differences between the pixantrone and comparator arms for complete or unconfirmed complete response, progression-free survival or overall survival in the subgroup of patients with aggressive B-cell lymphoma confirmed by central independent pathological review who had previously received rituximab.

3.41 The ERG considered whether the treatments of physician's choice in PIX301 represented clinical practice in England and Wales. Following input from its clinical specialists, the ERG noted that there is no consensus on which chemotherapy regimens should be used after second-line treatment fails and that there is a lack of comparative data on their clinical effectiveness. The ERG concluded that this meant the choice of treatment in the comparator arm of PIX301 was unlikely to be a key issue. It also concluded that the small number of patients receiving each treatment meant that the choice of treatment in the comparator group could not be reliably analysed.

3.42 The ERG was concerned about the statistical power of PIX301 to detect a

difference between treatment groups. According to the manufacturer's revised power calculation, 81% power with 70 patients per group (the intention-to-treat population) would be achieved if the true proportion of patients with complete or unconfirmed complete response was 22% in the pixantrone group and 5% in the comparator group. However, the observed proportions of patients with a complete or unconfirmed complete response in the intention-to-treat population were 20.0% in the pixantrone group and 5.7% in the comparator group. The ERG noted that the difference between groups did not always reach statistical significance, and that results of the analyses in the subgroups confirmed by central independent pathological review should be interpreted with caution because they are likely to be underpowered to detect a difference between treatment groups. For these reasons, the ERG had reservations about whether pixantrone had been shown to have superior efficacy in PIX301.

3.43 The ERG was concerned about the reliability of the diagnosis of aggressive non-Hodgkin's lymphoma at study entry. It noted that central independent pathological review by consensus was undertaken retrospectively (that is, after the trial), rather than at enrolment, and that aggressive disease was subsequently confirmed in only 104 of the 140 patients who were randomised. Consequently, it felt that results from the full trial population might not reflect the benefit of pixantrone in patients with aggressive B-cell lymphoma. The ERG acknowledged that the manufacturer said it had not been practical to confirm aggressive disease by central independent pathological review at enrolment, but considered it was important to evaluate data from the subgroup of patients with disease confirmed by central independent pathological review. The ERG noted that, as a subgroup analysis, the statistical power of PIX301 would be less than the intention-to-treat population.

3.44 The ERG considered the different patient populations in the subgroup analyses presented by the manufacturer. The ERG viewed the data from the post-hoc subgroup of patients with aggressive non-Hodgkin's B-cell lymphoma that was histologically confirmed by central independent pathological review to be more relevant to the marketing authorisation and the decision problem in the NICE scope than the other 2 subgroups categorised according to type of lymphoma determined by onsite

pathological review (patients with aggressive non-Hodgkin's B-cell lymphoma and patients with diffuse large B-cell lymphoma). The ERG noted that retrospective central independent pathological review revealed 23% of patients receiving pixantrone and 29% of patients receiving a comparator in the intention-to-treat population had disease that was not subsequently confirmed as being aggressive. The ERG was aware that disease severity is an important factor in deciding treatment strategy because patients without aggressive disease are likely to have a more favourable response than those with aggressive disease.

3.45 The ERG considered the statistical robustness of the subgroup analyses. It observed that the comparative clinical-effectiveness results for most of the subgroups were based on post-hoc subgroup analyses. It also noted that the number of patients in the analysis was generally small, increasing uncertainty around the results. For subgroups based on retrospective histological confirmation of aggressive disease and previous rituximab treatment, the ERG noted the potential for unbalanced groups because randomisation had not been stratified by these factors. The ERG concluded that the results of the subgroup analyses should be interpreted with caution.

3.46 The ERG considered the adverse events reported to occur more often in the pixantrone group than the comparator group receiving treatment of physician's choice to be consistent with the common adverse events associated with pixantrone reported in the summary of product characteristics.

3.47 Overall, the ERG considered the manufacturer's original model to be in line with current best practice recommendations, generally well constructed and largely transparent. The ERG considered that an important limitation of the manufacturer's original base-case analysis was that it used data from patients whose disease had not been histologically confirmed as aggressive. The ERG indicated that the subgroup of patients with aggressive non-Hodgkin's B-cell lymphoma confirmed by central independent pathological review for all lines of treatment in PIX301 was the most informative to the decision problem because it excluded patients who were later found to have disease that was irrelevant to the decision problem (for example, indolent disease).

However, the ERG noted that the manufacturer's estimate of cost effectiveness in this patient population was highly uncertain because it used post-hoc subgroup data and because the subgroups were not powered to detect a difference in efficacy between treatment with pixantrone and the comparators.

3.48 The ERG considered the utility weights used by the manufacturer in its original economic model to be potentially inappropriate. It noted that the utility values were from a population of patients receiving first-line treatment for aggressive non-Hodgkin's lymphoma and were derived from a study that had initially been rejected by the manufacturer in its systematic review. It further noted that the manufacturer's reported utility values were higher than those that have been derived for healthy older patients in the UK.

3.49 The ERG noted that the results of the manufacturer's original economic model may potentially be biased towards pixantrone because of an overestimation of pixantrone's relative progression-free survival benefit compared with treatment of physician's choice for the populations with aggressive B-cell lymphoma (whether confirmed by onsite or central independent pathological review). Clinical specialist opinion received by the ERG expressed concern that the data used in the model may not be sufficient to reach reasonable conclusions about the clinical or cost effectiveness of pixantrone.

3.50 The ERG identified other areas of inaccuracy or uncertainty in the assumptions and parameter estimates used in the manufacturer's original model and indicated the most significant of these were structural assumptions made about treatment discontinuation, disutility, and the cost parameters used:

- The potential double-counting of treatment discontinuation because of disease progression.
- Excluding adverse event disutilities for patients on further lines of treatment.
- Discrepancies between the manufacturer's and ERG's interpretation of the literature on disutilities for adverse events.

- Using weighted average adverse event rates to inform costs and disutilities associated with adverse events for patients on original treatment.
- Missing data from data used to inform average adverse event costs.
- Excluding costs associated with treating leukopenia and thrombocytopenia.
- Using costs from BNF 62 (published September 2011) rather than BNF 64 (published September 2012).

3.51 The ERG critiqued the manufacturer's additional evidence submitted in response to the first consultation. Although there were some uncertainties in the definition and labelling of the manufacturer's subgroups, the ERG was able to validate the terminology used and check that the changes the manufacturer had made to its model were appropriate. The ERG indicated that, based on the European marketing authorisation and clinical practice in England and Wales, it was important to evaluate patients with aggressive B-cell lymphoma confirmed by retrospective central independent pathological review who had previously received rituximab. However, it noted that it was also appropriate to evaluate a subgroup of these patients receiving third- or fourth-line treatment.

3.52 The ERG critiqued the manufacturer's patient access scheme submission. It validated the changes made to the economic model in the July 2013 and November 2013 submissions and agreed that the subgroup of patients covered by the patient access scheme was characteristic of patients in England and Wales who were likely to be eligible for treatment with pixantrone.

3.53 The ERG validated the manufacturer's deterministic and probabilistic sensitivity analyses on the updated base case in the patient access scheme submitted in November 2013, which were conducted in the same way as in the manufacturer's original submission. The ERG had commented in its critique of the manufacturer's original submission that the manufacturer's assessment of uncertainty was very detailed and that the probabilistic and one-way sensitivity analyses, including various scenario analyses, were satisfactorily reported.

3.54 The ERG commented that the absence of utility data in patients with

relapsed or refractory aggressive non-Hodgkin's lymphoma results in a great deal of uncertainty. The ERG stated that although the utility values derived from patients receiving second-line treatment for renal cell carcinoma were less favourable than those used in the manufacturer's original submission, they may still overestimate the utility of patients with aggressive non-Hodgkin's B-cell lymphoma receiving third- or fourth-line treatment.

3.55 The ERG stated that the manufacturer's original base-case cost-effectiveness results (before inclusion of any patient access scheme) were generated deterministically rather than probabilistically (that is, mean values rather than distributions were used to inform the value of each parameter). However, the ERG noted that probabilistic cost-effectiveness results could be assessed using the manufacturer's original model. It noted a wide range in the 95% confidence interval for the mean probabilistic ICER. The ERG considered this showed substantial uncertainty in the manufacturer's cost-effectiveness results.

3.56 Using the manufacturer's original model (before inclusion of any patient access scheme), the ERG carried out exploratory sensitivity analyses to investigate the impact of alternative assumptions or parameters on the manufacturer's cost-effectiveness results. The ERG judged the population with aggressive B-cell lymphoma confirmed by central independent pathological review for all lines of treatment in PIX301 to be the most relevant to the decision problem (because it excluded patients who were later found to have disease that was not relevant to the decision problem [for example, indolent disease]) and used it in all its exploratory analyses with the original model.

3.57 Because it had concluded that the utility values used by the manufacturer in its original model (before inclusion of any patient access scheme) may have been inappropriate, the ERG investigated how alternative utility values affected the manufacturer's original base case. The ERG presented a markedly increased ICER for pixantrone compared with treatment of physician's choice when it used utility data from chronic lymphocytic leukaemia patients receiving third- or later-line treatment to inform the utility of progression-free survival and progressive disease (0.428 for the pre-progression health state and

0.279 for the post-progression health state).

3.58 The ERG discussed the probabilistic cost-effectiveness results generated by the manufacturer using the patient access scheme submitted in November 2013, and validated the changes by the manufacturer to the economic model. The ERG commented that the manufacturer's probabilistic analysis showed that, after incorporating the patient access scheme, the probability of pixantrone being cost-effective compared with treatment of physician's choice was 49.3% at up to £20,000 per QALY gained and 55.7% at up to £30,000 per QALY gained. The ERG considered it important to note that, although 68% of probabilistic iterations showed a greater benefit for pixantrone than treatment of physician's choice, around 32% of probabilistic iterations indicated that patients treated with pixantrone fared worse than those who received treatment of physician's choice.

3.59 Full details of all the evidence are in the evaluation report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of pixantrone, having considered evidence on the nature of multiply relapsed or refractory non-Hodgkin's B-cell lymphoma and the value placed on the benefits of pixantrone by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee discussed the treatment pathway for multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. It heard from the clinical specialists that rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (also known as R-CHOP) was the standard first-line treatment in England and Wales, and that most patients would also receive a rituximab-containing regimen second line. If their disease did not relapse within 6 months of first-line treatment, patients would be treated with rituximab. The Committee also noted that the clinical specialists stated that people treated with rituximab were less likely to respond to any subsequent treatment. The Committee heard that a platinum-based regimen was offered as second-line treatment but that there was no consensus on third- or fourth-line treatment. The Committee heard from the clinical specialists and the patient expert that the aim of treatment at this disease stage was to reduce the impact of symptoms on quality of life, as well as extending life, and could include chemotherapy or participating in clinical trials. The clinical specialists highlighted that fifth-line options include palliative care or participating in clinical trials. The Committee also noted that the marketing authorisation states that the benefit of pixantrone treatment has not been established in patients when used as fifth-line or further chemotherapy in patients whose disease is refractory to last therapy.

4.3 The Committee heard from the patient expert about the impact of multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma on daily life and that the symptoms of the disease can reduce quality of life. It heard that patients are normally told at the start of their treatment that they are being treated with curative intent and that experiencing multiple relapses can be devastating; consequently, they

would value any new treatment that could offer symptom relief, have a positive impact on quality of life and increase survival. The Committee acknowledged the demands that living with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma can place on patients and accepted that a treatment option for these patients is important.

Clinical effectiveness

4.4 The Committee reviewed the suitability of the clinical trial evidence submitted by the manufacturer and expressed several concerns about the PIX301 trial. It considered PIX301 to be underpowered because it had failed to recruit the planned number of patients. It also noted that European regulators prefer a primary end point of overall survival or progression-free survival for clinical trials of anticancer drugs, but the primary end point for PIX301 was complete or unconfirmed complete response. The Committee heard from the clinical specialists that although this end point would have been acceptable when the trial began in 2004, positron emission tomography (PET) scans have made unconfirmed complete response obsolete in trials that have begun more recently. The Committee also heard from the clinical specialists that they considered studies that were powered to detect a difference in overall survival to be more useful for clinical decision-making. The Committee concluded that these fundamental concerns about the design of PIX301 meant that there was considerable uncertainty in the validity and robustness of its results.

4.5 The Committee discussed the relationship between the marketing authorisation, the PIX301 population and clinical practice in England and Wales. The Committee was aware that the intention-to-treat population included around 10% of patients who did not have aggressive B-cell lymphoma, making them ineligible for treatment with pixantrone according to the terms of the marketing authorisation. The Committee further noted that the marketing authorisation is for multiply relapsed or refractory disease (that is, it is approved for patients who have received at least 2 previous lines of treatment) and that this does not necessarily restrict its use to third- and fourth-line treatment. However, it also noted the comments received during consultation stating that patients

receiving fifth-line or further treatment would likely have palliative treatment or participate in a clinical trial. The Committee was persuaded that pixantrone would most likely be used, within its marketing authorisation, as a third- or fourth-line treatment in clinical practice in England and Wales. The Committee concluded that, when assessing the PIX301 results, it would be more appropriate to consider the population with aggressive B-cell lymphoma who had received third- or fourth-line treatment.

4.6 The Committee discussed how the tumour histologies were determined in the PIX301 population and whether this was generalisable to clinical practice in England and Wales. It was aware that tumour histology in the intention-to-treat population of PIX301 had been determined by onsite review by a single pathologist. The Committee heard from the clinical specialists that this was not representative of clinical practice in England and Wales, in which multidisciplinary team review is routine and specimens are examined by 2 or 3 pathologists. It noted that the Evidence Review Group (ERG) had also been advised by clinical specialists that a population with disease confirmed by central independent pathological review was more relevant to clinical practice in England and Wales. It also noted that a considerable proportion of patients were excluded after the central independent pathological review (for example, if indolent disease had been confirmed). The Committee concluded that it would be more appropriate to consider the PIX301 population with tumour histology confirmed by retrospective central independent pathological review by consensus than by onsite review by a single pathologist.

4.7 The Committee discussed whether the comparator arm (treatment of physician's choice) in PIX301 was relevant to clinical practice in England and Wales. It heard from clinical specialists that, apart from PIX301, there was no evidence base for selecting a third- or fourth-line treatment for multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma and that there was wide variation in the treatments used in clinical practice in England and Wales. The Committee concluded that all of the comparators used in the treatment of physician's choice arm in PIX301 were clinically relevant (although there was some uncertainty in the proportions in PIX301 compared with clinical practice in England and

Wales), and the comparator arm was therefore acceptable for decision-making.

4.8 The Committee discussed the generalisability of previous treatments received by the PIX301 population to clinical practice in England and Wales. The Committee heard from the clinical specialists that rituximab is an integral part of standard first-line treatment in the NHS and is also often used as a second-line treatment. The Committee noted that the manufacturer's subgroup analyses showed a reduced benefit of pixantrone in patients who had previously received rituximab, and that many of the results showed no statistically significant difference between treatment arms (see sections 3.11 and 3.16–3.18). It also noted a clinical specialist's concern that statistical significance was not reached for the parameters complete or unconfirmed complete response, progression-free survival and overall survival for this subgroup. The Committee accepted the non statistically significant results because of the positive trend in all 3 outcomes for this subgroup. It was aware from comments received during consultation that this reduced benefit applied to other drugs in clinical development and was not specific to pixantrone. It was also aware of the obligation to the European Medicines Agency in pixantrone's European marketing authorisation requiring a trial to confirm the clinical benefit in patients who have previously received rituximab. However, the Committee acknowledged the comments received in response to consultation that the complete response rates with pixantrone in PIX301 were among the highest reported to date in trials for patients with diffuse large B-cell lymphoma who had previously received rituximab. The Committee concluded that it was appropriate to evaluate the subgroup of patients in PIX301 who had previously received rituximab because this would apply to almost all patients with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma in England and Wales.

4.9 The Committee considered the clinical-effectiveness results for the whole intention-to-treat trial population and all the post-hoc subgroups. It noted that in the intention-to-treat population, PIX301 was inadequately powered to detect a difference between treatment groups because it had accrued less than half of the planned 320 patients. It noted that the difference in response rates, progression-free survival and

overall survival between treatment groups did not always reach statistical significance in the intention-to-treat population (see section 3.17) and the post-hoc subgroups, and that there was no statistically significant difference in overall survival between treatment arms for any groups presented by the manufacturer. The Committee had reservations about whether superior efficacy of pixantrone had been shown for the intention-to-treat trial population.

4.10 The Committee then discussed the clinical effectiveness for the subgroup of patients it considered to be most appropriate for decision making (those receiving third- or fourth-line treatment and who had previously received rituximab [see section 3.18]). It concluded that there was an increase in response rates, progression-free survival, and overall survival for pixantrone compared with treatment of physician's choice, and that the mean survival advantage of pixantrone compared with treatment of physician's choice was 2.0 months. However, these results were not statistically significant (see section 3.18). The Committee also concluded that there was limited and non-robust evidence to show that pixantrone was more clinically effective than treatments currently used in the Committee's preferred subgroup.

4.11 The Committee discussed the adverse events associated with pixantrone. It noted the manufacturer's assertion that pixantrone was associated with less cardiotoxicity than anthracyclines. The Committee was aware that the final scope issued by NICE did not include any anthracyclines as comparators and that mitoxantrone was the only anthracenedione out of the 6 comparators. It heard from clinical specialists that doxorubicin (an anthracycline) was used as first-line treatment, and that none of the comparators for third- or fourth-line treatment were associated with the similarly raised cardiovascular risk associated with anthracyclines. The Committee was aware that there were more cardiac adverse events in the pixantrone group than in the comparator group, who received treatment of physician's choice (35% compared with 21%). However, it heard from the clinical specialists that efficacy is considered key in this patient population and that, because of its cardiovascular safety profile compared with anthracyclines, pixantrone offered an opportunity for response in patients who had previously shown sensitivity to anthracyclines but who could not receive

further lines of anthracycline treatment after relapse because they had reached the maximum lifetime dose. It concluded that pixantrone had an acceptable adverse-effect profile although it was associated with more cardiotoxicity than treatments such as oxaliplatin and gemcitabine that are routinely used in this population in clinical practice in England and Wales.

Cost effectiveness

4.12 The Committee discussed the manufacturer's general approach to developing the submitted pixantrone economic models. It noted that the ERG considered the manufacturer's approach to follow current best practice and was largely transparent. The Committee concluded that the outlined structure of the models adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of pixantrone.

4.13 The Committee considered the manufacturer's cost-effectiveness analyses that included the patient access scheme for the Committee's preferred patient subgroup (that is, the subgroup with aggressive B-cell lymphoma confirmed by central independent pathological review for third- or fourth-line treatment and who had previously received rituximab [see section 4.10]). In particular the Committee discussed how quality of life had been incorporated into the manufacturer's economic modelling. It was aware that the base-case analysis in the manufacturer's patient access scheme submitted in November 2013 used utility values for patients receiving second- and subsequent-line treatment for renal cell carcinoma (0.76 for the pre-progression health state and 0.68 for the post-progression health state). It noted the absence of published utility values in the relevant patient population and that the manufacturer intends to fund additional research in this area. The Committee noted that the utility value for the pre-progression health state (0.76) was similar to that expected for a healthy older population in the UK, and it considered that the quality of life of patients receiving third- or fourth-line treatment for aggressive non-Hodgkin's B-cell lymphoma could be lower than this. The Committee then reviewed the utility values selected by the ERG for its exploratory analyses using the manufacturer's original model and the revised model supplied with the patient access scheme

submission, which were for patients receiving final-line treatment for chronic lymphocytic leukaemia (0.428 for the pre-progression health state and 0.279 for the post-progression health state). The Committee heard from the clinical specialists that there were differences between the 2 conditions that could mean these utility values were too low, and decided that the ERG's utility values were likely to underestimate the quality of life for this population. Having excluded the ERG's low utility values, the Committee considered that the manufacturer's deterministic sensitivity analysis on the base case in the patient access scheme submission using various utility values (see section 3.37) showed that utility values were not a key driver of cost effectiveness. The Committee concluded that, although there was some uncertainty as to the true utility value, the utility values used in the manufacturer's revised model with the patient access scheme were acceptable for use in the Committee's decision-making.

4.14 The Committee considered the incremental cost-effectiveness ratios (ICERs) and considered those presented in the manufacturer's most recent cost-effectiveness analyses, which included the patient access scheme for the Committee's preferred patient subgroup. For the comparison of pixantrone with treatment of physician's choice, it noted that the manufacturer's deterministic and mean probabilistic ICERs incorporating the patient access scheme for this population were £18,500 and £22,000 per quality-adjusted life year (QALY) gained respectively. The Committee noted that the ERG had validated the changes made to the manufacturer's model as part of the patient access scheme submission in November 2013. The Committee concluded that the manufacturer's analysis was appropriate for its decision-making.

4.15 The Committee discussed the amount of uncertainty in the cost-effectiveness estimates for the Committee's preferred subgroup of patients, that is people with aggressive B-cell lymphoma confirmed by central pathological review receiving third- or fourth-line treatment and who have previously received rituximab. The Committee was persuaded that the manufacturer's mean probabilistic ICER of £22,000 per QALY gained could overestimate the uncertainty associated with the survival modelling and that the true value of the ICER might be lower. It was aware that the median probabilistic ICER was £14,700 per QALY gained

and that the probabilistic ICER reduced to £10,000 per QALY gained when assuming that progression-free survival and overall survival did not change independently of each other. The Committee noted that the manufacturer's exploratory probabilistic sensitivity analysis showed that the probability of pixantrone being cost effective compared with treatment of physician's choice was 56% at a maximum acceptable ICER of £30,000 per QALY gained, and approximately 50% at a maximum acceptable ICER of £20,000 per QALY gained. Additionally, although pixantrone was less clinically effective in 32% of simulations, it was less expensive than treatment of physician's choice in a high proportion of these at a maximum acceptable ICER of £20,000 per QALY gained. The Committee therefore agreed that the probability of pixantrone being cost-effective compared with treatment of physician's choice was acceptable. The Committee concluded that the most plausible ICER was likely to be less than £22,000 per QALY gained, and it concluded that pixantrone was recommended as a cost-effective use of NHS resources.

4.16 The Committee discussed whether pixantrone was innovative in its potential to make a significant and substantial impact on health-related benefits. It observed that pixantrone is the first drug that has been tested in a randomised phase III trial in patients with multiply relapsed or refractory aggressive non-Hodgkin's lymphoma. It examined whether pixantrone had the potential to make a significant and substantial impact on health-related benefits but heard from the clinical specialists that it was uncertain whether pixantrone could be considered a step change in treatment. On the basis of currently available evidence, the Committee did not consider pixantrone to be a step change in managing multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. The Committee observed that there were no additional gains in health-related quality of life over those already included in the QALY calculations. The Committee concluded that there were no additional QALYs that had not been incorporated into the economic model and the cost-effectiveness estimates.

4.17 The Committee understood that pixantrone's conditional marketing authorisation is linked to results from the ongoing PIX306 study, which should be available in 2015. It noted that this larger randomised phase III study (n=350) will compare the effectiveness of pixantrone plus

rituximab with gemcitabine plus rituximab in patients with relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma who have already received a rituximab-containing regimen. Given the relevance of the patient population (because virtually all patients with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma in England and Wales will have previously received rituximab [see section 4.8]), the Committee recommended that the technology appraisal guidance on pixantrone for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma should be considered for review by NICE once the PIX306 results are available in 2015.

4.18 The Committee considered whether NICE's duties under the equality legislation required it to alter or to add to its recommendations. It noted that no equality issues had been raised during scoping, in any of the consultees' submissions, during consultation or during the Committee meetings. The Committee concluded that its decision on the use of pixantrone does not have a particular impact on any group with a protected characteristic in the equality legislation and that there was no need to alter or add to its recommendations.

Summary of Appraisal Committee's key conclusions

TA306	Appraisal title: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma	Section
Key conclusion		

Pixantrone monotherapy is recommended as an option for treating adults with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma only if: • the person has previously been treated with rituximab and • the person is receiving third- or fourth-line treatment and • the manufacturer provides pixantrone with the discount agreed in the patient access scheme. The Committee concluded that there was limited and non-robust evidence to show that pixantrone was more clinically effective than treatments currently used in clinical practice for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. It further concluded that there was an increase in response rates, progression-free survival, and overall survival for pixantrone compared with treatment of physician's choice. However, these results were not statistically significant. The Committee noted that using the revised model that incorporated the patient access scheme, the manufacturer's deterministic ICER was £18,500 per quality-adjusted life year (QALY) gained and that the mean probabilistic ICER was £22,000 per QALY gained. The Committee agreed that the probability of pixantrone being cost effective compared with treatment of physician's choice was acceptable and that the most plausible ICER was likely to be less than £22,000 per QALY gained. It therefore concluded that pixantrone could be recommended as a cost-effective use of NHS resources.	1.1, 3.18, 4.8, 4.9, 4.10, 4.14, 4.15
Current practice	

Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialists and the patient expert that the aim of treatment at this disease stage was to reduce the impact of symptoms on quality of life, as well as extending life, and could include chemotherapy and participating in clinical trials. The Committee heard from the patient expert that patients would value any new treatment that could offer symptom relief, have a positive impact on quality of life and increase survival. The Committee acknowledged the demands that living with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma can place on patients and accepted that a treatment option for these patients is important.	4.2, 4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Pixantrone (Pixuvri, Cell Therapeutics) is an aza-anthracenedione analogue and inhibitor of topoisomerase II. The Committee concluded that there was limited and non-robust evidence to show that pixantrone was more clinically effective than treatments currently used in clinical practice to treat multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. It further concluded that there was an increase in response rates, progression-free survival, and overall survival for pixantrone compared with treatment of physician's choice. However, these results were not statistically significant. The Committee examined whether pixantrone had the potential to make a significant and substantial impact on health-related benefits. On the basis of currently available evidence, the Committee concluded that using pixantrone would not be a step change in managing multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma and that there were no additional QALYs that had not been incorporated into the economic model and the cost-effectiveness estimates.	2.1, 4.8, 4.9, 4.10, 4.18

What is the position of the treatment in the pathway of care for the condition?	Pixantrone has a conditional marketing authorisation 'as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy'. In light of consultee and commentator responses to consultation, the Committee considered that it was appropriate to restrict its assessment of pixantrone to third- and fourth-line treatment. The Committee concluded that the subgroup in PIX301 with aggressive B-cell lymphoma confirmed by central independent pathological review receiving third- or fourth-line treatment and who had previously received rituximab was the most appropriate for decision-making.	2.1, 4.5, 4.8, 4.9, 4.10
Adverse reactions	The summary of product characteristics states that the most common toxicity with pixantrone is bone marrow suppression (particularly the neutrophil lineage) and that other toxicities such as nausea, vomiting and diarrhoea are generally infrequent, mild, reversible, manageable and as expected in patients treated with cytotoxic agents. Although the occurrence of cardiac toxicity indicated by congestive heart failure appears to be lower than that expected with related drugs like anthracyclines, the summary of product characteristics recommends monitoring left ventricular ejection fraction. The Committee concluded that pixantrone had an acceptable adverse-event profile although it was associated with more cardiotoxicity than treatments such as oxaliplatin and gemcitabine that are routinely used in this population in clinical practice in England and Wales.	2.2, 4.11
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The Committee considered that the PIX301 trial was underpowered because it had failed to recruit the planned number of patients. It also noted that European regulators prefer a primary end point of overall survival or progression-free survival for clinical trials of anticancer drugs, but the primary end point for PIX301 was complete or unconfirmed complete response. The Committee considered that although the PIX301 study had included a high proportion of patients who would be eligible for treatment under the terms of the marketing authorisation, the intention-to-treat population was not appropriate for evaluation and decision-making. The Committee concluded that these fundamental concerns about the design of PIX301 meant that there was considerable uncertainty in the validity and robustness of its results.	4.4, 4.5
Relevance to general clinical practice in the NHS	Because tumour specimens would be examined by 2 or 3 pathologists in clinical practice in England and Wales, the Committee concluded that it would be more appropriate to consider results from the PIX301 trial using a population with tumour histology confirmed by retrospective central independent pathological review by consensus than by onsite review by a single pathologist.	4.6
Uncertainties generated by the evidence	The Committee was concerned that only just over half of patients in the PIX301 trial had previously received rituximab because it heard from the clinical specialists that rituximab is an integral part of standard first-line treatment in the NHS and also often used as a second-line treatment. It was aware of the obligation to the European Medicines Agency in pixantrone's marketing authorisation requiring a trial to confirm the clinical benefit in patients who have previously received rituximab. The Committee noted a reduced benefit of pixantrone in the subgroup of patients who had previously received rituximab, but concluded that it was appropriate to evaluate this subgroup because this would apply to almost all patients with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma in England and Wales.	4.8, 4.19

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee was aware that the intention-to-treat population included patients whose tumour histology would make them ineligible for treatment with pixantrone according to the terms of the European marketing authorisation. The Committee concluded that the subgroup of patients in PIX301 with aggressive B-cell lymphoma confirmed by central independent pathological review receiving third- or fourth-line treatment and who had previously received rituximab was the most appropriate for decision-making.	4.5, 4.9, 4.10
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that for the subgroup of patients it considered to be most appropriate for decision making (those receiving third- or fourth-line treatment and who had previously received rituximab) there was an increase in response rates, progression-free survival, and overall survival for pixantrone compared with treatment of physician's choice, and that the mean survival advantage of pixantrone compared with treatment of physician's choice was 2.0 months. However, these results were not statistically significant. The Committee concluded that there was limited and non-robust evidence to show pixantrone was more clinically effective than treatments currently used in clinical practice for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma.	4.9, 4.10
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee concluded that the outlined structure of the models adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of pixantrone.	4.12

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee was persuaded that the manufacturer's mean probabilistic ICER of £22,000 per QALY gained could overestimate the uncertainty associated with the survival modelling and that the true value of the ICER might be lower. It further concluded that there was an increase in response rates, progression-free survival, and overall survival for pixantrone compared with treatment of physician's choice. However, these results were not statistically significant.	4.9, 4.10, 4.15
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee was aware that the utility value used by the manufacturer in its revised model incorporating the patient access scheme for the pre-progression health state was similar to that expected for an older population in the UK. The Committee considered that the quality of life of patients receiving third- or fourth-line treatment for aggressive non-Hodgkin's B-cell lymphoma could be lower than this. The Committee concluded that, although there was some uncertainty as to the true utility value, the utility values used in the manufacturer's revised model that was part of the patient access scheme submission were appropriate for use in the Committee's decision-making. The Committee observed that there were no additional gains in health-related quality of life over those already included in the QALY calculations and concluded that there were no additional QALYs that had not been incorporated into the economic model and the cost-effectiveness estimates.	4.13, 4.18

Are there specific groups of people for whom the technology is particularly cost effective?	The patient access scheme applies to patients with histologically confirmed aggressive non-Hodgkin's B-cell lymphoma who have previously received rituximab and are receiving pixantrone as a third- or fourth-line treatment.	3.34–3.38
What are the key drivers of cost effectiveness?	The Committee concluded that there was limited and non-robust evidence to show pixantrone was more clinically effective than treatments currently used in clinical practice for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. It further concluded that there was an increase in response rates, progression-free survival, and overall survival for pixantrone compared with treatment of physician's choice. However, these results were not statistically significant. The patient access scheme reduced the mean probabilistic ICER to £22,000 per QALY gained. The Committee was persuaded that this ICER could overestimate the uncertainty associated with the survival modelling and that the true value of the ICER might be lower.	4.10, 4.14, 4.15

Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that, for the subgroup of patients with aggressive B-cell lymphoma confirmed by central independent pathological review for third- or fourth-line treatment and who had previously received rituximab, the manufacturer's deterministic ICER incorporating the patient access scheme was £18,500 per QALY gained and the manufacturer's mean probabilistic ICER was £22,000 per QALY gained. The Committee noted that the exploratory analysis showed a high level of uncertainty around the ICER. However, the Committee was persuaded that this analysis could overestimate the uncertainty associated with the survival modelling and that the true value of the ICER might be lower. The Committee concluded that because the probabilistic ICER was likely to be less than £22,000 per QALY gained pixantrone was recommended as a cost-effective use of NHS resources.	4.14, 4.15
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer of pixantrone has agreed a patient access scheme with the Department of Health that makes pixantrone available with a discount. The size of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.	2.3
End-of-life considerations	Not appropriate.	4.16, 4.17
Equalities considerations and social value judgements	The Committee concluded that its decision on the use of pixantrone does not have a particular impact on any group with a protected characteristic in the equality legislation and that there was no need to alter or add to its recommendations.	4.20

5 Implementation

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

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma and the doctor responsible for their care thinks that pixantrone is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 The Department of Health and the manufacturer have agreed that pixantrone will be available to the NHS with a patient access scheme which makes pixantrone available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Mr Dilip Patel, DPatel@cti-lifesciences.com, 01494 596722.

5.4 NICE has developed tools to help organisations put this guidance into practice (listed below).

- Costing template and report to estimate the national and local savings and costs associated with implementation.

6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the NICE website.

- Rituximab for aggressive non-Hodgkin's lymphoma. NICE technology appraisal guidance 65 (2003).
- Improving outcomes in haematological cancers. NICE cancer service guidance (2003).

7 Review of guidance

7.1 The guidance on this technology will be considered for review when the PIX306 trial results are available and at the latest in November 2016. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
February 2014

8 Appraisal Committee members and NICE project team

8.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Professor Kathryn Abel
Director of Centre for Women's Mental Health, University of Manchester

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS

Trust

Dr Andrew Burnett
Formerly – Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler
Lay Member

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Dept of Primary Care and Population Health, University College London

Dr Maria Dyban
General Practitioner, Kings Road Surgery, Glasgow

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell
Consultant in Public Health, Bradford and Airedale Primary Care Trust

Dr Wasim Hanif
Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson
Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital

Trust

Emily Lam
Lay Member

Dr Allyson Lipp
Principal Lecturer, University of South Wales

Dr Claire McKenna
Research Fellow in Health Economics, University of York

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Grant Maclaine
Formerly Director, Health Economics and Outcomes Research, BD, Oxford

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Dr Paul Miller
Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Anna O'Neill
Deputy Head of Nursing and Healthcare School/Senior Clinical University Teacher, University of Glasgow

Alan Rigby
Academic Reader, University of Hull

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Tim Stokes
Senior Clinical Lecturer, University of Birmingham

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Dr Judith Wardle
Lay Member

8.2 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.

Linda Landells and Carl Prescott
Technical Leads

Nicola Hay
Technical Adviser

Lori Farrar
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ Technology Assessment Group:

- Edwards SJ, Barton S, Nherera L et al. Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma: a single technology appraisal, February 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation documents (ACDs). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Cell Therapeutics

II. Professional/specialist and patient/carer groups:

- British Society for Haematology
- Cancer Research UK
- Leukaemia CARE
- Lymphoma Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- Greater Manchester (PCT Cluster)
- South Essex (PCT Cluster)
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- BMJ Group
- Bristol-Myers Squibb Pharmaceuticals
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Lilly UK
- MRC Clinical Trials Unit
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme
- Pfizer

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Andrew McMillan, Consultant Haematologist, nominated by the Royal College of Physicians – clinical specialist
- Dr Ruth Pettengell, Reader in Haemato-Oncology, nominated by the Royal College of Physicians – clinical specialist

- Jacky Wilson, Medical Writer, nominated by Lymphoma Association – patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Cell Therapeutics

Changes after publication

April 2014: Wording changes in sections 4.8 and 4.9.

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

It has been incorporated into the NICE pathway on blood and bone marrow cancers along with other related guidance and products.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility
This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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